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EPIDEMIOLOGICAL STUDIES OF MEDICATION USE AND EFFECTIVENESS IN BIPOLAR DISORDER

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Karolinska Institutet

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Epidemiological studies of medication use and effectiveness in bipolar disorder

Louise Wingård

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To my patients

ABSTRACT

In the last decades, new treatments for bipolar disorder (BD) have emerged, prompting a decrease in the use of lithium – the former "gold standard" for relapse prevention, and increasing the possibilities for individualized treatment. The aims of this thesis were to: 1) explore the use of relapse prevention in the early phases of bipolar illness, 2) add to the current knowledge concerning the comparative effectiveness of various pharmacological maintenance treatments, including combination therapies, and 3) explore the use of benzodiazepines and non-benzodiazepine hypnotics (so called Z-drugs) in BD. All four studies were population based cohort studies, using data from Swedish national registers.

In Study I, 31 770 individuals with newly diagnosed BD were followed for one year with regard to initiation of relapse prevention. Three months after diagnosis, 72% had initiated such treatment. Patients diagnosed with BD during a long hospitalization were most likely to initiate treatment, followed by patients who had used lithium, anticonvulsants or antipsychotics prior to diagnosis. Our findings indicate that efforts to reduce treatment delay should especially target patients who are naïve to mood-stabilizers and antipsychotics or diagnosed with BD during a brief hospitalization.

In Study II, we followed patients for one year after a hospitalization for a manic episode. The study included follow-up data from 6 502 hospitalizations. We classified patients by various prophylactic drug regimens, based on prescription fills during the first four weeks after hospital discharge, and assessed the one-year rehospitalization risk associated with each regimen. Combination therapy with olanzapine and valproate or lithium was associated with the lowest rehospitalization risk.

Study III had a design similar to Study II, but investigated the risk of treatment failure with various treatment alternatives. Treatment failure was defined as treatment switch/discontinuation or rehospitalization during ongoing treatment. We found that treatment failure was less common in patients on combination therapy, and that combination therapies including lithium, valproate and quetiapine or olanzapine were associated with the lowest risks of treatment failure.

In Study IV, we included 21 883 BD patients with no history of benzodiazepine/Z-drug use in the past year and followed them for one year with regard to benzodiazepine/Z-drug initiation and long-term use (continuous use for $\geq$6 months). In total, 6 307 patients (29%) initiated benzodiazepine/Z-drug treatment, of whom more than one in five became long-term users. Most notably, patients who initiated treatment with clonazepam or alprazolam had greatly increased odds for long-term use. In addition, long-term use was common among patients who used two or more benzodiazepines and/or Z-drugs.

LIST OF SCIENTIFIC PAPERS

I. **Predictors for initiation of pharmacological prophylaxis in patients with newly diagnosed bipolar disorder—A nationwide cohort study**
Louise Scheen (now Wingård), Lena Brandt, Robert Bodén, Jari Tiihonen, Morten Andersen, Helle Kieler, and Johan Reutfors
Journal of Affective Disorders, 2015(172):204–210

II. **Reducing the rehospitalization risk after a manic episode: A population based cohort study of lithium, valproate, olanzapine, quetiapine and aripiprazole in monotherapy and combinations**
Louise Wingård, Robert Bodén, Lena Brandt, Jari Tiihonen, Antti Tanskanen, Helle Kieler, Morten Andersen, and Johan Reutfors
Journal of Affective Disorders, 2017(217):16–23

III. **Monotherapy vs. combination therapy as maintenance treatment after a manic episode: a population based cohort study of lithium, valproate, olanzapine, quetiapine, and aripiprazole**
Louise Wingård, Lena Brandt, Robert Bodén, Helle Kieler, Morten Andersen, and Johan Reutfors
Manuscript submitted for publication

IV. **Initiation and long-term use of benzodiazepines and Z-drugs in bipolar disorder**
Louise Wingård, Heidi Taipale, Johan Reutfors, Anna Westerlund, Robert Bodén, Jari Tiihonen, Antti Tanskanen, and Morten Andersen
Manuscript submitted for publication

CONTENTS

LIST OF ABBREVIATIONS

aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
ATC	Anatomical Therapeutic Chemical Classification
BD	Bipolar disorder
CDR	The Cause of Death Register
CI	Confidence interval
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
HR	Hazard ratio
ICD-9	International Classification of Diseases, 9th revision
ICD-10	International Classification of Diseases, 10th revision
LISA	The Longitudinal Integration Database for Health Insurance and Labor Market Studies
NPR	The Swedish National Patient Register
OR	Odds ratio
PDR	The Prescribed Drug register
RCT	Randomized controlled trial
SD	Standard deviation
TPR	The Total Population Register

1 INTRODUCTION

Although the first writings capturing bipolar disorder date back to the ancient Egyptians,[1] it took until the early 20th century before the nature of the illness was described in greater detail. In 1921, German psychiatrist Emil Kraepelin distinguished "manic-depressive insanity" from the previously unitary concept of psychosis,[2] enabling subsequent studies of its specific features and treatments.

1.1 Bipolar disorder

Bipolar disorder is characterized by recurrent episodes of mania and depression, typically with onset during adolescence or early adulthood.[3] Mania distinguishes bipolarity from unipolar depressive illness and involves elevated or irritable mood, increased activity, inflated self-esteem, pressure of speech and decreased need for sleep.[4] Nevertheless, the clinical presentation is usually dominated by depression, both in terms of number of episodes throughout life, and of days spent symptomatic.[5-7]

The DSM-5 recognizes two distinct subtypes of bipolar disorder: type I and type II.[4] Bipolar disorder type I encompasses a more severe form of manic episodes with significant loss of function and/or psychotic symptoms, whereas individuals with bipolar disorder type II experience a less severe form referred to as hypomania. The lifetime prevalence of bipolar disorder type I is about 1% in both men and women.[8,9] The lifetime prevalence for bipolar disorder type II is slightly higher, with a small female overrepresentation.[3] Yet another 2% of the population is estimated to suffer from subthreshold forms of bipolar illness, resulting in a lifetime prevalence of so called bipolar spectrum disorders of over 4%.[3]

Epidemiological studies have found that the prevalence of bipolar disorder has increased in the last decades,[10-12] possibly reflecting a diagnostic shift from schizophrenia to other psychiatric disorders.[11,12] Despite this increased recognition of bipolar symptomatology, there is still a considerable lag time between the onset of bipolar illness and bipolar disorder diagnosis,[13,14] which may lead to delayed initiation of adequate treatment.[13-15]

1.2 Morbidity

Until recently, the view of bipolar disorder has been heavily influenced by Kraepelin's description of manic depressive illness, with a return to normal mood – euthymia – and unimpaired functioning between episodes.[2] However, recent evidence shows that a majority of patients suffer from significant inter-episodic morbidity, experiencing subsyndromal manic and depressive symptoms,[7,16,17] as illustrated in Figure 1. The characteristic relapses of threshold mania and/or depression affect over 90% of patients.[18] Observational studies estimate the two-year syndromic relapse risk to around 50%,[6,19] with five-year relapse risks ranging from 70% to 90%.[19,20] In addition to affective

morbidity, up to 75% of bipolar disorder patients suffer from at least one comorbid psychiatric condition.[21] Anxiety disorders and substance use disorders are the most common comorbidities, affecting between 25% and 50% of patients at some point in life.[22,23]

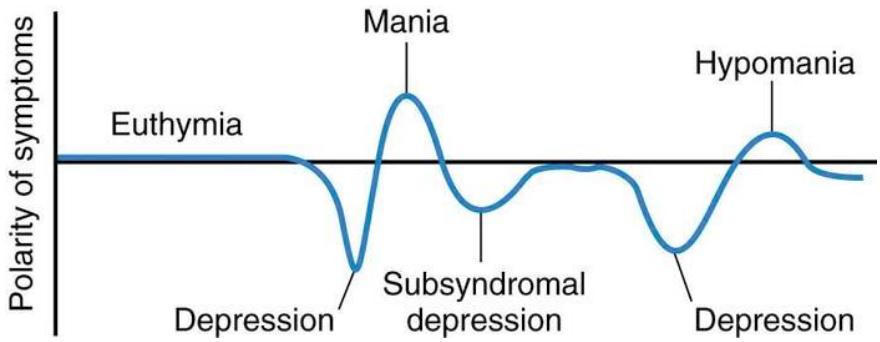

Figure 1. *The typical variable course of bipolar disorder.*

1.3 Social and economic aspects

Bipolar illness has significant social and economic impacts on personal life. It affects interpersonal relationships, as illustrated by a 50% lower marriage rate among patients compared to the general Swedish population.[24] Starting out with an educational level similar to that of their peers,[25] future employment rates were found to be up to 60% lower among individuals with bipolar disorder in a systematic review of 25 studies from Europe, USA and China.[26] Many patients report that their illness forces them to change their job to a less demanding position, resulting in a downward drift of occupational status.[26]

Further, bipolar disorder also has economic implications on society. The annual cost per bipolar disorder patient in Sweden was estimated to 28 011 Euro in 2008, of which indirect costs due to sick leave and early retirement represented 75%.[24] The total cost was six times higher during threshold mood-episodes and increased drastically during hospitalizations (55 500 vs 22 200 Euro).[24] Between 50% and 60% of all direct costs could be attributed to hospitalization.[24,27]

1.4 Mortality

Although a majority of patients with bipolar disorder die from somatic disease, bipolar disorder is associated with the highest suicide risk of all psychiatric conditions.[28] The risk of suicide is significantly increased throughout the lives of bipolar disorder patients, though most pronounced in younger ages and in the first years after diagnosis, when the risk is seven times higher compared to the general population.[29] Between 25% and 50% of all patients attempt suicide at some point,[30,31] usually during a depressive or mixed

episode.[32] In Sweden, suicide accounts for between 5% and 10% of deaths in individuals with bipolar disorder, compared to circa 1% in the general population.[33]

1.5 Bipolar disorder treatment – an historical overview

After Kraepelin's characterization of bipolarity in the early 20th century, a variety of treatments targeted against manic depressive illness were launched. Psychodynamic theories for psychotherapy in depression were developed based on Freud's psychoanalytical doctrine,[34] followed by surgical procedures including prefrontal lobotomy, introduced in the 1930's.[34,35] Shortly thereafter, electroconvulsive therapy was developed,[36] and has remained a viable treatment option for drug resistant bipolar depression, mania, mixed state and catatonia.[37]

In the 1950's, the treatment of psychiatric illness took a leap forward due to the development of effective psychotropic drugs,[34] including first generation antidepressants,[34] antipsychotics,[34] and benzodiazepine anxiolytics.[38] The Australian physician John Cade showed that lithium – a natural salt used to treat gout – could reduce "psychotic excitement" related to mania,[39] paving the way for a subsequent clinical trial by Danish psychiatrist Mogens Schou. Schou and colleagues published their results in 1954, concluding that lithium could be used for relapse prevention in bipolar disorder.[40] This caused a therapeutic shift from only focusing on the alleviation of acute manic or depressive symptoms to preventing new affective episodes from developing.

