Treatments and outcomes in bipolar disorder

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Cover photograph 'Nyköpingsgruvan at Utö" by Erik Joas

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To Allan

Abstract

Bipolar disorder is defined by recurring mood episodes and patients have a markedly increased risk of suicide. Pharmacological and psychological treatments for bipolar disorder have proven efficacy in clinical trials yet the generalizability of current evidence to routine clinical practice is contested. This thesis presents studies on treatments and outcomes relevant to bipolar disorder patients using data from national registers. In study *I, II, IV*, we studied the effectiveness of different treatments using within-individual study designs to reduce the impact of confounding-by-indication. In study *I*, we showed that commonly used drugs, such as lithium, several anticonvulsants, and atypical antipsychotics, were associated with a reduced risk of psychiatric hospital admissions. The association between treatment and hospital admission was stronger for lithium compared to the atypical antipsychotics olanzapine and quetiapine. This differs from previous clinical trial evidence. In study *II*, we showed that lithium, but not valproate, was associated with a lower risk of suicide-related behaviour. In study *III*, we studied risk factors for completed suicide in the Swedish National Quality Register for Bipolar Disorder (BipoläR). We identified several risk factors for suicide, e.g., recent affective episodes and psychiatric comorbidity. In study *IV*, psychoeducation was associated with a reduced risk of recurrence and hospital admission in BipoläR. Finally, in study *V*, we studied the impact of *CYP2C19* polymorphisms on antidepressant treatment patterns as well as the risk for treatment emergent mania using a large sample of patients with bipolar disorder. The mainly negative results suggest that information on *CYP2C19* genotype has limited clinical value. These studies showcase the possibility of conducting psychiatric treatment research in national registers to fill important knowledge gaps. The studies can be used as supporting evidence when there is a lack of evidence on the effectiveness of different treatments in routine clinical care. We also underline the unique position of lithium in bipolar disorder treatment and extend current knowledge on risk factors for suicide.

Keywords: bipolar disorder, lithium, psychoeducation, CYP2C19, antidepressants, epidemiology, valproate, quetiapine, olanzapine, suicide

Sammanfattning på svenska

Bipolär sjukdom utmärks av återkommande affektiva skov och en förhöjd suicidrisk. Farmakologiska och psykologiska behandlingar har visat effekt i kliniska prövningar men det är omstritt om resultaten kan generaliseras till den kliniska vardagen. I denna avhandling presenteras studier av både behandlingar och utfall som är relevant för patienter med bipolär sjukdom. I studie *I, II* och *IV* använde vi oss av nationella register för att studera behandlingseffekter med s.k. inom-individ analyser för att minska påverkan av störfaktorer. I studie *I* studerade vi läkemedelsbehandling och risk för inläggning i den psykiatriska slutenvården. Resultaten visade ett samband mellan behandling med vanligt förekommande läkemedel, såsom litium, ett flertal antiepileptika och antipsykotiska läkemedel, och en minskad risk för inläggning i psykiatrisk slutenvård. Sambandet för litium var starkare jämfört med de atypiska antipsykotika, kvetiapin och olanzapin. Dessa resultat skiljer sig från resultat i tidigare kliniska prövningar. I studie *II* visade vi att behandling med litium var associerat med en lägre risk för suicidala handlingar, något som inte var fallet för behandling med valproat. I studie *III* studerade vi riskfaktorer för fullbordat suicid vid bipolär sjukdom i kvalitetsregistret BipoläR och kunde visa ett samband mellan en ökad risk för suicid och ett flertal faktorer, t.ex. psykiatrisk komorbiditet och tidigare affektiva skov. I studie *IV* kunde vi se ett samband med lägre risk för återfall i skov och inläggningar i psykiatrisk slutenvård efter patientutbildning. Slutligen undersökte vi i studie *V* huruvida genetiska variationer i *CYP2C19* påverkar behandlingsmönster av antidepressiva läkemedel samt risk för maniskt överslag. Studien visade inte på några övertygande samband med dessa utfall. Dessa fem studier visar på möjligheten att göra studier i nationella register som utvärderar behandlingseffekter i den psykiatrisk vården och fyller viktiga kunskapsluckor. Dessa resultat kan användas som stöd vid behandlingsutvärderingar när det saknas övertygande evidens för behandlingseffekter i den kliniska vardagen. Resultaten visar också på litiums särställning vid behandling av bipolär sjukdom. Slutligen har vi även kunnat bredda kunskapen om riskfaktorer för fullbordat självmord vid bipolär sjukdom.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. *Erik Joas, Alina Karanti, Jie Song, Guy M. Goodwin, Paul Lichtenstein & Mikael Landén.* (2017). Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder. *The British Journal of Psychiatry*, 210 (**3**), 197-202.

II. *Jie Song, Arvid Sjölander, Erik Joas, Sarah E. Bergen, Bo Runeson, Henrik Larsson, Mikael Landén & Paul Lichtenstein.* (2017). Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder, *American Journal of Psychiatry*, 174 (**8**), 795-802.

III. *Caroline Hansson, Erik Joas, Erik Pålsson, Keith Hawton, Bo Runeson & Mikael Landén.* (2018). Risk factors for suicide in bipolar disorder: a cohort study of 12 850 patients. *Acta Psychiatrica Scandinavica*, 138 (**5**), 456-463.

IV. *Erik Joas, Kristoffer Bäckman, Alina Karanti, Timea Sparding, Francesc Colom, Erik Pålsson & Mikael Landén.* (2020). Psychoeducation for bipolar disorder and risk of recurrence and hospitalization–a within-individual analysis using registry data. *Psychological Medicine*, 50 (**6**), 1043-1049.

V. *Erik Joas, Lina Jonsson, Alexander Viktorin, Erik Smedler, Erik Pålsson, Guy M. Goodwin & Mikael Landén.* Effect of *CYP2C19* polymorphisms on antidepressant prescription patterns and treatment emergent mania in bipolar disorder. *Manuscript*.

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Abbreviations

ADHD – Attention deficit hyperactivity disorder
ATC - Anatomical Therapeutic Chemical Classification System
BipoläR – Swedish National Quality Register for Bipolar Disorder
BMI – Body mass index
CI – Confidence interval
CYP – Cytochrome P450
DDD – Defined Daily Dose
DSM - Diagnostic and Statistical Manual of Mental Disorders
GAF – Global Assessment of Functioning
GWAS – Genome-wide association study
HR – Hazard ratio
ICD – International Classification of Diseases
OR – Odds ratio
RCT – Randomized controlled trial
SNP – Single nucleotide polymorphisms
SWEBIC – Swedish Bipolar Cohort Collection

1. Introduction

Bipolar disorder is a psychiatric disorder defined by severe mood swings towards either mania or depression, with considerable variation in the severity and content of these mood states. Pharmacological treatment to treat acute episodes and to prevent relapse or recurrence is the foundation of bipolar disorder management. Lithium was the first treatment shown to treat acute mania without increasing the risk for depression (Cade, 1949) and, importantly, to prevent new episodes (Baastrup *et al.*, 1970, Schou, 1968). More recently introduced treatment options include several anticonvulsant and atypical antipsychotic drugs. Unfortunately, none of these medications is a panacea and the relapse rate remains high (Pallaskorpi *et al.*, 2015). Several adjunctive psychological treatments have been developed including family focussed therapy, cognitive behavioural therapy, and psychoeducational programs (Goodwin *et al.*, 2016). Although evidence from clinical trials is essential to evaluate the effects of both pharmacological and psychological interventions, the generalizability of current evidence in bipolar disorder remains contested and decisive effectiveness trials and convincing observational studies are hard to come by (Ghaemi and Selker, 2017, Miura *et al.*, 2014).

The detrimental consequences of bipolar disorder are staggering, not only with respect to the suffering for the afflicted individuals and their next-of-kin but also in terms of societal costs (Ekman *et al.*, 2013). Life expectancy is lower in bipolar disorder patients than in the general population (Chesney *et al.*, 2014, Kessing *et al.*, 2015). The risk of suicide is particularly high among bipolar disorder patients, even compared with other psychiatric disorders (Baldessarini and Tondo, 2020, Ösby *et al.*, 2001).