1.6 Modern treatment approaches

Maintenance treatment with lithium or anticonvulsants (jointly referred to as "mood-stabilizers") or atypical antipsychotics is currently the cornerstone of bipolar disorder management, for which the ultimate goals are relapse prevention, reduction of subthreshold symptoms, and enhanced social and occupational functioning.[41] In addition, acute pharmacological treatment is used during depressive and manic/hypomanic/mixed relapses to achieve faster symptomatic recovery.[41] These complementary pharmacological approaches are illustrated in Figure 2.

Table 1 shows all mood-stabilizers and antipsychotics with regulatory approval for the treatment of bipolar disorder in Sweden, and their specific indications.[42] In addition to the listed drugs, antidepressants are widely used to tackle the depressive symptomatology in bipolar disorder.[43] There has been a long-standing debate about the potential pros and cons with such treatment, including mood-destabilization and manic switch.[44] However, new data suggest that the risk for manic switch is low, if the antidepressant is used in combination with a mood-stabilizer.[45]

Short-term add-on treatment with benzodiazepines or non-benzodiazepine hypnotics may also be necessary when an acute stressor is imminent or present, that may trigger

relapse. Such drugs are further used to tackle early symptoms of relapse (especially insomnia) and prominent anxiety.[46]

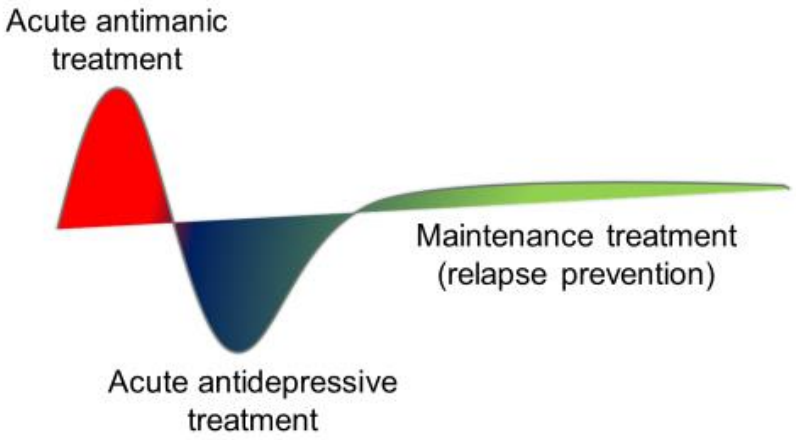

Figure 2. *Pharmacological approaches throughout the course of bipolar disorder (modified from Frank et al. 1991[47]).*

Table 1. Mood-stabilizers and antipsychotics with regulatory approval for treatment of bipolar disorder in Sweden

	Indication:		
	Acute mania	Acute depression	Relapse prevention
Lithium	x		x
Anticonvulsants:			
Lamotrigine			x
Valproate	x		x
Antipsychotics:			
Aripiprazole	x		x
Chlorprothixene	x		
Haloperidol	x		
Levomepromazine	x		
Olanzapine	x		x
Paliperidone	x		
Perphenazine	x		
Quetiapine	x	x	x
Risperidone	x		
Ziprasidone	x		
Zuclopenthixol	x		

1.7 Maintenance treatment

As illustrated in Table 1, only six out of the 14 drugs approved for bipolar disorder treatment in Sweden are indicated for relapse prevention: lithium, lamotrigine, valproate, aripiprazole, olanzapine and quetiapine. Just as for acute treatment, these drugs differ in terms of their relative antimanic versus antidepressive preventive efficacy (so called polarity index).[48] In brief, lithium and quetiapine have been shown to prevent both manic and depressive episodes, whereas lamotrigine mainly prevents depressive episodes and olanzapine and aripiprazole mainly prevent manic episodes.[48] Data on the polarity index of valproate have so far been inconclusive,[48,49] although its prophylactic efficacy is well established.[49]

Despite the growing pharmacopoeia of mood-stabilizers and antipsychotics, lithium remains the first line maintenance treatment recommended by the Swedish National Board of Health and Welfare.[50] The British Association for Psychopharmacology (BAP), the World Federation of Societies of Biological Psychiatry (WFSBP), and the National Institute for Health and Care Excellence (NICE) have the same approach in their treatment guidelines,[46,51,52] whereas the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International College of Neuro-Psychopharmacology (CINP) have shifted towards recommending monotherapy with lithium *or* specific anticonvulsants or antipsychotics.[53,54] So far, CANMAT is the only large-scale guideline to also recommend combination treatments as first-line.[53]

Comparative effectiveness of maintenance treatments

Treatment recommendations are so far primarily based on findings from RCTs. To date, the majority of clinical trials of maintenance treatment in bipolar disorder have evaluated the efficacy of one atypical antipsychotic (in monotherapy or as add-on), compared to one or two mood-stabilizers and/or placebo. Furthermore, the real-world effectiveness of maintenance treatment has been assessed through observational studies, which have typically included a greater number of treatment alternatives. However, these observational studies have also been restricted to only studying one atypical antipsychotic at a time, and few, if any, combination therapies.[55-59] As studies from around the world show a rapid increase in the use of antipsychotics and combination therapies,[60-62] the lack of comparative data on these treatments has become increasingly problematic.

Discrepancies between RCT findings and observational data add to the complexity when choosing between different treatment options. Whereas RCTs have typically shown an equal or superior effectiveness of antipsychotics compared to lithium or valproate,[49,63] the majority of observational studies have found a superior effectiveness of lithium over other drugs.[57-59,64,65] How can this be? For one, translating findings from RCTs to clinical reality is challenging. For practical and scientific reasons, RCTs have narrow inclusion and exclusion criteria, limiting their generalizability.[66,67] Furthermore, the vast majority

of maintenance treatment RCTs have a so called "enrichment design", meaning that they only include patients who have responded well to the new drug of study during an acute affective episode.[66,67] Patients are thereafter randomized to either continuing with the new drug or using an older treatment alternative, which makes it difficult to demonstrate the effect of old drugs. Likewise, patients who are satisfied with their current treatment are likely less prone to participate in a randomized trial evaluating the efficacy of a new drug, also favoring new treatment alternatives.

Observational studies on their part may contain unrecognized confounding factors that distort results, as patients are not randomized to treatments.[68] For this reason, randomized controlled trials top the hierarchy of study designs traditionally used in evidence based medicine (after systematic reviews and other types of evidence synthesis), followed by cohort and case-control studies (Figure 3).[69,70] However, two comprehensive reviews comparing the estimated efficacy of drugs in RCTs versus observational studies, each including over 100 studies, show that well-designed observational studies (with either a cohort or case–control design) do not systematically over- or underestimate the magnitude of the effects of treatment as compared with RCTs on the same topic.[71,72] These insights, and the discrepancies between RCT findings and real-world clinical experience, have led to a call for a shift from the pyramidal shaped hierarchy of study designs to a broader multi-domain perspective when psychiatric treatment guidelines are created (Figure 3).[70]

Early versus late initiation of maintenance treatment

Despite the increasing recognition of bipolar disorder in clinical settings, there is often a considerable delay from illness onset to diagnosis and to initiation of prophylactic treatment.[13,15,25,73,74] Delayed treatment initiation has been associated with poorer social adjustment, more frequent hospitalizations, and increased suicidal behavior.[15,74] Furthermore, the higher employment rates in early versus late bipolar disorder [26] suggest that early intervention may be beneficial with regard to maintaining the capacity to work.

In line with these findings, consistent evidence show that early pharmacological intervention is more effective than intervention later during the illness course, with regard to response rates, relapse rates, time to recurrence, symptomatic recovery, and remission.[75-78] However, most treatment guidelines do not specify when long-term prophylactic treatment should be initiated.[79] The guidelines on bipolar disorder management published by the Swedish National Board of Health and Welfare in 2010 stated that treatment should be initiated "urgently".[50]

In addition to delayed initiation of treatment due to diagnostic lag time and for other reasons, treatment non-adherence greatly contributes to an impaired prognosis.[80] Previous observational studies have estimated that 20%–70% of patients are non-

adherent to medication in the early phases of prophylactic treatment.[81-88] Among the factors most consistently associated with non-adherence to maintenance treatment are substance abuse [80,81,86,88,89] and comorbid personality disorder.[90,91]

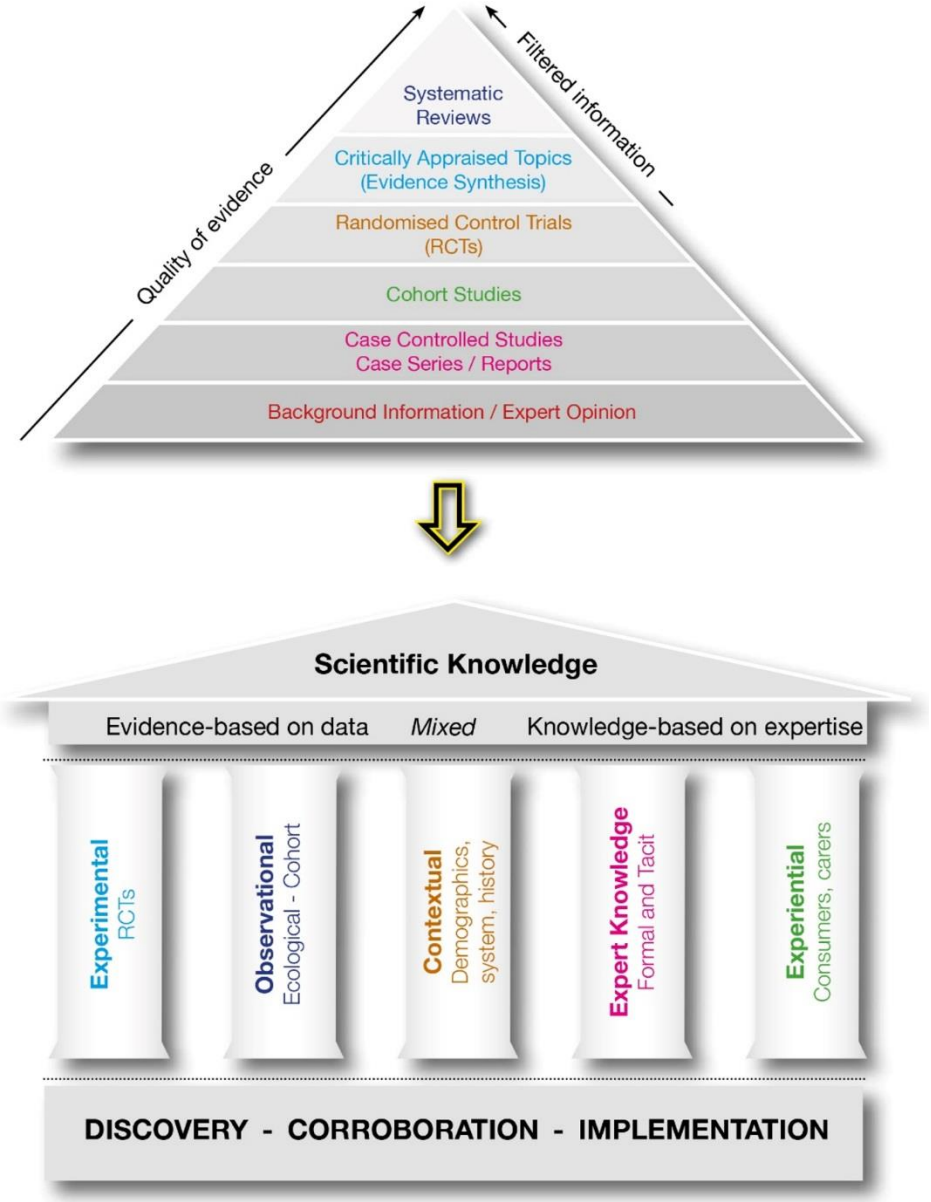

Figure 3, *from Salvador-Carulla et al. 2017,[70] illustrating the shift from a pyramid shaped hierarchy of study designs to a broader multi-domain perspective: the Greek temple model of scientific knowledge.*

1.8 Benzodiazepines and Z-drugs

Benzodiazepines and sleep inducing hypnotics (so called "Z-drugs") are the third most used group of psychotropics in bipolar disorder in Sweden, after antidepressants and atypical antipsychotics.[60] These substances are effective and well tolerated in the short-term management of anxiety and insomnia,[92,93] through binding to the γ-aminobutyric

acid ($GABA_A$) ionotropic receptor and facilitating its inhibiting actions on neuronal activity.[94,95] The anxiolytic and hypnotic effects of benzodiazepines and Z-drugs can be used to reduce the risk of relapse in patients experiencing acute stress. They are further prescribed to patients with early symptoms of relapse in order to prevent development of full-scale manic or depressive episodes, and to treat anxiety, agitation and/or insomnia during manic, mixed or depressed episodes.[46] Lastly, comorbid anxiety disorders[96] and inter-episodic sleep disturbances[97] may require benzodiazepine treatment.

Tolerance, dependence and abuse

Although benzodiazepines are demonstrated to be safe for short-term use,[98] the risks of tolerance, dependence and abuse during long-term treatment have been increasingly recognized.[99] Tolerance means that chronically treated patients become less sensitive to some treatment effects over time, specifically to the anticonvulsant, sedative, hypnotic, and myorelaxant effects of benzodiazepines.[100] Dependence is characterized by a combination of tolerance, withdrawal symptoms when drug intake is stopped, and dose escalation,[101] and develops in approximately half of all patients who use benzodiazepines for longer than one month.[102] Dependence and an activation of dopaminergic neurons in the brain's "addiction network" may further result in benzodiazepine/Z-drug abuse.[103]

Other risks associated with long-term benzodiazepine use

In addition to tolerance, dependence, and abuse, continuous use of benzodiazepines has been associated with impaired cognitive functioning[104,105] and increased risk of accidental falls[106,107]. Further, studies suggest a dose-response relationship between benzodiazepines and the development of Alzheimer's disease[108] and all-cause mortality[109]. Bipolar disorder patients with a regular use of benzodiazepines show higher levels of treatment resistance to mood-stabilizers[110] and have a greater risk for both manic and depressive relapses, independently from the effects of comorbid anxiety and insomnia.[60] Benzodiazepines also seem to have direct depressogenic effects,[111,112] which may be particularly harmful to individuals with bipolar disorder.

Epidemiology of long-term benzodiazepine use

Due to the potentially harmful effects described above, benzodiazepine use has decreased in the past decades,[60,92,113] and clinical guidelines consistently recommend that treatment with benzodiazepines/Z-drugs should be kept as short as possible, with a maximum of four weeks.[114-116] However, observational studies have found that 15%–35% of benzodiazepine users continue with their treatment for substantially longer periods of time.[117-120] Elderly patients seem to have the highest rates of long-term use.[119,120] Other identified risk factors include male gender, short-acting or mixed type agents, and high initial doses.[117,118]

2 OBJECTIVES

The overall objectives of this thesis were to explore the use of maintenance treatment and benzodiazepines in bipolar disorder, to assess if and how prescription patterns diverge from treatment guidelines, and to compare outcomes across patients using various pharmacological maintenance treatments, including combination therapies.

Specific objectives for each of the four studies were:

I. To assess the use of, and predictors for, maintenance treatment in newly diagnosed bipolar disorder patients.

II. To study the rehospitalization risk in patients discharged from a hospitalization for mania, and to compare rehospitalization risks across the entire span of treatment options approved for prophylactic use after a manic episode, including combination therapies.

III. To compare risks of treatment failure after a manic episode across the entire span of treatment options approved for prophylactic use after a manic episode, including combination therapies.

IV. To study the incidence of, and predictors for, long-term use of benzodiazepines and Z-drugs in bipolar disorder.

3 MATERIALS AND METHODS

3.1 Setting

The four studies included in this thesis were performed in Sweden. Sweden has a long tradition of recording the major life events of all residents, dating back to the 17th century. The collection of sociodemographic data was originally a task for the Swedish Lutheran church, but was gradually taken over by state agencies during the 20th century. In the 1960's, the Swedish National Board of Health and Welfare started to collect healthcare data for quality control, which became the starting point for the longitudinal population-based health registers on which our studies are based. As reporting to these registers is mandatory for all healthcare providers, coverage is high. Further, healthcare is public and equally accessible to all Swedish residents, preventing selection processes due to insurance coverage. The unique personal identification number assigned to all Swedish residents at birth or immigration enabled us to link information across registers, merging socioeconomic, demographic and healthcare data.

3.2 Data sources

The Swedish National Patient Register (NPR)

The NPR is kept by the Swedish National Board of Health and Welfare. It covers all inpatient care in Sweden from 1987 and onwards. Further, psychiatric outpatient care provided by public or private caregivers has been fully covered since 2001. Registered information include hospital admission and discharge dates, dates for outpatient visits, and diagnoses assigned by the treating physician coded according to the International Classification of Diseases, 9th revision (ICD-9), since 1987, and 10th revision (ICD-10), since 1997.[121] External validations show that 99% of all somatic and psychiatric hospital discharge diagnoses are recorded in the NPR.[122] The validity of bipolar disorder diagnoses recorded in psychiatric outpatient care has never been assessed, however, the validity of a bipolar disorder diagnosis recorded in psychiatric inpatient care is high, with a positive predictive value of 0.81.[123]

The Prescribed Drug Register (PDR)

The PDR contains information on all drugs dispensed in Swedish pharmacies since July 2005.[124] Available data include the date of dispensing, amount, substance name and World Health Organization's Anatomical Therapeutic Chemical Classification (ATC) code. Eighty-four percent of the total drug utilization in Sweden is covered in the PDR, with the remaining 16% representing over-the-counter drugs.[125] As all drugs studied in this thesis were prescription drugs, we expect missing data on drug exposure to be minimal.

The Cause of Death Register (CDR)

The CDR was established in 1961, and contains information on the date and cause of death of all Swedish residents who have passed away since. From 2011 and onwards, it

also includes information on Swedish residents who have passed away abroad.[126] The register is complete with regard to capturing all deaths along with the date.[126] However, the validity of the registered causes of death (recorded through ICD diagnosis codes) vary, with the highest validity seen in patients who die in hospitals.[127] For this thesis, dates of death were used for exclusion or censoring purposes, whereas causes of death were not considered.