This dissertation is concerned with pharmacological treatment and adjunctive psychological treatments used in bipolar disorder to prevent recurrence and suicidal behaviour. One study addresses risk factors for suicide in bipolar disorder. Finally, the issue of personalized medicine through pharmacogenomics is addressed by analysing polymorphisms in *CYP2C19* and their association

with treatment patterns of several antidepressants and treatment-emergent mania.

These research questions are addressed using an epidemiological approach with datasets from national registers and material collected for genome-wide analyses. Although there are limitations regarding causal inferences from epidemiological datasets, I make the case that epidemiological inquiries of treatment effects and adverse events add valuable complementary evidence to randomized clinical trials. Not only is evidence from randomized trials often hard to come by, clinical trial evidence is also mired in problems such as selective study designs and atypical patient samples due to strict exclusion criteria. In addition, large administrative registers provide an opportunity to study risk (and protective) factors for rare outcomes such as suicide.

1.1 Bipolar disorder

1.1.1 History of bipolar disorder

Psychiatric disorders have been described since antiquity. Descriptions resembling affective disorders have been noted in both biblical figures (Stein, 2011) and characters in classical literature (Toohey and Toohey, 2004). But the first mentions of a clinical concept similar to what bipolar illness currently imply appeared during the 19th century (Carvalho *et al.*, 2020). The pivotal moment was Kraepelin's definition of manic-depressive illness in the 6th edition of his textbook *Psychiatrie: Ein Lehrbuch fur Studierende und Ärzte* published in 1899 (Kendler, 2018, Kendler, 2017). Kraepelin's depiction has profoundly influenced our constructs and understanding of bipolar disorders. Kraepelin did not differentiate between unipolar depression and bipolar disorder as is done today, but he distinguished manic depressive illness from dementia praecox (which would later become known as schizophrenia). The term bipolar disorder, coined by Leonhardt, was developed to differentiate it from recurrent unipolar depression. The term was introduced in the third edition

of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1980. It was also during this era that differentiation into subtypes of bipolar disorder was developed based on the patient's episodic history (Goodwin and Jamison, 2007).

1.1.2 Characteristic and subtypes

During a manic episode, an individual's mood is abnormally and persistently elevated, elated, or irritated. Other commonly occurring symptoms are hyposomnia, distractibility, racing thoughts and flights of ideas, pressured speech, hypersexuality, and engaging in risky behaviours. Psychotic symptoms are common during manic episodes. The term hypomania denotes a less severe form of mania with similar symptoms but less functional impairment. A hypomanic episode should not require hospitalization or feature psychotic symptoms, but the symptoms should be noticeable to others. Depressive episodes encompass depressed mood or anhedonia and other symptoms such as appetite changes, sleep disturbances, loss of energy, unwarranted feelings of guilt, difficulties in decision making and thinking, and returning thoughts of death and suicidal ideation (Carvalho *et al.*, 2020).

Several subtypes of bipolar disorder have been suggested. The DSM-system includes bipolar disorder type 1, which requires that the patient has had a manic episode, and type 2 where patients have had at least a major depressive episode and a hypomanic episode, but no manic episode. Other categories in the bipolar spectrum include cyclothymia characterized by multiple subthreshold depressive and hypomanic episodes over a period of at least two-years, unspecified bipolar disorders encompassing patients with bipolar features that causes significant distress but who do not fulfil criteria for the other diagnostic categories, and substance-induced or medically related bipolar disorders (American Psychiatric Association, 2013). Although the diagnostic reliability of bipolar disorder is considered high when made by experienced psychiatrists (Simpson *et al.*, 2002), authors have questioned the reliability and even validity of the bipolar type 2 diagnosis, not least against the backdrop that the prevalence seems to be rising (Gitlin and Malhi, 2020).

There have been several attempts to estimate the prevalence of bipolar disorder. The World Mental Health Survey estimated the prevalence to 1% and 2.4% when including sub-threshold bipolar disorder (Merikangas *et al.*, 2011). In Europe, an expert-based "best estimate" based on community studies arrived at 0.9% (Wittchen *et al.*, 2011), while a Dutch study estimated the prevalence to 1.9% (ten Have *et al.*, 2002).

Bipolar disorder is highly heritable with heritability estimates ranging between 60% and 85% (Kieseppä *et al.*, 2004, Lichtenstein *et al.*, 2009, McGuffin *et al.*, 2003). This has spurred research into the genetic underpinning of the disorder. Indeed, recent genome-wide association studies (GWAS) have successfully identified several single nucleotide polymorphisms (SNPs) associated with bipolar disorder. Individually, however, these SNPs have small effect sizes yielding little power to predict bipolar disorder in an individual (Stahl *et al.*, 2019). The susceptibility to bipolar disorder is also linked to an underlying propensity for several other, genetically correlated, psychiatric disorders. This means that having family members with a related psychiatric disorder increases the risk for bipolar disorder (Anttila *et al.*, 2018, Cross-Disorder Group of the Psychiatric Genomics, 2013, Lichtenstein *et al.*, 2009). Environmental risk factors for bipolar disorder have not been conclusively determined (Carvalho *et al.*, 2020); yet, it is generally believed that stressful life-events precede and might trigger mood episodes (Koenders *et al.*, 2014).

1.1.5 Course and consequences

Kraepelin claimed that the number of different life course manifestations of manic-depressive illness was "inexhaustible" (Goodwin and Jamison, 2007, Kraepelin, 1913). Nevertheless, studies show that some typical patterns may be discernible. The debut of bipolar disorder is often in late adolescence or early adulthood, but symptoms are usually present years prior to diagnosis and treatment. The first episode is often depression, resulting in the actual bipolar disorder diagnosis being made later when an elated episode has been confirmed (Goodwin and Jamison, 2007). Aside from mood symptoms, bipolar disorder is associated with functional impairment. Job prospects and

the patients' financial situation are often substantially impacted, and it is not uncommon for individuals to accumulate financial debt or lose jobs during episodes. The societal impact of the disorder is significant. Interestingly, the societal costs of bipolar disorder are not first and foremost due to costs for clinical care. Instead, indirect costs, e.g., sick leave and early retirement, represent three-quarters of the societal costs of bipolar disorder (Ekman *et al.*, 2013).

Before the advent of effective pharmacological treatment, episode recurrence was very common for persons with bipolar disorder (Goodwin and Jamison, 2007). Pharmacological treatments have improved the quality of life and outcomes for patients with bipolar disorder over the last half-century. Yet, relapse is still common. Over a four- or five-year period, more than half, and in some studies almost all, suffer some sort recurrence (Gignac *et al.*, 2015, Pallaskorpi *et al.*, 2015). Thus, even during the modern era with modern pharmacotherapy, bipolar disorder patients have a high risk of episode recurrence.

Patients with bipolar disorder have markedly higher mortality than the general population (Ösby *et al.*, 2001). Although several factors contribute to the excess in mortality, e.g., poor physical health, drug abuse, unemployment, and smoking, the risk of suicide stands out (Goodwin and Jamison, 2007) with rates more than twenty times higher than the average population (Carvalho *et al.*, 2020). When compared against other psychiatric disorders, there is still a high risk of suicide in bipolar disorder, especially in patients with mixed or psychotic features (Baldessarini and Tondo, 2020). A recent systematic review found that risk factors for suicide in bipolar disorder included a bipolar type 2 diagnosis, early-onset bipolar disorder, family history of suicide, previous suicide attempts, and substance abuse. Yet, the conclusion of the review was that there are far fewer studies on completed suicides than on suicide attempts and that further studies are needed (Plans *et al.*, 2019)

In study III, we studied risk factors of completed suicide in bipolar disorder.

1.2 Treatment of bipolar disorder

1.2.1 Historical overview

Lithium was the first pharmacological treatment shown to be effective in bipolar disorder. Although lithium was suggested to be useful to remedy psychiatric conditions as early as the 19th century (Fortinguerra *et al.*, 2019), it was not until Cade injected acutely ill patients with lithium salts that the effect was scientifically shown. Cade found that manic patients became well, the condition of depressed patients did not deteriorate, and the condition of psychotic patients remained unchanged. He also noted relapses in patients who discontinued treatment (Cade, 1949). Cade's report was largely ignored and the mistake of promoting lithium salts as a sodium chloride 'replacement' for patients with cardiovascular diseases in the US cast lithium in disrepute (Shorter, 2009). The ground-breaking randomized studies by Schou and Baastrup (Baastrup *et al.*, 1970, Schou, 1968, Schou *et al.*, 1954) rekindled the interest in lithium. There were several staunch lithium opponents, notably in the UK, fiercely opposing the notion that lithium was an effective drug (Shorter, 2009). But the results were replicated (Coppen *et al.*, 1971, Melia, 1970) and lithium still plays a leading role in bipolar disorder treatment guidelines (NICE, 2014, Sakurai *et al.*, 2020).