The Total Population Register (TPR)

The TPR is maintained by the government agency Statistics Sweden and holds information on major life events of all residents, including birth, death, marital status, and migration within Sweden, and to and from other countries. Updated information is transmitted daily from the Tax Agency.[128] A recent validation study found that virtually 100% of births and deaths, 95% of immigrations, and 91% of emigrations are reported to the TPR within 30 days.[128]

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

The LISA database is maintained by Statistics Sweden in collaboration with the Social Insurance Agency. It integrates data from the labor market, educational and social sectors, and is updated annually. Registered information include the disposable income and highest level of education of all Swedish residents.[129]

3.3 Cohort study design

The studies comprising this thesis were all nationwide population based cohort studies. A cohort study is designed to investigate the association between one or several *exposures* and *outcomes*. At baseline, the included subjects have to be free from, but susceptible to, the outcome of interest. Study participants are grouped based on exposure status, and followed with regard to study outcomes. Exposures can either be assessed just once or be time dependent, allowing for patients to change exposure status during follow-up. Likewise, outcome events can be measured either at the end of the study period, without considering when during follow up the outcome event occurred, or in a time dependent fashion, using "time to outcome event" as primary outcome. Each study subject contributes with person-time during the period he or she is part of the study and remains susceptible to the outcome. Typically, the accumulated person-time from all study subjects is summarized in person-years. Potential confounders associated with the study exposure and outcome can be measured in the same fashion as exposures, and accounted for in the analyses. Cohort studies are especially useful if the investigated exposure(s) is rare and the outcome(s) is expected to be relatively common among study subjects. The basic cohort study design is illustrated in Figure 4. An overview of the four studies in this thesis is presented in Table 2.

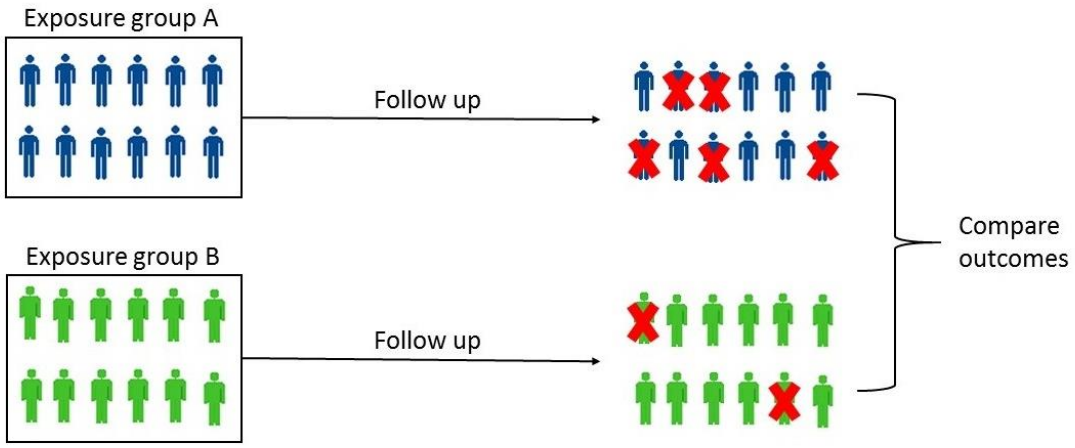

Figure 4. *Illustration of the basic cohort study design, in which the occurrence of outcome events (illustrated with red X's) is compared between exposure groups at the end of the study period.*

Table 2. Overview of studies included in the thesis

	Study I	**Study II**	**Study III**	**Study IV**
Design	Cohort	Cohort	Cohort	Cohort
Population	Swedish residents aged 18–75 years with a first time BD diagnosis	Swedish residents aged 18–75 years hospitalized for a manic episode	Swedish residents aged 18–75 years hospitalized for a manic episode	Swedish residents aged 18–75 years with a BD or mania diagnosis and no ongoing benzodiazepine/Z-drug use
Number	31 770	6 502 index hospitalizations representing 4 250 patients	5 713 index hospitalizations representing 3 772 patients	21 883
Study period	July 2006 – December 2012	July 2006 – December 2014	July 2006 – December 2014	July 2006 – December 2014
Data sources	NPR PDR CDR	NPR PDR CDR TPR LISA-register	NPR PDR CDR TPR LISA-register	NPR PDR CDR TPR LISA-register
Exposures	Age, sex, BD characteristics, psychiatric history and concurrent medication	Pharmacotherapy used for relapse prevention during the first four weeks after discharge (monotherapies & combinations)	Active treatment periods with maintenance treatment after discharge (monotherapies & combinations)	Sociodemographic characteristics, BD characteristics, physical health characteristics and concurrent medication
Outcomes	Initiation of prophylactic treatment within three months and one year after BD diagnosis	Rehospitalization within one year	Treatment failure within one year	Initiation of benzodiazepine/Z-drug treatment within one year and subsequent long-term use

BD – bipolar disorder

3.4 Study I

Study population

All patients aged 18 to 75 years with a first time bipolar disorder diagnosis in specialist psychiatric care between July 1, 2006 and December 31, 2012 were identified in the NPR and included in the study (N=31 978). A first time bipolar disorder diagnosis was defined as having no previously registered bipolar disorder diagnosis in the NPR since 1987. Patients with a diagnosis of schizophrenia or schizoaffective disorder registered on the same day as the bipolar disorder diagnosis were excluded due to the risk of misclassification, resulting in a final study population of 31 770 individuals.

Exposures

The following factors were studied as potential predictors for initiation of prophylactic treatment within three months after diagnosis: age, sex, affective state at diagnosis, presence of psychotic symptoms at diagnosis, psychiatric care in the past five years, self-harm in the past five years, duration of the index hospitalization, use of any psychotropic medication in the past year and comorbid substance abuse.

Outcomes

The primary outcome was time to filling a prescription of a mood-stabilizer or an antipsychotic within one year after diagnosis. The secondary outcome was time to filling a prescription of a mood-stabilizer or an antipsychotic within three months after diagnosis. Mood-stabilizers were defined as lithium, carbamazepine, lamotrigine, and valproate.

3.5 Study II

Study population

All individuals aged 18 to 75 years who were hospitalized for a manic episode at any point between July 1, 2006 and December 31, 2014 were identified in the NPR and included in the study upon hospital discharge (N=5 234). 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. Patients with a previous diagnosis of schizophrenia, schizoaffective disorder, or dementia were excluded, as were patients who were not Swedish residents or who emigrated from Sweden, died, or were rehospitalized within four weeks after hospital discharge. The final study included follow-up data from 6 502 index hospitalizations, representing 4 250 patients.

Exposures

Patients were allocated to different exposure groups based on what type of pharmacological relapse prevention they used during the first four weeks after hospital discharge. Lithium, valproate, olanzapine, quetiapine and aripiprazole were the only

drugs considered as relapse prevention, based on their regulatory approval for prophylactic use after a manic episode. Patients who filled one or more prescriptions of the same drug were classified as using monotherapy, whereas patients who filled prescriptions of two or more different drugs were considered to use combination therapy.

Outcome

The primary outcome was time to rehospitalization within one year after discharge. Follow-up started four weeks after discharge.

Potential confounders

The results were adjusted for potential confounders, including prescription fills of other psychotropic drugs, proxy variables for the severity of the manic index episode, the psychiatric history of the patient and socioeconomic and demographic data.

3.6 Study III

Study population

Swedish residents aged 18 to 75 years who were hospitalized for a manic episode at any point between July 1, 2006 and December 3, 2014 were identified in the NPR and included in the study upon hospital admission. Individuals with several hospitalizations for mania during the study period were included upon each such hospitalization. Patients were not allowed to have a previous diagnosis of schizophrenia, schizoaffective disorder, or dementia. This rendered a total of 4 628 included patients and 7 635 included index hospitalizations. Hospitalizations ending later December 3, 2014 were excluded, as were patients who: 1) had not been Swedish residents for a full year prior to hospital admission, 2) died during the index hospitalization, 3) did not start maintenance treatment within four weeks after hospital discharge, 4) were readmitted before starting maintenance treatment, or 5) fulfilled criteria for medication switch during the index hospitalization. The final cohort included 3 772 patients and 5 713 index hospitalizations.

Exposures

Patients were allocated to different exposure groups based on what type of maintenance treatment they used after hospital discharge. Whereas Study II had more of an observational "intention-to-treat" design in which only treatment initiation was considered, active treatment periods of lithium, valproate, olanzapine, quetiapine, and aripiprazole, alone or in combinations, were recorded in Study III. An 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. Patients who filled prescriptions of more

than one drug in a time period of less than two weeks were considered to use combination therapy.

Outcomes

Time to treatment failure was our primary outcome. We defined treatment failure as: 1) stopping of medication, 2) switch of medication, or 3) readmission to inpatient psychiatric care during an active treatment period. Stopping of medication was defined as not having access to medication for a period of ≥28 days, based on our calculations. Patients who started off with a combination therapy and subsequently stopped one drug while continuing with the other/others were not considered to have stopped medication. Medication switch was defined as filling a prescription of another psychotropic drug (mood-stabilizer, antipsychotic, antidepressant, or anxiolytic) 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 inpatient care due to suicide attempts.

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.

Potential confounders

As in Study II, information on potential confounders, including prescription fills of other psychotropic drugs, proxy variables for the severity of the manic index episode, the psychiatric history of the patient and socioeconomic and demographic data were included in the analyses.

3.7 Study IV

Study population

All patients aged 18–75 years with a registered diagnosis of bipolar disorder or mania in specialist care between July 1, 2006 and December 31, 2012 were identified through the NPR (N=46 535). Patients with no recorded use of any benzodiazepine or Z-drug in the preceding year (N=23 282) were included in the study on the day of their first registered bipolar disorder or mania diagnosis during the study period (defined as the bipolar disorder index date). Patients who had not been Swedish residents for a full year or had a previous diagnosis of schizophrenia, schizoaffective disorder, or dementia, were excluded. In total, 21 883 patients were included in the *bipolar disorder cohort*. Patients in the bipolar disorder cohort who initiated benzodiazepine or Z-drug treatment within one year (N=6 307) were subsequently transferred to the *benzodiazepine initiator cohort* on the day of their first benzodiazepine/Z-drug prescription fill (defined as the index dispensing date).

Exposures

Sociodemographic characteristics, bipolar disorder related characteristics, physical health characteristics and concomitant psychotropic medication were investigated as potential predictors for benzodiazepine or Z-drug initiation and subsequent long-term use. In addition, the association between factors related to the first filled benzodiazepine/Z-drug prescription and subsequent long-term use was explored.

Outcomes

The primary outcome in the first part of the study was benzodiazepine or Z-drug initiation within one year after study inclusion, defined as at least one prescription fill of diazepam, oxazepam, lorazepam, alprazolam, clonazepam, nitrazepam, flunitrazepam, triazolam, zopiclone, zolpidem, or zaleplon. Patients were followed for up to one year from the bipolar disorder index date. The primary outcome in the second part of the study was long-term benzodiazepine/Z-drug use, defined as continuous use of one or several benzodiazepines and/or Z-drugs for more than 180 days, from the index dispensing date.

3.8 Statistical analyses

The Kaplan-Meier estimator (Study I-III)

The Kaplan-Meier estimator is a non-parametric statistical tool that estimates the survival function – the probability to stay alive over time,[130] or, as in our studies, the probability not to acquire the studied outcome. It takes into account all observed outcome events and can be used with censored data, under the premise that the reason for censoring is independent of the outcome (non-informative censoring).

We used the Kaplan-Meier estimator to study the proportion of patients in each exposure group without rehospitalization or treatment failure in Study II and III. The complement of the survival curve generated by the Kaplan-Meier estimator – the cumulative incidence curve – was further used to illustrate rates of prescription fills of prophylactic drugs after a first time bipolar disorder diagnosis in Study I.

Cox proportional hazard regression (Study I-III)

The Cox proportional hazard regression model is a statistical survival model that estimates the risk of acquiring the outcome, referred to as the hazard function. It estimates the ratio between two hazard rates, but cannot estimate each individual hazard rate, which in theory describes the outcome rate for an item at a given time point.[131] Unlike the Kaplan-Meier estimator, the Cox proportional hazard regression model allows the estimation of the hazard ratio of an exposure while simultaneously accounting for the effects of other variables. This so called multivariable regression is used to adjust for confounding factors. The Cox proportional hazard regression model is based on the key assumption of proportional hazards, meaning that the survival curves of two exposures

must have hazard functions that are proportional over time (i.e. that the hazard ratio is constant). For the estimated ratio and confidence interval to be accurate, the variance in the data also has to be constant.

We used the Cox proportional hazard regression model to estimate hazard ratios for the initiation of pharmacoprophylaxis in Study I and for rehospitalization and treatment failure in Study II and III, assuming that the investigated hazards were proportional.

The sandwich covariance estimator (Study II-III)

For data that consists of small groups of correlated observations, the standard covariance estimate of the Cox model may be invalid due to non-constant variance in the sample because of dependence among group members. We therefore used a sandwich covariance estimate to account for intra-cluster dependence[132] due to the same patient sometimes being included multiple times in Study II and III. In short, the sandwich covariance estimator does not assume that the variance is constant and therefore provides more valid estimates of the standard error in data with some degree of dependence.

Logistic regression (Study IV)

The logistic regression model is a regression model that can be used when the outcome is binary and can take only two values. It predicts the odds of acquiring the outcome based on the values of different exposures.[133] The odds can be defined as the probability that an individual with a specific exposure acquires the outcome of interest divided with the probability that the same individual does not. The association between the studied exposure and outcome is measured as an odds ratio. As in Cox proportional hazard regression, several exposures/covariates can be taken into account, allowing adjustment for confounding factors. We used logistic regression to study odds ratios for benzodiazepine initiation and long-term use in Study IV, as we were interested in *if* rather than *when* the patients initiated benzodiazepine treatment or became long-term users.

4 RESULTS

4.1 Study I

Sixty-two percent of the included patients with a first-time bipolar disorder diagnosis were female and the mean age at diagnosis was 40 years (SD 14.5). In total, 72% of patients filled a prescription of a mood-stabilizer or antipsychotic within three months after diagnosis, and after one year, 79% of all patients had filled at least one prescription of a prophylactic drug. Rates of prescription fills were somewhat higher among patients diagnosed in inpatient care compared to outpatient care.

Table 3 shows potential predictors and their association with treatment initiation within three months after diagnosis. For patients diagnosed in inpatient care, the strongest predictors for treatment initiation were the length of the index hospitalization (aHR 2.18, 95% CI 2.02–2.35, for hospitalizations of ≥28 days, compared to <7 days), previous use of mood-stabilizers or antipsychotics (aHR 1.24, 95% CI 1.17–1.31), and a mixed episode at the time of diagnosis (aHR 1.23, 95% CI 1.09–1.38). Comorbid personality disorder and alcohol/substance abuse were negatively associated with treatment initiation.

For patients diagnosed in outpatient care, the strongest predictors for treatment initiation were previous use of mood-stabilizers or antipsychotics (aHR 1.78, 95% CI 1.73-1.84) and a mixed episode at the time of diagnosis (aHR 1.32, 95% CI 1.23–1.41), whereas a manic episode at the time of diagnosis significantly reduced the probability of treatment initiation.

Table 3. Predictors for initiation of prophylactic treatment within three months after a first time bipolar disorder diagnosis

	Diagnosed in inpatient care (N=6 868)			Diagnosed in outpatient care (N=24 902)		
	Patients	Initiated prophylactic treatment	Adjusted hazard ratio	Patients	Initiated prophylactic treatment	Adjusted hazard ratio
	N	%	(95% CI)	N	%	(95% CI)
Gender						
Male	2 805	75.9	Ref=1	9 191	74.3	Ref = 1
Female	4 063	79.1	1.03 (0.97-1.09)	15 711	75.0	1.02 (0.99-1.05)
Age at BD diagnosis (years)						
<25	1138	80.4	Ref=1	4 506	74.1	Ref=1
25-59	4 512	78.0	1.00 (0.92-1.08)	17 922	75.1	0.97 (0.93-1.01)
≥60	1 218	74.5	0.90 (0.84-0.96)	2 474	73.1	0.95 (0.91-0.98)
Previous psychiatric care, past five years	4 591	78.5	1.02 (0.96-1.09)	17 456	75.5	1.04 (1.00-1.07)
Affective state at BD diagnosis						
Depressed	1 258	83.7	1.13 (1.05-1.22)	4 079	77.0	1.09 (1.05-1.13)
Manic	1 748	76.9	1.01 (0.93-1.09)	1 449	44.2	0.51 (0.47-0.56)
Hypomanic	549	71.9	1.02 (0.91-1.13)	1 575	66.0	0.93 (0.87-0.99)
Mixed	387	85.5	1.23 (1.09-1.38)	1107	82.4	1.32 (1.23-1.41)
Unspecified	2 926	75.8	Ref=1	16 692	77.2	Ref=1
Presence of psychotic symptoms at BD diagnosis	1145	80.7	1.01 (0.93-1.10)	726	55.0	0.96 (0.86-1.07)
Duration of index hospitalization (days)						
<7	2 167	63.6	Ref=1			
27-jul	2 755	81.9	1.86 (1.73-1.99)			
≥28	1 946	87.8	2.18 (2.02-2.35)			
Filled prescriptions of any mood stabilizing drug the year before BD diagnosis	2 995	83.9	1.24 (1.17-1.31)	11 242	88.2	1.78 (1.73-1.84)
Comorbid personality disorder	753	74.1	0.87 (0.79-0.96)	2 305	75.3	0.99 (0.94-1.04)
Comorbid substance/alcohol use disorder	1 361	71.5	0.86 (0.80-0.93)	3 568	73.0	1.00 (0.96-1.05)

4.2 Study II

Pharmacological relapse prevention with lithium, valproate, olanzapine, quetiapine or aripiprazole was used after 78% of the included index hospitalizations for mania. Monotherapies and combination therapies were equally common. The overall rehospitalization risk for patients who started relapse prevention was 39%, compared to 46% for patients who did not fill any prescriptions of prophylactic drugs during the first four weeks after discharge.

Patients on combination therapy with two drugs had a significantly lower rehospitalization risk compared to untreated patients (aHR 0.76, 95% CI 0.77-0.94). Similar non-significant trends were seen for monotherapies and combination therapies of three or more drugs. One year rehospitalization risks ranged from 32% to 65% across treatment groups (Table 4). In the monotherapy group, no drug was associated with a significantly altered risk of rehospitalization compared with lithium (Table 4). Combination therapy with olanzapine and valproate or olanzapine and lithium were associated with the lowest rehospitalization risks of all treatment options (aHRs 0.76, 95% CI 0.62-0.93, and 0.83, 95% CI 0.70-0.98, respectively) (Table 4 and Figure 5).

Table 4. Risks of psychiatric rehospitalization in relation to prescription fills after hospital discharge

	Total	Rehospitalizations		Rehospitalization, Hazard Ratio (95% CI)	
	N	N	%	Unadjusted	Adjusted
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)

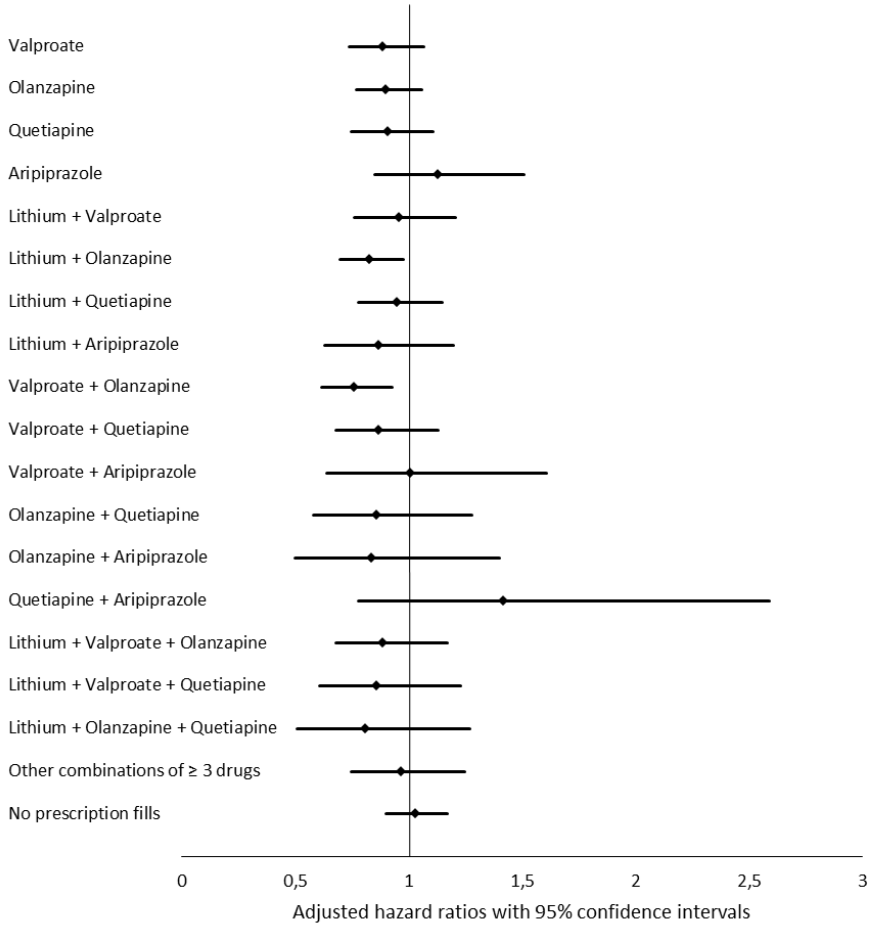

Figure 5. *Adjusted hazard ratios of rehospitalization by prescription fills after hospital discharge (lithium monotherapy used as reference with aHR 1.0).*

4.3 Study III

Treatment failure within one year after a manic episode was seen in 85% of patients (4 871 cases). Of these, 2 667 patients switched treatment, 1 108 discontinued treatment and 1 096 were rehospitalized during ongoing treatment.