Observations of patients treated for epilepsy experiencing effects on psychiatric outcomes led to tests of many of these drugs for their psychotropic effects (Lambert *et al.*, 1966). Reports of anticonvulsant drugs as possible treatments for bipolar disorder were published in the late seventies and early eighties (Nolen, 1983). Since then several anticonvulsants have emerged as treatment alternatives, including valproate (Bowden *et al.*, 1994, Freeman *et al.*, 1992), lamotrigine (Calabrese *et al.*, 2000), and carbamazepine (Nolen, 1983).

Antipsychotics have been used to treat bipolar disorder for a long time. Evidence for the treatment of acute manic episodes with antipsychotic medication was shown as early as the 1960s (McElroy and Keck, 2000). Its use was,

however, mainly limited to treatment of acute mania (Jauhar and Young, 2019) where their efficacy is well documented (Cipriani *et al.*, 2011). The use of antipsychotics as maintenance treatment in bipolar disorder was limited until the turn of the century when atypical antipsychotics were tested in clinical trials. The first was olanzapine, then quetiapine, followed by aripiprazole, risperidone, ziprasidone, and lurasidone (Lindstrom *et al.*, 2017). In recent years, atypical antipsychotics have come to dominate treatment of bipolar disorder in the United States both as acute treatment as well as prophylactic treatments (Rhee *et al.*, 2020), and have increased in popularity also in Europe (Hayes *et al.*, 2011, Karanti *et al.*, 2016, Kessing *et al.*, 2016, Pålsson and Landén, 2019). However, treatment guidelines and the underlying evidence does not support this radical shift in treatment practice (Goodwin *et al.*, 2016, NICE, 2014). Aggressive marketing and creative study designs have been vented as potential culprits (Ghaemi and Selker, 2017, Rhee *et al.*, 2020). Similarly, the usage of antidepressants has risen dramatically despite scant evidence of efficacy in bipolar depression (Pacchiarotti *et al.*, 2013, Rhee *et al.*, 2020).

The term mood stabilizer is often used in conjunction with treatment of bipolar disorder. There are several definitions of a mood stabilizer: it can mean a medication that is effective in both mania and depression (either in the acute phase or in preventing relapse) and also a medication that treats one polarity while not exacerbating the other polarity, but there is no standard definition (Goodwin and Malhi, 2007). Labelling atypical antipsychotics and lamotrigine as mood stabilizers has been especially controversial (Goodwin and Malhi, 2007, Ketter, 2018, Malhi *et al.*, 2018). This thesis will sometimes use mood stabilizers referring to lithium and the anticonvulsants valproate, lamotrigine, and carbamazepine due to this being common usage (Fazel *et al.*, 2014, Rhee *et al.*, 2020).

1.2.2 LITHIUM

Figure 1. *Nyköpingsgruvan at Utö in Sweden where lithium was discovered in 1818.*

Lithium is the third element in the periodic system. It was first discovered in mineral deposits from Utö, an island in the Stockholm archipelago, in 1818 (Lodin, 2018). It was also the first modern treatment for bipolar disorder and it is still the most studied drug. Despite considerable efforts, the mechanism of action is not yet fully understood (Alda, 2015). Yet, lithium is still a first-line treatment for bipolar disorder, especially for maintenance treatment, with high quality evidence to support its use (Miura *et al.*, 2014). One of lithium's peculiarities is that it has a narrow therapeutic range that makes regular monitoring necessary (Goodwin *et al.*, 2016). This may have added to its decline in popularity, especially in countries where private practice is common and the necessary equipment and knowledge to perform monitoring is lacking (Rhee *et al.*, 2020). Furthermore, lithium has potential side effects, including nausea, tremor, polyuria, renal function deterioration, hypothyroidism, and

hypercalcemia that might have contributed to its declining popularity (Gitlin, 2016). Modern treatment practices, with better monitoring and lower target serum concentration, might have lowered the risk of very serious adverse events of lithium treatment such as end-stage renal disease (Aiff *et al.*, 2014).

About two-thirds of lithium-treated patients are responders to some degree, and one third are estimated to be excellent responders with almost no new episodes after starting lithium (Baldessarini and Tondo, 2000, Garnham *et al.*, 2007). Interestingly, lithium has consistently shown to have anti-suicidal effects, but evidence from clinical trials is still limited given the rarity of the outcome (Smith and Cipriani, 2017).

In study II, we studied the effectiveness of lithium and valproate on reducing suicide-related behaviour.

1.2.3 Anticonvulsants

As a sizable portion of patients are non-responders to lithium, there is a need for alternative treatments. Carbamazepine has been used (Nolen, 1983) both as an acute anti-manic drug and as maintenance treatment, but the evidence of efficacy as a prophylactic treatment is not convincing (Miura *et al.*, 2014). Valproate was introduced in the nineties and almost supplanted lithium as the most common maintenance treatment for bipolar disorder in the US around the turn of century (Blanco *et al.*, 2002). During the early nineties, valproate was tested in randomized trials as an antimanic drug (Bowden *et al.*, 1994, Freeman *et al.*, 1992) and later for its efficacy as maintenance treatment for bipolar disorder (Bowden, 2000). Although the evidence for the efficacy of valproate is stronger than that of carbamazepine, the number of trials is limited (Cipriani *et al.*, 2013b). As valproate has been a common alternative to lithium, the relative anti-suicidal effect of these two drugs is of great interest. Yet, the literature is limited and conflicting with some studies showing no difference (Oquendo *et al.*, 2011, Smith *et al.*, 2014) whereas other report favour lithium therapy in this regard (Goodwin *et al.*, 2003, Sondergard *et al.*, 2008).

Lamotrigine was the latest significant addition from the anticonvulsant medication cabinet for the treatment of bipolar disorder. Although it neither prevents (Miura *et al.*, 2014) nor mitigates manic episodes (Cipriani *et al.*, 2011), it prevents depressive episodes making it a popular choice in bipolar II disorder (Karanti *et al.*, 2016). Several other anticonvulsants drugs have also been tested, such as topiramate, but the evidence for their efficacy in maintenance treatment is not convincing (Goodwin *et al.*, 2016).

1.2.4 Atypical Antipsychotics

Atypical antipsychotics are widely used for bipolar disorder maintenance treatment (Rhee *et al.*, 2020). Commonly used drugs are olanzapine, quetiapine, and aripiprazole, followed by less common drugs such as risperidone, lurasidone, and ziprasidone. Although many trials have demonstrated that the drugs prevent relapse, the quality of the evidence and generalizability is limited (Lindstrom *et al.*, 2017). Despite this and concerns regarding side-effects, their popularity has surged. Some atypical antipsychotics, especially quetiapine, are used to treat bipolar depression, boosted by concerns about using antidepressants to treat bipolar depression and backed by trial evidence (Young *et al.*, 2013).

A key criticism of the evidence regarding atypical antipsychotics regards the use of enrichment or discontinuation designs (Cipriani *et al.*, 2014, Ghaemi and Selker, 2017). With few exceptions, these designs have been used in bipolar relapse prevention treatment trials of atypical antipsychotics in bipolar disorder. In an enriched design, the patient is first stabilized during an acute phase by the atypical antipsychotic. Those who respond in this acute run-in phase of the study will continue to the next phase. Patients that do not respond are excluded, in several studies this amounts to around 50% of those included in the run-in phase (Tohen *et al.*, 2006, Weisler *et al.*, 2011), in some cases almost 75% (Tsai *et al.*, 2011). This "enriched" set of treatment responders is then randomized to either continue or discontinue treatment and thereafter followed to examine the effect on relapse. Although this study design answers the reasonable but narrow clinical question, "should one continue

with the treatment that worked in the acute phase?", studies only provide evidence for this subset of patients. One would therefore assume that the average treatment effect would be much smaller in a non-enriched general population (Cipriani *et al.*, 2014); how much smaller is, however, debated. A potential clue to the extent of this bias is a comparison between early and late lithium trials. Early trials often used some sort of enrichment and showed dramatically larger effect sizes when compared with non-enriched samples (Deshauer *et al.*, 2005). Another line of evidence comes from observational studies on maintenance treatment in bipolar disorder. These often show that lithium is superior to alternatives (Hayes *et al.*, 2016a, Kessing *et al.*, 2012, Kessing *et al.*, 2011). It should be noted, however, that such studies might be biased because individuals receiving different treatments might also differ substantially in their clinical manifestation of the disorder which is also related to the outcome, introducing so called "confounding-by-indication".