Whereas a slight majority (58%) of patients used monotherapy, the risk of treatment failure was significantly lower for patients on combination therapy (Figure 6 and Table 5). Combination treatment with lithium + valproate + quetiapine or lithium + valproate + olanzapine was 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. The same combination treatments were associated with the lowest rates of medication switch and discontinuation of all treatment options. Further, lithium + valproate + quetiapine was the only treatment alternative associated with a significantly lower rehospitalization risk than lithium monotherapy (aHR 0.57, 95% CI 0.32–0.99).

Comparing monotherapies only, all atypical antipsychotics were associated with a significantly higher risk of treatment failure compared to single use of lithium, whereas monotherapy with valproate was associated with a non-significantly higher risk compared to lithium (Figure 6).

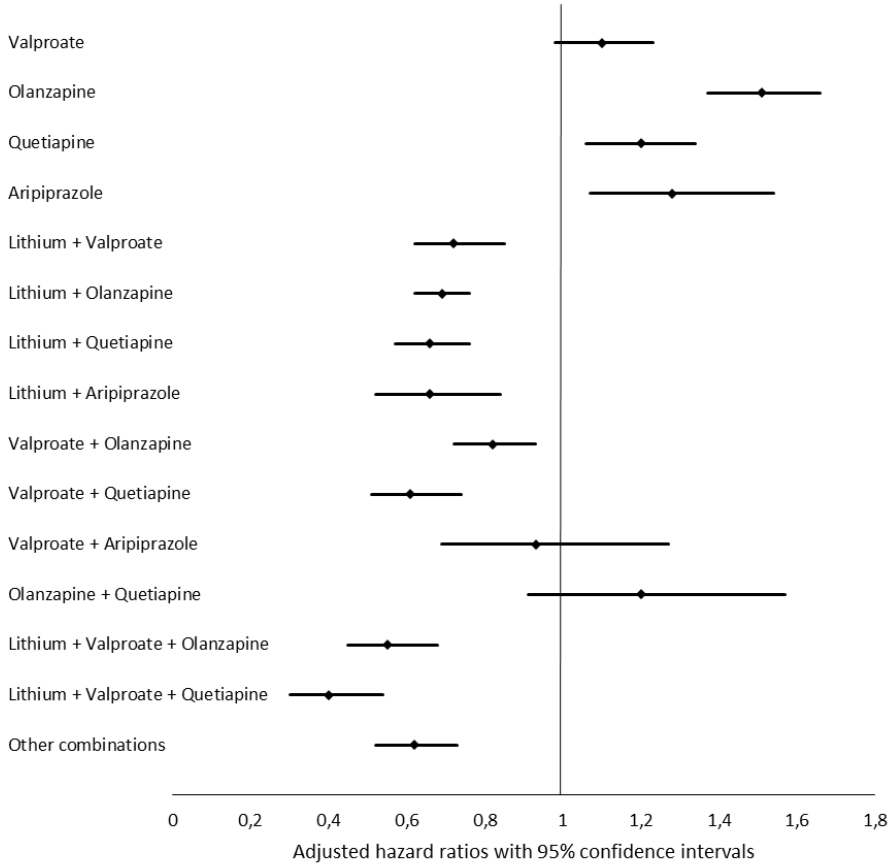

Figure 6. *Adjusted hazard ratios of all cause treatment failure by type of active treatment (lithium monotherapy used as reference with aHR 1.0).*

Table 5. 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	%	Adjusted HR (95% CI)	%	Adjusted HR (95% CI)	%	Adjusted HR (95% CI)	%	Adjusted HR (95% CI)
Monotherapies									
Lithium	1 133	87.0	Ref=1	46.5	Ref=1	20.2	Ref=1	20.4	Ref=1
Valproate	525	87.4	1.10 (0.98–1.23)	44.2	1.06 (0.91–1.24)	26.1	1.38 (1.11–1.71)	17.1	0.94 (0.74–1.21)
Olanzapine	1 013	93.3	1.51 (1.37–1.66)	53.5	1.59 (1.40–1.80)	26.1	1.73 (1.43–2.09)	13.7	1.06 (0.85–1.32)
Quetiapine	468	90.2	1.20 (1.06–1.34)	56.0	1.34 (1.15–1.56)	16.5	0.99 (0.76–1.29)	17.7	1.02 (0.79–1.32)
Aripiprazole	146	92.5	1.28 (1.07–1.54)	60.3	1.48 (1.17–1.86)	15.8	1.09 (0.71–1.69)	16.4	0.95 (0.62–1.45)
Combination therapies									
Lithium + Valproate	217	83.4	0.72 (0.62–0.85)	38.2	0.62 (0.49–0.79)	17.5	0.63 (0.44–0.89)	27.6	1.05 (0.78–1.40)
Lithium + Olanzapine	696	76.5	0.69 (0.62–0.76)	41.8	0.72 (0.63–0.84)	16.9	0.50 (0.40–0.62)	17.9	0.84 (0.67–1.04)
Lithium + Quetiapine	314	79.6	0.66 (0.57–0.76)	40.4	0.61 (0.50–0.74)	12.7	0.43 (0.30–0.60)	26.4	1.08 (0.84–1.39)
Lithium + Aripiprazole	92	79.3	0.66 (0.52–0.84)	45.7	0.74 (0.54–1.01)	13.0	0.46 (0.26–0.83)	20.7	0.70 (0.44–1.13)
Valproate + Olanzapine	415	83.6	0.82 (0.72–0.93)	45.5	0.86 (0.73–1.02)	21.0	0.67 (0.52–0.86)	17.1	0.85 (0.65–1.11)
Valproate + Quetiapine	171	76.6	0.61 (0.51–0.74)	38.6	0.59 (0.45–0.76)	14.0	0.45 (0.30–0.69)	24.0	0.86 (0.61–1.20)
Valproate + Aripiprazole	50	86.0	0.93 (0.69–1.27)	40.0	0.78 (0.50–1.23)	22.0	0.94 (0.51–1.72)	24.0	1.13 (0.63–2.03)
Olanzapine + Quetiapine	62	91.9	1.20 (0.91–1.57)	64.5	1.33 (0.96–1.84)	8.1	0.66 (0.27–1.61)	19.4	1.13 (0.63–2.04)
Lithium + Valproate + Olanzapine	136	76.5	0.55 (0.45–0.68)	32.4	0.46 (0.34–0.63)	15.4	0.39 (0.25–0.61)	28.7	0.99 (0.70–1.39)
Lithium + Valproate + Quetiapine	68	64.7	0.40 (0.30–0.54)	38.2	0.45 (0.30–0.66)	7.4	0.18 (0.07–0.44)	19.1	0.57 (0.32–0.99)
Other combinations	207	75.8	0.62 (0.52–0.73)	42.0	0.64 (0.51–0.81)	7.7	0.26 (0.16–0.44)	26.1	0.99 (0.73–1.33)

4.4 Study IV

Out of the 21 883 included patients, 6 307 (29%) filled at least one prescription of a benzodiazepine or Z-drug within one year. The median duration of benzodiazepine/Z-drug use was 30 days (interquartile range: 14–100). In total, 1 376 patients (22% of all initiators) became long-term users.

The likelihood of benzodiazepine/Z-drug initiation decreased steadily with age, with an aOR of 0.64 (95% CI 0.56-0.73) for patients ≥60 years, compared to patients <30 years. Women were more likely to initiate treatment, as were individuals with a high education or income level. Further, a first time bipolar disorder diagnosis strongly predicted benzodiazepine/Z-drug initiation (aOR 1.87, 95% CI 1.74-2.02), as did a recent psychiatric hospitalization (aOR 2.27, 95% CI 2.08-2.47). Other predictors for benzodiazepine initiation included a recent diagnosis of mania or depression, comorbid anxiety disorder/OCD, concomitant use of antipsychotics without mood-stabilizing indication, and concomitant use of four or more psychotropic drugs.

Contrary to what was seen for initiation, high age strongly predicted long-term use, with sixty plus year olds having almost twice the odds of becoming long-term users compared to patients <30 years. Low income and being divorced or widowed also predicted long-term use. Indicators for bipolar disorder disease activity and current affective morbidity were not associated with long-term use, although concurrent use of antidepressants or lamotrigine was (aORs 1.24, 95% CI 1.07-1.42, and 1.21, 95% CI 1.04–1.42). Other factors associated with increased odds of long-term use included a first-time bipolar disorder diagnosis, history of suicidality or self-harm, comorbid non-borderline personality disorder, and concurrent use of psychostimulants (aOR 1.78, 95% CI 1.33-2.39), non-mood-stabilizing antipsychotics (1.53, 95% CI 1.29-1.82), or ≥4 psychotropic drugs (aOR 1.47, 95% CI 1.20-1.82).

Prescription related factors and their association with long-term use are displayed in Table 6. Among those who filled a prescription of alprazolam or clonazepam, the aOR for long-term use was 2.03 (95% CI 1.30-3.18), and 3.78, (95% CI 2.24-6.38), respectively, compared to diazepam users. Patients who were initiated on ≥2 benzodiazepines and/or Z-drugs also had significantly increased risk of becoming long-term users (aOR 2.46, 95% CI 1.79-3.38).

Table 6. Prescription related factors and their association with long-term use

	Total number of patients	Subsequent short-term users	Subsequent long-term users	Crude OR for long-term use	Adjusted OR for long-term use
	N	%	%	OR (95% CI)	aOR (95% CI)
Substance					
Diazepam	422	81.5	18.5	Ref=1	Ref=1
Oxazepam	1 043	80.3	19.8	1.09 (0.81–1.45)	1.09 (0.81–1.46)
Lorazepam	27	81.5	18.5	-	-
Alprazolam	142	68.3	31.7	2.05 (1.33–3.15)	2.03 (1.30–3.18)
Clonazepam	80	53.8	46.3	3.80 (2.29–6.28)	3.78 (2.24–6.38)
Nitrazepam	170	75.9	24.1	1.40 (0.91–2.15)	1.46 (0.93–2.27)
Flunitrazepam	34	88.2	11.8	-	-
Triazolam	5	100.0	0.0	-	-
Zopiclone	2 750	79.4	20.7	1.15 (0.88–1.49)	1.19 (0.91–1.56)
Zolpidem	1 041	81.6	18.4	1.00 (0.75–1.34)	1.12 (0.83–1.51)
Zaleplon	53	88.7	11.3	-	-
≥2 substances	540	64.1	35.9	2.47 (1.83–3.35)	2.46 (1.79–3.38)
Size of prescription					
≤28 tablets	2 584	84.0	16.0	Ref=1	Ref=1
>28 tablets	3 723	74.1	25.9	1.83 (1.61–2.09)	-
Prescriber					
General Practitioner	99	83.8	16.2	Ref=1	Ref=1
Psychiatrist	1 571	74.6	25.4	1.43 (1.09–1.87)	1.36 (1.02–1.81)
Other	158	67.7	32.3	1.51 (1.07–2.13)	1.29 (0.89–1.86)

5 METHODOLOGICAL CONSIDERATIONS

5.1 Potential sources of error in the presented studies

The reliability of study results depends on what errors may have afflicted the study design and data. Studies can contain two general types of error: systematic error (bias) and random error.[68] Bias is defined as any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions systematically different from the truth.[134] It can be classified into three main categories: selection bias, information bias and confounding.

Selection bias

Selection bias refers to a situation where there is a difference in the association between exposure and outcome between individuals who participate in the study versus those who do not.[68] The study populations in this thesis were selected based on data from the NPR and/or PDR, two national population-based registers with an estimated 99% coverage of the Swedish population. This basis for selection strongly limits the risk for selection bias, since virtually all eligible patients in Sweden were included and loss to follow-up was minimal.

Information bias

Information bias arises when information on the studied exposures and/or outcomes is incorrect.[68] The use of prospectively collected register data prevents misclassification of exposures based on outcome status. However, register-data have a lower resolution compared to, for example, hospital records, resulting in blunter measurements of clinical factors. We aimed to reduce the number of patients misclassified as having bipolar disorder through excluding patients with a diagnosis of schizophrenia or schizoaffective disorder on the same day as their first bipolar disorder diagnosis (Study I), patients with a previous diagnosis of schizophrenia, schizoaffective disorder or dementia (Study II and IV), or considered these patients non-eligible (Study III). This resulted in 1%–15% of eligible patients being excluded.

In general, the prevalence of psychiatric comorbidities recorded through recent psychiatric diagnoses in the NPR was somewhat lower than expected, indicating missing data. For example, the estimated prevalence rates of anxiety disorders ranged from 9% to 14% in our study populations, whereas the lifetime prevalence of anxiety disorders in bipolar disorder may be as high as 50%,[22] with an estimated point prevalence of generalized anxiety disorder alone of 12%.[96] Any missing data on comorbidities is likely to be non-differential, and would therefore have diluted the observed associations. The dilution of associations between comorbodities and study outcomes, and the missing data itself, may have resulted in some degree of residual confounding (discussed below).

Prescription fills were used as a proxy for initiated or ongoing treatment in all four studies. This may be an imperfect measure, as we do not know to what degree patients use their dispensed drugs. Further, combination treatments were defined based on fills of two or more prophylactic drugs within a period of two (Study III) or four (Study II) weeks, which could have resulted in some degree of misclassification, as it is impossible to distinguish the addition of one drug to another from a prompt change of monotherapy through register data. These misclassifications are also likely to be non-differential, and would therefore have diluted the observed drug effects, especially the effects of combination treatments. Lastly, the lack of data on drug prescriptions that were never filled limited the strictness of the intention-to-treat design used in Study II, and prevented us from reaching firm conclusions on adherence to prescribed medication.

Confounding

A confounder is a variable that influences both the exposure and the outcome and may distort the observed association between exposure and outcome through increasing or decreasing its strength.[68] For example, high age was found to be an important risk factor for psychiatric rehospitalization in Study II. As patients who have lived longer are more likely to have a history of self-harm, we therefore had to consider and adjust for the impact of age when studying the association between self-harm and rehospitalization.

In pharmacoepidemiological studies, *confounding by indication* is one of the most important limitations to consider. Confounding by indication arises from the fact that patients who take one drug usually differ from those who take another drug, with regard to disease severity or other factors that may impact the outcome.[68] We handled potential confounding by indication through: 1) investigating the association between potential confounders (clinical and sociodemographic characteristics) and the outcome of interest, 2) stratification (Study I), and 3) adjusting for the effects of confounders through multivariable regression models (Study I–IV). Several different clinical parameters available in register data were used as proxies for illness severity in Study II and III, including the length of the index hospitalization, a discharge- or secondary diagnosis indicating psychotic symptoms, the number of previous psychiatric admissions and psychiatric comorbidities. As already mentioned, missing data due to underreporting of psychiatric comorbidities and a lack of indicators of more subtle differences in illness severity between patients have likely resulted in some degree of residual confounding.

An alternative strategy for adjusting for confounding would have been to use so called propensity score matching. Propensity scores can be seen as a data reduction method, through which many covariates are reduced into a single score that can be used to adjust for the effects of these. The benefits of propensity score matching are that it saves degrees of freedom and therefore does not require the same sample size as multivariable regression, and that it can be used to adjust for numerous confounders.[135] Because our studies were generally well powered, we chose to use multivariable regression, as this

allowed us to investigate each specific confounder with regard to its association with the study outcome as well as other confounders. We believe this approach is more informative and, most importantly, deepens the understanding of the impact of clinical and sociodemographic characteristics on treatment choices.

5.2 Random error

Random errors are chance findings caused by uncontrolled variation between a measured value and "the truth". If the number of observations is sufficiently large, random errors cancel each other out, and their sum approaches zero. Random error can therefore be limited through increasing the study population.[68] The likelihood of an observed association to be subject to random error can be estimated statistically through confidence intervals. In this thesis, we used a significance level of 0.05, meaning that if each study was to be repeated 100 times, the confidence interval would be expected to include the true value in 95 of those studies, respectively. The large number of included patients in our studies limited the risk for random error. As the risk for random error increases with the number of performed statistical tests, we thoroughly selected the potential confounding factors included in our analyses. Even so, random errors due to multiple testing cannot be ruled out.

6 INTERPRETATIONS AND CONCLUSIONS

At the time of our first study, it was largely unknown to what extent newly diagnosed bipolar disorder patients used prophylactic treatment. We found that slightly less than three out of four patients started prophylactic treatment within three months of diagnosis, and that one in five patients still did not have access to relapse prevention after one year. Considering that the mean age at diagnosis was almost 40 years and that a majority of patients had been in contact with psychiatric care in the past years, these numbers suggest a considerable treatment delay, as reported by others.[13,25,73] Such treatment delay is problematic as the effectiveness of prophylactic drugs seem to be higher in the early phase of bipolar illness,[75,76] and may impair the prognosis.[15,74]

Interestingly, the length of the index hospitalization was the strongest predictor for initiation of prophylactic treatment among inpatients. A long hospitalization likely reflects a more severe affective episode, which may increase the incentive for subsequent prophylactic treatment. Further, a short hospitalization may be a result of a weaker therapeutic alliance. It may however also be the case that long hospitalizations per se are conducive to treatment adherence through allowing complete remission and facilitating individually tailored pharmacotherapy. Not surprisingly, previous use of mood-stabilizers or antipsychotics strongly predicted continuous use of prophylactic treatment after diagnosis, whereas patients who were diagnosed with mania in outpatient care had the lowest treatment initiation rate, likely reflecting the difficulty of managing manic patients in outpatient care.

In the second study, we found that the rehospitalization risk after a manic episode remains high, despite a wide use of modern treatment alternatives. Contrary to our hypothesis and to previous observational findings,[57-59,64,65,136] we did not observe a superior effectiveness of lithium monotherapy. Instead, patients initiated on combination therapy with two prophylactic drugs was the only group with a significantly lower rehospitalization risk compared to untreated patients. A combination of olanzapine and valproate or lithium appeared to be most successful with regard to reducing the rehospitalization risk. Other combinations such as olanzapine and aripiprazole also appeared favorable, although the estimated hazard ratios were non-significant due to small numbers of patients.

Similarly, in Study III we found that combination therapies were associated with a significantly lower risk of overall treatment failure compared with monotherapies. Patients combining lithium, valproate, and quetiapine had a 60% lower risk of treatment failure compared to patients on lithium monotherapy, with lower rates of medication switch, discontinuation, and rehospitalization compared with patients on any other regimen. Although lithium monotherapy did not appear to significantly reduce the rehospitalization risk compared to other monotherapies in Study II,

continuous monotherapy with lithium or valproate did appear more favorable with regard to treatment failure than single use of olanzapine, quetiapine, or aripiprazole in Study III, supporting previous observational findings.[57-59]

Despite the majority of treatment guidelines recommending monotherapy as first-line treatment,[46,52,54,79] 43% of patients used two or more anti-manic drugs after hospital discharge. We observed lower rates of discontinuation and medication switch among patients on combination therapy, somewhat contrary to previous findings indicating a lower tolerability of combination treatments vs. monotherapies.[137] Possibly, this reflects a higher tolerability of combination treatment after a manic episode, or that the perceived benefits of combination treatments with regard to symptomatic and syndromic remission are high enough to outweigh any negative effects.