> *In study I, we studied the effectiveness of maintenance treatment drugs to prevent psychiatric hospital admission in bipolar disorder.*

1.2.5 Antidepressants

The use of antidepressants to treat bipolar depression is a contested subject. Guidelines suggest that it should be used with caution and not as monotherapy (Fountoulakis *et al.*, 2016, Pacchiarotti *et al.*, 2013). However, the use of antidepressant is widespread among bipolar disorder patients, both in the US (Rhee *et al.*, 2020) and in Europe (Karanti *et al.*, 2016). Although the efficacy of antidepressants, and especially selective serotonin reuptake inhibitors, has been contested, there is plenty of trial evidence showing efficacy of antidepressants in unipolar depression (Cipriani *et al.*, 2018). But extrapolating evidence from unipolar to bipolar depression is not straightforward. Although available trials point to some level efficacy of treating bipolar depression, even as prophylactic treatment, the amount of trial evidence is small (Liu *et al.*, 2017).

It has also been suggested that antidepressants could have a destabilizing effect on the course of illness resulting in more recurrences and thus should be

avoided for that reason (Ghaemi *et al.*, 2003). Antidepressant treatment of bipolar depression also carries the risk of the feared adverse event: antidepressant induced treatment-emergent mania, i.e., a manic episode caused by treatment with an antidepressant (Melhuish Beaupre *et al.*, 2020). The extent of this risk is not fully understood, but evidence suggests that the risk is reduced with concomitant mood-stabilizing treatment (Viktorin *et al.*, 2014) and higher when using tricyclic antidepressants. Well defined risk factors for antidepressant induced treatment-emergent mania are still lacking (Melhuish Beaupre *et al.*, 2020).

1.2.6 Adjunctive psychological treatments

Although pharmacological treatment is the cornerstone for bipolar disorder treatment, not everyone responds to treatment and adherence is often poor. Several adjunctive psychological interventions have been developed. These include, for example, cognitive behaviour therapy and cognitive and functional remediation therapy. Psychoeducation is the most common and most studied psychological treatment for bipolar disorder (Salcedo *et al.*, 2016). Psychoeducation comes in many forms; its general formulation is intended to give the patient a deeper understanding of the disorder. Programs often include sections on early warning signs, the importance of maintaining sound sleep routines, the significance of medication adherence, and the detrimental effects of drugs and alcohol. Psychoeducational programs for bipolar disorder emerged in the nineties (Perry *et al.*, 1999) but it was the pivotal studies from Barcelona that showed remarkable efficacy of psychoeducation on relapse by using a powerful study design that included an active control that showcased it as an effective therapy (Colom *et al.*, 2003, Colom *et al.*, 2009). The Barcelona program consists of 21 sessions of 90 minutes each. It is thus an extensive program stretching over months. A recent study, independent from the Barcelona group, showed a considerably smaller effect size, and was only significant in a subset of patients who had experienced few prior episodes (Morriss *et al.*, 2016), which could potentially be an effect modifier (Reinares *et al.*, 2010). A meta-analysis of trials shows an effect of treatment

on recurrence and relapse. However, since the treatments have vastly different designs, it is yet undecided what the "active ingredient" of psychoeducation is (Bond and Anderson, 2015). The number of sessions and commitment required by, for example, the Barcelona program necessitates a large well-functioning organization and highly motivated staff that might not be feasible in smaller psychiatric clinics. Many clinics opt to use shorter programs with effect sizes that have been shown to be comparable too much longer and more expensive cognitive behavioural treatments (Parikh *et al.*, 2012). These can consist of around eight sessions and are usually conducted in a group setting (Askland and Ahmad Sadik, 2016). However, given that little is known about these locally constructed programs the effect of the psychoeducation in routine clinical practice is not well understood.

In study IV, we studied the effectiveness of psychoeducation in routine clinical practice.

1.2.7 Pharmacoepidemiology and real-world evidence

The most trustworthy evidence on treatment efficacy comes from randomized controlled trials (RCT) (Guyatt *et al.*, 2008). Randomization ensures that participants have the same chance of receiving the experimental treatment as the control condition. The goal is to create treatment groups without systematic differences that can bias treatment effect estimates. If properly executed, this design gives reliable information on the efficacy of an intervention (Cipriani and Geddes, 2009). However, randomized controlled trials are seldom flawless and bias can arise from multiple sources such as poor masking, poor choice of comparator (Furukawa *et al.*, 2014), poorly designed outcome measures (Hieronymus *et al.*, 2020), and inadequate statistical power (Guyatt *et al.*, 2008). One example is enriched clinical trials alluded to above (Ghaemi and Selker, 2017), another is strict exclusion criteria (co-morbidity, suicidal ideation, and drug or alcohol abuse) that leave many patients ineligible for a trial and creates an unrepresentative group of study subjects. It has been estimated that between 55% and 96% of the bipolar patient population would be excluded in a regular contemporary clinical trial of a bipolar disorder treat-

ment (Wong *et al.*, 2018). Notably, suicidal patients are often excluded in clinical trials leading to limited evidence of several drugs anti-suicidal effects (Wong *et al.*, 2018, Zimmerman *et al.*, 2016). Randomized controlled trials are great tools to demonstrate the efficacy of a treatment, i.e., the effect of a treatment under controlled conditions on selected outcomes. A treatment's effectiveness, i.e., its effect in routine clinical practice, is often lower. Effectiveness trials, where routine clinical practice is simulated in a trial setting, is one way of "bridging the efficacy–effectiveness gap". However, due to the larger variability of patients and their treatment responses in routine clinical practice compared to in a controlled experiment larger sample sizes are often needed which increases costs (Eichler *et al.*, 2011).

Observational study designs can be used to study treatment effectiveness in routine clinical practice. Datasets based on national registers of whole population data handle many of the issues of generalizability as they include the entire diagnosed patient population and are readily available. This strength comes with the costs of confounding and other biases related to observational data. In studies of treatments, confounding-by-indication is a frequently encountered problem (Lu, 2009). Treatment is not randomized in clinical practise, but the result of clinical decisions based on information about the patient. Imagine a study where blood pressure is measured in two outpatient groups. One receives antihypertensive treatment, and the other does not. In such a study one will likely find that patients taking antihypertensive treatment have a higher systolic blood pressure than their non-medicated counterparts. This is because they were prescribed antihypertensive treatment in the first place. Even though medication has lowered their abnormally high blood pressure, they are nevertheless likely to have a higher blood pressure on average than persons who never needed antihypertensive treatment in the first place. In the same vein, even though observational studies on maintenance treatment in bipolar disorder often show the superiority of lithium (Hayes *et al.*, 2016a, Kessing *et al.*, 2012, Kessing *et al.*, 2011), such results could have been biased by confounding-by-indication as there might be important differences between patients receiving lithium and those receiving other drugs that are related to the risk of relapse.

In study I, II, & IV, we used within-individual study designs to minimize the impact of confounding-by-indication

Pharmacogenetics has the potential to personalize drug treatment in bipolar disorder, both in terms of efficacy and safety. Previous research has identified common genetic variants associated with lithium response, and one study showed that bipolar disorder patients with a higher polygenic risk score for schizophrenia showed a lower chance of lithium response (International Consortium on Lithium, 2017). Unfortunately, these findings are still too weak to be useful in a clinical setting (Song *et al.*, 2015). Pharmacogenetics can be used to study drug pharmacokinetics. For instance, differences in drug metabolism can be detected by examining genetic variants in genes coding for different cytochrome P450 (CYP) enzymes. The CYP2D6 and CYP2C19 enzymes are involved in the metabolism of many psychiatric drugs (Hicks *et al.*, 2015, Hicks *et al.*, 2017). *CYP2D6* genotype have been linked to risperidone and aripiprazole treatment failure (Jukic *et al.*, 2019), and differences in metabolism due to *CYP2C19* genotype have equally been shown to affect treatment failure rates of citalopram (Jukić *et al.*, 2018). Metabolic phenotypes can be defined based on *CYP2D6* or *CYP2C19* genotypes (Hicks *et al.*, 2015, Hicks *et al.*, 2017). These metabolic phenotypes range from poor-, intermediate-, extensive- or normal-, to ultra-rapid metabolizers. Poor metabolizers will have reduced clearance of the drug, leaving the subject at risk of higher plasma concentrations (Zanger and Schwab, 2013) with possible adverse events and adherence problems as a consequence. This has been shown in the case of citalopram and escitalopram. But higher plasma concentration could also lead to better treatment effects as has been suggested in studies of citalopram and escitalopram (Fabbri *et al.*, 2018). Whether *CYP2C19* metabolic phenotypes also affect antidepressant treatment patterns in bipolar disorder remains unknown.

In study V, we studied the impact of CYP2C19 metabolic phenotypes on treatment patterns and antidepressant induced treatment-emergent mania.

2. Aims

The overarching aims of this thesis were to advance our understanding of bipolar disorder treatments and of risk factors for suicide in bipolar disorder. The specific aims were:

I. to study the effectiveness of drugs commonly used as maintenance treatment in preventing psychiatric hospital admission.

II. to study the effectiveness of lithium and valproate treatment on reducing the risk of suicide-related behaviour

III. to identify risk factors for suicide in bipolar disorder

IV. to evaluate the effectiveness of psychoeducation for bipolar disorder.

V. to investigate *CYP2C19* polymorphisms influences: antidepressant treatment patterns or risk for antidepressant induced treatment-emergent mania in bipolar disorder.

3. Methods

3.1 Material

3.1.1 Swedish national registers

All studies in this thesis make use of Swedish registers. Sweden's history of keeping population registers stretches back centuries. In its modern form, every individual residing for at least one year in Sweden is assigned a unique personal identification number. This enables linkages of individual data between registers managed by differing agencies (Ludvigsson *et al.*, 2016).

3.1.1.1 Total population register

The Total Population Register was created in 1968 and is administered by Statistics Sweden. The data are extracted from the Population register, which is administered by the Swedish National Tax Agency and contains information on births and deaths, immigration and emigration, civil status, citizenship, and other household and family-related variables (Ludvigsson *et al.*, 2016).

3.1.1.2 Cause of death register

The Cause of Death Register contains information on all deaths in Sweden (excluding stillborn babies), and the death of Swedish nationals abroad. The register contains cause of death coded according to the International Classification of Diseases (ICD), date of death, and further information regarding for example place of death. The register contains data from 1961 and onwards (National Board of Health and Welfare, 2019).

3.1.1.3 The Prescribed Drug Register

The Prescribed Drug Register includes information on every prescribed drug purchase in Sweden as of July 2005. It does not contain information on drugs dispensed during inpatient care or drugs purchased without a prescription. Both dates of prescription and the date of purchase or dispense are recorded in the register. The register also contains information on the amount of Defined Daily Dose (DDD) dispensed, generic drug name, Anatomical Therapeutic Chemical Classification System (ATC) codes, and tablet or solution strength (National Board of Health and Welfare, 2020a).

3.1.1.4 The Patient Register

The National Patient Register covers Swedish inpatient care from 1964, with information on psychiatric care from 1973. The register has a complete coverage from 1987 when the last county was included (National Board of Health and Welfare). The register includes information on the main and secondary diagnoses. Diagnoses are coded according to the ICD system: ICD-8 1973–1986, ICD-9 1987–1996, and ICD-10 from 1997 and onwards. The patient register also contains information on type of health care facility, county of treatment, date of visit, and date of discharge (Ludvigsson *et al.*, 2011, National Board of Health and Welfare, 2020b). It does not cover primary care but includes information on specialized outpatient care from 2001 and onwards. However, early data was unsatisfactory, in 2001, more than 80% of psychiatric patient visits were missing a main diagnosis, which had dropped to 20% in 2008 (Welfare, 2014).

3.2 Swedish National Quality Register for Bipolar Disorder

The Swedish National Quality Register for Bipolar Disorder (BipoläR) is a national register for benchmarking Swedish outpatient management of bipolar disorder patients. Swedish quality assurance registers were created to improve care for specific diagnostic groups or for safety and follow-up of certain medical procedures (Pålsson and Landén, 2019). BipoläR was established in

2004 and includes individualized data on diagnosis, treatments, outcomes, and demographic information. Clinicians register the data, usually the treating psychiatrist, nurse, or psychologist. Individuals can enter the register at any time during their illness meaning that the first assessment does not necessarily coincide with disorder onset. The register includes data from annual follow-ups to provide longitudinal data on outcomes. The register can be used for research, but its main purpose is to provide data to health care organizations to evaluate clinical care.

3.3 SWEBIC

The Swedish Bipolar Cohort Collection (SWEBIC) is a genetic study designed to collect and genotype a large sample of bipolar disorder patients. The study has been used in international collaborative studies aimed at finding genetic risk loci for bipolar disorder (Charney *et al.*, 2017, Stahl *et al.*, 2019). It has also been used to study lithium response (Song *et al.*, 2015) and long term progression in bipolar disorder (Smedler *et al.*, 2019).

Individuals were primarily recruited to SWEBIC through BipoläR, but also through the National Patient Register through a validated algorithm (Sellgren *et al.*, 2011), and the St. Göran study, which is a clinical study on bipolar disorder with patient samples from Stockholm and Gothenburg (Ryden *et al.*, 2009).

The samples in SWEBIC were collected between 2009 and 2013. Eligible patients were contacted through mail or phone and those who volunteered to participate were interviewed by phone by research nurses to collect complementary information not available in BipoläR or the National Patient Register. Blood samples for genotyping were collected at nearby labs and sent to the Karolinska Institutet Biobank for DNA extraction and storage. Genotyping was conducted at the Broad institute of Harvard and MIT. Samples were analysed in three waves using different genotyping chips: Affymetrix 6.0 (wave 1) (Affymetrix, Santa Clara, CA, USA), Illumina OmniExpress (wave 2) chips (Illumina, San Diego, CA, USA), and Infinium PsychArray-24 v1.2

BeadChip (wave 3) (Illumina, San Diego, CA, USA). Genotype imputation was done using the Haplotype Reference Consortium reference panel (version 1.1) (Lewis *et al.*, 2020, McCarthy *et al.*, 2016). This procedure has been described in more detail previously (Charney *et al.*, 2017).

3.4 Ethical approval

All data collection and registry linkages have been approved by regional ethics committees in Gothenburg and Stockholm, Sweden.

3.2. Statistical methods

All studies used standard statistical methods adapted to the study design. In study *I, II, III, & V*, Cox regression was used to analyse time to event data. In study *IV*, logistic regression was used as the outcomes were dichotomous.

In study *I, II & IV*, we analysed the data using within-individual designs with so called fixed effects regression models. We chose this design as it has one distinct advantage over other approaches: the individual is used as its own control adjusting for all non-time-varying confounders. We thus adjust for non-time-varying confounders by design, without having to explicitly measure confounders such sex, age, and genetic makeup. However, this is not done without costs. First, it requires longitudinal data. Second, using only within-individual variation also means that only individuals who vary over time in the outcome variable can contribute information and only variables that vary over time can be estimated (Allison, 2005). Finally, time-varying confounding can of course still influence the results. Thus, the method should not be seen as a remedy for confounding-by-indication but as a way of adjusting for between-individual differences.

In study *I & II*, stratified Cox regression was used to perform within-individual analyses of treatment outcomes. In this setting each separate strata, in this case an individual, has a separate baseline hazard function. Only within-indi-

vidual information is used during estimation but coefficient estimates are constrained so that they do not differ between strata. Since there is no information in strata without events, only individuals who have experienced the event during follow-up can contribute information (Allison, 2005). Furthermore, in study *I, II, & III,* the time-dependent covariates were used as both treatments and covariates differed across follow-up. In Cox-regression, this can be done by splitting the risk time into several intervals each with the last known covariates values. For example, an individual can be followed during day 0 to 75, 75 to 100, and 100 to 200, where each interval have different covariate values (Therneau *et al.*, 2017). In some instances, individuals in our between-individual analyses had repeated events and thus several observations per person. In such cases, each individual was treated as a cluster and robust standard errors were calculated (Therneau and Grambsch, 2000).