The more successful outcomes associated with combination therapy after a manic episode observed in Study II and III provide real-world evidence in support of existing RCT-findings.[138-142] Notably, previously performed observational comparative-effectiveness studies have either not included any combination therapy,[58,64,65] lumped all combination therapies together in one group,[55,57,143] or studied a very limited number of combination treatments.[56] The majority have further included a mix of patients with bipolar disorder type I and II,[57-59,64,65] which may limit possible comparisons with our data and most RCTs.

In the fourth and final study, we found that more than one in five patients with bipolar disorder who initiated benzodiazepine/Z-drug treatment continued such treatment for six months or more, despite recommendations stating that these drugs should be used for a maximum of four weeks. The highest risk of long-term use was observed in patients who used clonazepam or alprazolam, both of which belong to the most common drugs of abuse worldwide.[144-146] Clonazepam and alprazolam are known to cause a more severe physical dependence than other benzodiazepines,[147-149] which may explain the higher rates of long-term use. In addition, both substances are used in the acute management of panic attacks, which sometimes require a long treatment duration. The higher rate of long-term use among patients on benzodiazepine/Z-drug polytherapy supports previous findings, [118] and may be explained by combinations of different substances likely boosting dependence.

The strong correlation between high age and long-term benzodiazepine/Z-drug use found in our study and seen in several previous studies[117-120,150] is concerning, given that physiological age-related changes make patients more vulnerable to harmful side effects.[107,151] Conversely, the youngest age group had the highest benzodiazepine/Z-drug initiation rate, possibly prompted by higher levels of mixed symptoms, agitation and suicidal thoughts.[152,153] Notably, acute affective morbidity predicted benzodiazepine initiation but was unrelated to long-term use. The finding that

concurrent use of psychostimulants strongly predicted long-term use will warrant further study. In conclusion, a circa 20% risk for long-term use was observed across all benzodiazepines and Z-drugs, suggesting that a certain level of vigilance is needed whenever patients initiate benzodiazepine/Z-drug treatment.

Conclusions:

- A substantial proportion of newly diagnosed bipolar disorder patients do not use prophylactic treatment.
- Efforts to reduce treatment delay should especially target patients who are naïve to mood-stabilizers and antipsychotics or diagnosed with bipolar disorder during a brief hospitalization.
- Longer psychiatric hospitalizations may per se be conducive to increased use of prophylactic treatment after diagnosis.
- The one-year rehospitalization risk after a manic episode is considerable also for patients who initiate prophylactic treatment.
- Combination therapies including olanzapine and a classic mood-stabilizer seem beneficial for reducing the rehospitalization risk after a manic episode.
- Our results suggest that polytherapy is more effective, in terms of lower rates of treatment failure, than monotherapy after a manic episode.
- Likewise, lithium monotherapy seems to be more effective than monotherapy with olanzapine, quetiapine or aripiprazole with regard to treatment failure.
- Benzodiazepines and Z-drugs are widely used during acute affective episodes, but affective morbidity is largely unrelated to long-term benzodiazepine use.
- Patients who use clonazepam or alprazolam are at high risk for long-term use, and these substances should therefore be used restrictively when treating anxiety or insomnia in bipolar disorder.
- Polytherapy with benzodiazepines and/or Z-drugs should be avoided.

7 FUTURE PERSPECTIVES

Several questions and ideas for future studies have emerged during the course of this doctoral project:

- Is there a certain time point when combination therapies stop being beneficial after a manic episode?
- Do suicide risks differ between patients on different maintanance treatments?
- Is combination treatment more effective than monotherapy in reducing the suicide risk?
- Is the comparative effectiveness of prophylactic drugs and combination therapies different in patients with bipolar disorder type II compared to bipolar disorder type I?
- Why does combination treatment seem more beneficial after a manic episode, despite previous data indicating higher levels of side effects?
- Does non-adherence to maintenance treatment predict benzodiazepine use?
- Is the increased risk of long-term benzodiazepine use in patients on concurrent treatment with psychostimulants a sign of a generally increased risk for abuse in this population?
- Comparative effectiveness studies also need to focus on interepisodic morbidity and function in bipolar disorder. One way to capture these aspects in Swedish register data is through work absenteeism/presenteeism, sick leave and disability pension.
- Is sick-leave associated with the type of maintenance teratment?
- Is disability pension associated with the type of maintenance teratment?

8 POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Bipolär sjukdom drabbar drygt två procent av befolkningen i Sverige och har en liknande utbredning globalt. Sjukdomen orsakar ett påtagligt lidande för den drabbade genom att medföra återkommande perioder av hyperaktivitet och förhöjd eller irritabel grundstämning (så kallade manier eller hypomanier) och depressioner. Patienter med bipolär sjukdom har därtill en kraftigt förhöjd självmordsrisk. Litium har sedan 1960-talet utgjort grundpelaren i behandlingen genom att motverka nya maniska och depressiva skov. Under senare år har ett stort antal moderna läkemedel godkänts som förebyggande behandling vid bipolär sjukdom och dessa har i snabb takt delvis kommit att delvis ersätta litium. I dagsläget finns det knapp kunskap kring vilka av dessa behandlingsalternativ och preparatkombinationer som är mest effektiva.

Syftet med detta doktorandprojekt har varit att undersöka användningen av förebyggande läkemedelsbehandling hos patienter med nydiagnostiserad bipolär sjukdom samt att jämföra effektiviteten mellan olika förebyggande behandlingsalternativ för att på sikt underlätta valet av behandling för läkare och patienter. Vi har vidare studerat riskfaktorer för att patienter med bipolär sjukdom ska bli långtidsanvändare av beroendeframkallande lugnande läkemedel och sömnmedel (bensodiazepiner och Z-preparat).

I de fyra kohortstudier som ingår i avhandlingen har vi följt upp stora grupper av patienter genom att länka data från rikstäckande hälsoregister vid Socialstyrelsen (Patientregistret, Läkemedelsregistret och Dödsorsaksregistret). Vi har därtill använt socioekonomisk och demografisk information från register vid Statistiska centralbyrån.

Studie I

Då förebyggande läkemedelsbehandling är som mest effektiv tidigt under sjukdomsförloppet är det angeläget att patienter erbjuds sådan behandling så snart som möjligt efter diagnos. I den första studien undersökte vi hur stor andel av alla patienter i Sverige som inleder behandling inom tre månader efter att ha diagnostiserats med bipolär sjukdom. Studien inkluderade 31 770 patienter som följdes under ett års tid. Vi fann att 72% av patienterna inledde behandling inom tre månader efter diagnos. Patienter som erhållit sin diagnos i samband med ett långt slutenvårdstillfälle (fyra veckor eller längre) i psykiatrin inledde förebyggande behandling i störst utsträckning. Likaså hade patienter som tidigare behandlats med något stämningsstabiliserande preparat (litium, antiepileptikum eller antipsykotikum) en högre sannolikhet att inleda eller fortsätta förebyggande behandling efter diagnos.

Studie II

I den andra studien jämförde vi risken för återinläggning mellan patienter som använt olika typer av återfallsförebyggande behandling efter ett slutenvårdstillfälle för mani. Studien innehöll uppföljningsdata från totalt 6 502 manivårdtillfällen. Patienterna klassificerades baserat på vilka läkemedel de hämtade ut under de första fyra veckorna efter utskrivning och följdes under ett års tid. Vi fann att återinläggningsrisken var något lägre hos patienter som inledde förebyggande behandling inom fyra veckor efter utskrivning (39%) jämfört med patienter som inte gjorde det (46%). Patienter som använde en kombination av olanzapin och litium eller valproat hade lägst återinläggningsrisk av alla, motsvarande 24% respektive 17% lägre risk att återinläggas jämfört med patienter som behandlades med litium i monoterapi.

Studie III

I den tredje studien jämförde vi risken för behandlingsmisslyckande (eng: ”treatment failure”) mellan patienter som använde olika typer av återfallsförebyggande behandling efter en manisk episod. Behandlingsmisslyckande definierades som byte av behandling, behandlingsavbrott eller återinläggning i psykiatrin trots pågående behandling. Studien innehöll uppföljningsdata från 5 713 manivårdtillfällen. Vi fann att risken för behandlingsmisslyckande var signifikant lägre hos patienter som behandlades med kombinationsterapi jämfört med monoterapi. Trippelterapi med litium, valproat och quetiapin eller olanzapin hade lägst risk att misslyckas och var associerad med 60% respektive 45% lägre misslyckanderisk jämfört med litium i monoterapi.

Studie IV

I den fjärde och sista studien undersökte vi omfattningen av långtidsanvändning av beroendeframkallande lugnande medel och sömnmedel bland patienter med bipolär sjukdom samt riskfaktorer för långtidsanvändning. Vi inkluderade 21 883 patienter som inte behandlats med bensodiazepiner eller Z-preparat under det senaste året och följde dessa under ett års tid. Patienter som hämtade ut bensodiazepiner eller Z-preparat under uppföljningstiden följdes i ytterligare ett år från behandlingsstart. Totalt inledde 6 307 patienter (29%) behandling med bensodiazepiner eller Z-preparat. Utav dessa fortsatte en femtedel med behandlingen i över 6 månader, trots att behandlings-rekommendationer förordar en maximal behandlingstid om fyra veckor. Patienter som använde preparaten klonazepam eller alprazolam hade fyra respektive två gånger högre risk att bli långtidsanvändare jämfört med patienter som använde diazepam. Därutöver var polyterapi med två eller flera bensodiazepiner/Z-preparat en viktig riskfaktor för långtidsanvändning.

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