In study *IV*, within-individual analysis was performed using conditional logistic regression. Variables that are the same within each stratum can be omitted in conditional logistic regression. In our case, this means individual characteristics that do not vary over time. Estimation is then based only on within-individual information: time-varying covariates and the outcomes for each individual. But just as with stratified Cox regression, the coefficient estimates do not vary between strata and only one set of coefficients are estimated. Additionally, strata that do not contain differences in the outcome variable cannot contribute information. The same applies to any independent variable that does not vary over time (Allison, 2005).

Propensity score is another popular statistical methodology in pharmacoepidemiology. In a propensity score analysis, the probability of receiving treatment is first predicted in one model. The output from this model can then be used as a propensity score to set up a counterfactual study design where, for example, one matches individuals who did get the treatment with individuals who had a similar propensity to get the treatment but did not get it. These study designs are however limited by their reliance on observed confounders (Guo and Fraser, 2014). Propensity score was used as a sensitivity analysis in study *II*.

3.3 Study designs

3.3.1. STUDY *I & II*

A similar study design was used in study *I & II and* both studies used data from national registers. First, bipolar disorder patients were identified in the National Patient Register using a modified version of a previously validated algorithm (Sellgren *et al.*, 2011). We included patients if they had two bipolar diagnoses (inpatient or outpatient diagnoses). Patients were excluded if they had more than one diagnosis of schizophrenia or schizoaffective disorder, or if the diagnosis of bipolar disorder was only based on diagnostic codes in ICD-8 and 9 that might indicate unipolar depression. In study *I,* we also included patients identified in BipoläR even if they did not fulfil the above-mentioned criteria in the National Patient Register.

In a second step, we defined treatment exposures for these individuals using data from the Prescribed Drug Register. We used a series of dispense dates, i.e., dates when the drugs were collected or purchased. A patient was deemed to be on treatment between two dispense dates that were no more than three months apart. When the time interval between two dispense dates was longer than three months, the treatment was considered to have ended at the last dispense. These treatment exposure times were created for all studied drugs and were combined to create a time-varying treatment exposure history for each patient across the study period. In a last step, the outcomes were added: psychiatric hospital admission with at least one overnight stay for study *I* and suicide-related behaviour for study *II*. Each individual time was reset to zero after each new event, i.e., psychiatric hospitalization or suicide-related behaviour. Using Cox regression, these data were then analysed using both conventional between-individual approaches and within-individuals analyses using stratified Cox regression to control for non-time varying confounders. These methods have also been described in detail in a supplement(Lichtenstein *et al.*, 2012).

Several extra analyses were made in both studies. These were both made to test the robustness of the results and to test specific hypotheses. For example, in both study *I & II* the definition of treatment exposure was modified. We also attempted to test treatment exposure closer to monotherapy. In study *II,* we changed the diagnostic algorithm to include a wider array of patients, e.g., those with only one diagnosis of bipolar disorder or all individuals who had ever been on lithium treatment. We also changed the definitions of the outcomes in both studies. In study *II*, propensity score analysis was also used to test the robustness of the analysis. Furthermore, study *II* included analyses of treatments and outcomes hypothesized to be unrelated to either lithium treatment or suicide-related behaviour to test whether the study design in and of itself produced results for these theoretically unrelated outcomes and exposures. Finally, in study *II* separate analyses were made in patients with comorbid substance abuse, bipolar type 1, and type 2 diagnosis.

3.3.3. STUDY *III*

We analysed presumptive risk factors of completed suicide in BipoläR. Our sample consisted of all individuals included from 2004 until December 2013 in the BipoläR registry. From 2014 and onwards, BipoläR used a substantially modified questionnaire . Data on mortality and cause of death were included up until December 31st, 2014. Individuals were followed from their inclusion in the register until suicide and were censored at death from other causes or end of follow-up. To use the complete information found in BipoläR, where many individuals having repeated assessments, we used Cox regression with time-dependent covariates (Therneau *et al.*, 2017), updating covariates at the annual assessments where possible. The analyses are presented unadjusted and adjusted for age and sex. Due to varying degrees of overlap between different questionnaire variants, several risk factors had a substantial amount of missing data. We therefore assessed each risk factor separately and did not opt to include them in a multivariate predictive model.

We tested an array of different risk factors. These included general risk factors such as sex, age, body mass index, and education; social factors such as living

arrangements, criminal convictions, and violent behaviour; and psychiatric risk factors such as recent affective episodes, previous suicide attempts, psychiatric comorbidity, family history of affective disorder, inpatient care, and bipolar disorder subtype.

3.3.2. STUDY *IV*

We studied the effectiveness of psychoeducation on several outcomes in bipolar disorder patients. We used longitudinal data from BipoläR – where individuals are assessed annually – to analyse the effect of psychoeducation using within-individual statistical models. In these analyses, the patient's psychoeducational status (yes or no) was correlated with the outcome measured at the next assessment. We used conditional logistic regression stratified on individuals.

Data were extracted from the register in several steps. First, we excluded individuals who had already had psychoeducation at baseline. Second, we included individuals who had three consecutive non-missing answers on whether they had received psychoeducation. Third, we assessed if they received psychoeducation during follow-up. The outcomes used were any affective relapse during the last twelve months, (hypo-)manic or mixed episode during the last twelve months, depressive episode during the last twelve months, suicidal attempt or self-harm, psychiatric hospitalization, and involuntary sectioning. We conducted both unadjusted analyses and analyses adjusted for the global assessment of functioning (GAF) symptom subscale, age, and mood stabilizing medication. Individuals who did not receive psychoeducation during follow-up could contribute information on confounder variables.

We performed four sensitivity analyses. First, for each patient we compared only the first period of psychoeducation with the periods without psychoeducation. Second, the period immediately before the first time period with psychoeducation was removed. Third, we analysed the sample using the information on psychoeducation and outcomes collected at the same time.

Fourth, using the same specification of time intervals as in the third analysis we removed the first time period with psychoeducation. These analyses were used to test the robustness of the results to misspecifications of treatment exposure and unobserved time-varying confounding. As a final analysis, we carried out a between-individual analysis using general estimating equations for comparative purposes.

3.3.4. Study *V*

In study *V*, we used three approaches to study the impact of *CYP2C19* polymorphisms on treatment with antidepressants metabolized by CYP2C19 in bipolar disorder patients. The antidepressants were citalopram, escitalopram, sertraline, amitriptyline, and clomipramine. We defined *CYP2C19* metabolic phenotypes according to a previous publication. Using two single nucleotide polymorphisms (SNPs), rs4244285 and the rs12248560, we divided patients into poor metabolizers, intermediate and intermediate+ metabolizers, extensive+ and extensive metabolizers, and ultra-rapid metabolizers (Fabbri *et al.*, 2018).

In the first analysis, we studied treatment discontinuation during the first year of treatment in relation to *CYP2C19* metabolic phenotypes. Using a similar approach to treatment exposure estimation as in study *I & II*, we used a series of dispense dates to estimate treatment exposure during the follow-up. But we also added the number of defined daily dosages (DDD) dispensed at the last date. If a treatment period consisted of only one dispense date, it was calculated based on the number of DDDs dispensed. Individuals were followed until treatment discontinuation and were censored at death, twelve months after treatment initiation, or end of follow-up (December 31st, 2016), whichever happened first. Similar designs have been used to study the treatment discontinuation of lithium (Kessing *et al.*, 2007) and ADHD medication (Zetterqvist *et al.*, 2013). The second method was used to investigate switching to treatment with another antidepressant in relation to *CYP2C19* metabolic phenotypes. We divided the data into separate months and included bipolar patients who had received any of the five antidepressants and who

had not received an antidepressant during the previous year. Baseline was set to the first dispense of the antidepressant. The outcome was defined as a prescription of a new antidepressant within twelve months, they were censored at death, after twelve months, or at end of study December 31st, 2016. This was a similar to a previous study (Jukić *et al.*, 2018). In a third set of analyses, we studied treatment-emergent manic switch within three months after treatment initiation in relation to *CYP2C19* metabolic phenotypes. Patients were followed from the start of antidepressant treatment (defined as in the analysis of treatment discontinuation) until a hospital admission for mania. Study subjects were censored at the end of treatment, death, three months after treatment initiation, or at study end, December 31st, 2016. All analyses used Cox regression with robust standard errors.

4. Results

4.1. Study *I*: Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder

We acquired data on 35,022 individuals diagnosed with bipolar disorder in the patient register. These individuals were followed between January 1st, 2006 and December 31st, 2009. A quarter of these patients (N=9,292) were admitted to a psychiatric hospital, requiring at least an overnight stay, during the follow-up period.

Using the within-individual model described in the method section, we found that lithium, valproate, lamotrigine, olanzapine, and quetiapine but not carbamazepine reduced the risk for all-cause psychiatric hospitalizations (table 1). We also found that the effect of lithium was better than that of olanzapine and quetiapine. Lithium, valproate, olanzapine, quetiapine, and carbamazepine but not lamotrigine reduced the risk of psychiatric hospitalizations for mania. Furthermore, lithium, valproate, olanzapine, quetiapine, and lamotrigine but not carbamazepine were associated with a reduced risk of psychiatric admission for depression. We found that lithium and valproate were associated with a reduced risk for psychiatric hospitalization due to mixed episodes. Sensitivity analyses were mainly in line with the main results. However, when adding 30 days to the end of each treatment period and including single dispenses as 30-day treatment periods, olanzapine and quetiapine were not associated with a reduced risk of psychiatric hospital admission. The effect of lithium was also attenuated when dispensed prior to another drug.

Between-individuals analyses yielded opposite results to within-individual analyses in several cases. For instance, lamotrigine treatment was associated with a decreased risk for mania whereas olanzapine was associated with an increased risk of mania.

Table 1. Within-individual analyses showing associations between treatments and psychiatric hospital admissions (n=35,022).

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

Models adjusted for earlier time spent in psychiatric inpatient care, age, and use of any of the other six medications.

4.2. STUDY *II:* SUICIDAL BEHAVIOR DURING LITHIUM AND VALPROATE TREATMENT: A WITHIN-INDIVIDUAL 8-YEAR PROSPECTIVE STUDY OF 50,000 PATIENTS WITH BIPOLAR DISORDER

Using the Swedish patient register, we identified 51,535 individuals with bipolar disorder. These patients were followed from 2005 until 2013, resulting in 273,140 person-years of follow-up. Among these individuals, 4,643 individuals had at least one suicide-related event, with a total of 10,648 suicide related events. During follow-up, 41% of patients received treatment with lithium and 16.3% received valproate treatment.

The within-individual analyses were restricted to 4,405 individuals who had variations in treatment or suicide-related events during follow-up. There was a decreased rate of suicide-related events during lithium treatment periods compared with periods off lithium (HR 0.86, 95% CI: 0.78–0.95). In contrast, the rates of suicide-related events were not related to being on/off valproate medication (HR 1.02, 95% CI: 0.89–1.15). There was a statistically significant difference in hazard ratios between lithium and valproate (p=0.038). The population attributable fraction based on the within-individual results for lithium was 12% (95 % CI: 4%–20%), suggesting that if the patients would have been on lithium treatment for the entire follow-up period, 12% of suicide-related events could have been averted. Between-individual analyses showed similar results with a lower rate of suicide-related events associated with lithium treatment but not with valproate treatment.

Several extra analyses were carried out to test the robustness of the results and test specific hypotheses regarding the link between lithium treatment and suicide-related events. These analyses were mainly consistent with the primary results, but with some specific results in sub-groups. When testing subtypes the effect of lithium was only significant for bipolar type 2 and a large portion of suicide-related events occurred within the subgroup of patients with comorbid substance abuse. Furthermore, individuals were more likely to experience suicide-related events shortly (<30 days) after discontinuing lithium treatment compared with periods off medication.

4.3. Study III: Risk factors for suicide in bipolar disorder: a cohort study of 12 850 patients

Our sample consisted of 12,850 bipolar disorder patients (4,844 men and 8,006 women) from the BipoläR register. Patients were followed from the first assessment until the end of 2014. The mean follow-up time from the first register assessment was 4.05 years and the mean number of register assessments were 2.45 (range 1–10). During follow-up, 55 men and 35 women committed suicide.

In the full sample, male sex, living alone, criminal conviction, recent affective episode, recent depressive episode, any comorbid psychiatric disorder, comorbid substance abuse, anxiety disorder, personality disorder, previous suicide attempt, psychiatric inpatient care, and involuntary commitment were all factors significantly associated with suicide after adjusting for age and sex.

Our analyses stratified by sex showed that among men, living alone, recent affective episode, comorbid psychiatric disorder, comorbid substance abuse disorder, previous suicide attempts, psychiatric inpatient care, and involuntary commitment were associated with suicide. In women, criminal convictions, recent depressive episodes, comorbid psychiatric disorder, comorbid personality disorder, previous suicide attempts, and psychiatric hospital admission were all associated with completed suicide.

4.4. Study *IV*: Psychoeducation for bipolar disorder and risk of recurrence and hospitalization–a within-individual analysis using registry data.

From a pool of 12,850 individuals in BipoläR, we extracted 2,819 cases who met our inclusion criteria. Of these, 402 patients received psychoeducation during follow-up. Our results show that psychoeducation was associated with reduced risk of affective episode recurrence, (hypo-)manic or mixed episode recurrence, and inpatient care, but not with suicidal attempts or self-harm, and involuntary sectioning (table 2). Sensitivity analyses showed similar results except in the analysis where we removed the time interval prior to the patient receiving psychoeducation. In this analysis, psychoeducation was only associated with a reduction in inpatient care in adjusted analyses. In addition, when using a between-individual analysis, there were no associations between psychoeducation or any of the outcomes.

4.5. Study *V*: Effect of *CYP2C19* polymorphisms on antidepressant prescription patterns and treatment emergent mania in bipolar disorder

We studied the impact of *CYP2C19* metabolic phenotypes on antidepressant treatment in 5,019 individuals. We analysed three outcomes. First, treatment discontinuation where we found limited effect of *CYP2C19* metabolic phenotypes. We did find that ultra-rapid metabolizers had a higher risk of discontinuing amitriptyline and clomipramine compared with extensive metabolizers, but these associations did not remain after adjustment for multiple testing. However, a post hoc analysis revealed a stronger association between treatment discontinuation and ultra-rapid metabolizers of amitriptyline and clomipramine during the first two months of treatment. Second, we analysed switching treatment to another antidepressant and found no significant differences based on *CYP2C19* metabolic phenotype. Third, we analysed the association between *CYP2C19* metabolic phenotype and treatment-emergent mania but found no association when analysing metabolic phenotypes as a categorical variable. We also conducted analyses using *CYP2C19* metabolic phenotype coded as a continuous variable. When combining all five medications, we found an association between poorer metabolism and risk for treatment emergent mania, but this association did not withstand correction for multiple testing.

Table 2. Within-individual analyses showing associations between psychoeducation and several clinical outcomes

Outcome	OR[1]	95% CI	p-value	Missing[2]	N with change on outcome	N with change on outcome + psychoeducation
All relapses	0.57	0.42–0.78	<0.01	591	1152	207
(Hypo-) manic or mixed episodes	0.54	0.39–0.76	<0.01	634	917	183
Depressive episodes	0.63	0.47–0.86	<0.01	634	1099	208
Suicide attempts or self-harm	1.22	0.54–2.76	0.64	635	146	32
Inpatient care	0.54	0.33–0.86	0.01	591	484	89
Involuntary sectioning	0.66	0.34–1.3	0.23	640	213	45

Total number of individuals = 2,819, individuals receiving psychoeducation during follow-up = 402, time intervals = 9,161

[1] Adjusted for age, mood stabilizing treatment, and GAF-symptom.

[2] The number of time intervals with missing data

5. Discussion

5.1. Study *I*: Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder

In a large cohort of bipolar disorder patients, we found that treatment with lithium, valproate, lamotrigine, quetiapine, or olanzapine were associated with a decreased risk of psychiatric hospital admissions. We also showed differential effects of the studied drugs depending on episode polarity. These results provide real world evidence on pharmacological treatment of bipolar disorder that complement results from clinical trials.

Our results are chiefly in line with previous RCTs, showing remarkably similar effect sizes compared to a previous network meta-analysis (Miura *et al.*, 2014) with two important exceptions: The effect sizes of quetiapine and olanzapine were smaller in our study compared with findings in clinical trials. We speculate that this is due to the fact that most of the evidence for these drugs are derived from enriched studies where study participants were selected based on acute response to the drug in question (Ghaemi and Selker, 2017, Miura *et al.*, 2014). Many early studies on lithium were also enriched, and these show larger effect sizes compared with later studies with non-enriched designs (Deshauer *et al.*, 2005). In more recent studies, lithium has often served as a comparator to newer drugs, and in some instances these studies have been enriched for the new drug (Weisler *et al.*, 2011) which introduces a negative bias against lithium. A recent small study (n=61) was enriched by using individuals stabilized on lithium *and* quetiapine. Patients were then randomized to continue with either lithium or quetiapine as relapse prevention. The effect of lithium was superior to that of quetiapine (Berk *et al.*, 2017). This demonstrates that lithium is a superior drug for relapse prevention when given similar baseline conditions. Caution is, however, warranted when comparing results from our study with relapse prevention studies as outcomes or methods are not directly comparable. Interestingly, our results on lamotrigine are similar to previous results, even though lamotrigine also have been tested using enriched trial designs (Goodwin *et al.*, 2004). However,

as lamotrigine has weak acute antidepressant effects this enrichment for tolerability would have little to no effect on relapse prevention effects (Ghaemi and Selker, 2017).

There are limitations in our study related to the use of registers, which are discussed in a general limitations section at the end of this chapter. In addition, our analyses adjusted treatment effects for concomitant treatment with other drugs. This is a simplification as combinations of different treatments might lead to interaction effects. However, a complete mapping of the different treatment combinations of treatments was beyond the scope of this study and might also have led to problems with overfitting, and potentially also lack of data since some treatment combinations are very rare. Furthermore, we studied psychiatric hospital admission, which is a hard, reliable and important outcome. But it does not capture the full breadth of morbidity in bipolar disorder. Thus, the effect on depression treated in outpatient clinics, potential impact on cognitive functioning, or sub-threshold symptoms of depression or mania are not captured in our study and remain important areas of treatment research (Lähteenvuo *et al.*, 2018).

Shortly after our study was published, a comprehensive study of treatment of bipolar disorder and risk of psychiatric hospital admission was published. The study used Finnish registry data, had a more wide-ranging list of treatments tested, and a more advanced method to assess treatment exposure from registry data (Lähteenvuo *et al.*, 2018). Importantly, it did also use the same within-individual study design to test the association between treatment and psychiatric hospital admission. The authors largely replicated our results. Showing similar effect sizes for lithium, lamotrigine, and valproate and even smaller effect sizes for quetiapine and olanzapine. These studies taken together with previous observational studies (Hayes *et al.*, 2016a, Kessing *et al.*, 2018, Kessing *et al.*, 2012, Kessing *et al.*, 2011) lend strong support to the preeminence of lithium treatment compared with alternative drugs used in bipolar disorder maintenance treatment. Studies such as this, using powerful methods to control for confounding-by-indication, contribute complementary evidence when evaluating the effect of different treatments in bipolar

disorder, but should not be seen as an excuse not to conduct randomized trials.

5.2. Study *II*: Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder

Using a large register-based sample, we showed an association between lithium treatment and lower rates of suicide-related behaviour. The anti-suicidal effects of lithium have been shown in many previous publications (Baldessarini *et al.*, 2006, Hayes *et al.*, 2016b, Kessing *et al.*, 2005, Smith and Cipriani, 2017). The difference in anti-suicidal properties of valproate and lithium has yielded conflicting results (Goodwin *et al.*, 2003, Oquendo *et al.*, 2011, Smith *et al.*, 2014). A recent meta-analysis showed evidence for a reduced rate of suicide but not self-harm (Smith and Cipriani, 2017) but with few events resulting in wide confidence intervals. Our use of within-individual models limited confounding, but the time-varying effects of lithium treatment cannot be ruled out, and well-powered randomized controlled trials are still needed.

We conducted a series of sub-analyses and sensitivity analyses that showed similar results to the main analysis, although some did not yield statistically significant results. Among bipolar disorder type 1 patients, we found no significantly reduced risk suicide associated with lithium treatment. However, in bipolar type 2 disorder patients, we found that lithium was associated with reduced risk of suicide related events. This could potentially be of interest for further personalization of treatment in high-risk bipolar disorder type 2 groups. We also found an effect in the group of individuals with substance abuse disorder. This is important, as this group has a specifically high risk of suicide (study *III*). In concordance with previous evidence, we also show a higher risk of suicide-related events shortly after discontinuing lithium (Smith *et al.*, 2014).

There are several potential limitations for this study, many are shared with other studies and are discussed at the end of this chapter. There are also study-specific limitations. Completed suicides were not studied separately in our study because non-repeated events cannot be analysed using this study-design. Additionally, since the exposure window is defined as being between dispenses it precludes the study of completed suicides. However, the first author on this paper, Jie Song, did additional analyses of this outcome in her thesis frame. By adding 14, 30, and 90 days onto each treatment exposure, she analysed completed suicides using logistic regression. In preliminary analyses, the results looked promising, but when using thyroid medication as a negative control she noted similar effects, which indicates time-varying confounding or misclassification of treatment exposure (Song, 2017). Related to this issue is the specific effects of lithium discontinuation where we show an effect. In the light of the above mentioned analysis, treatment exposure misclassification cannot be ruled out in this analysis which added 30 days to the end of the treatment periods.

Taken together, our results corroborate previous results on the preventive effect of lithium on suicidal behaviour and is the largest study to date. We also could not document an anti-suicidal effect of valproate, strengthening the case that this is a lithium specific effect. Well-designed RCTs are still warranted to further understand this effect. Future studies should also attempt to unravel the mechanism underlying lithium's specific anti-suicidal effect.

5.3. Study *III*: Risk factors for suicide in bipolar disorder: a cohort study of 12 850 patients

Suicides are rare events and large studies are needed to study risk factors. We followed 12,850 patients with bipolar disorder for an average of 4 years and identified 90 suicides. This study expands the understanding of risk factors for completed suicide in bipolar disorder using a large sample and a long list of potential risk factors.

The identified risk factors confirm previously known risk factors of suicide in the general population, including male sex, psychiatric disorders, substance abuse, and previous suicide attempts (Turecki and Brent, 2016), which have also previously been shown to be of importance for patients with bipolar disorder (Schaffer *et al.*, 2015, Webb *et al.*, 2014). Notably, in study *II* suicide-related events were heavily concentrated to the group of patients with diagnosed comorbid substance use disorder. Similarly, living alone and previous criminal convictions are known risk factors in the general population (Turecki and Brent, 2016). Previous studies on the importance of household status for suicide risk has been inconsistent (Hawton *et al.*, 2005).

The association between recent episodes, especially depressive episodes, and inpatient care was expected and has been shown previously (Schaffer *et al.*, 2015). These variables are likely to reflect illness severity and highlight the importance of appropriate follow-up after inpatient care. A recent study of Swedish registers showed that 36% of suicides in bipolar disorder patients occur within 120 days of discharge from inpatient care (Iliachenko *et al.*, 2020).

Our results also show differences between men and women in stratified analyses, with some risk factor being significantly associated with suicide in one sex but not the other. Both personality disorder and alcohol dependence have been reported as risk factors for suicide among bipolar disorder patients (Clements *et al.*, 2013). In our study, substance abuse disorder was a risk factor for suicide among men but not women. Previous results on alcohol abuse also show a similar pattern (Isometsä *et al.*, 1994). Conversely, comorbid personality disorder was a risk factor for suicide among women but not men. Criminal conviction similarly also showed a sex-dependent association with the effect being significant among women but not men. Previous literature on suicide in the general population has shown criminal convictions to be associated with suicide (Boardman *et al.*, 1999) and suicide rates in prisons are notably high (Fazel *et al.*, 2017).

There are several limitations to the current work, some of them are shared with other studies in this thesis and are discussed at the end of this chapter.

The first register entry can occur at any time and is not limited to illness onset. Suicides that occur shortly after disorder onset might therefore be missed. The rate of suicide is also probably lower than if the bipolar disorder patients would have been followed from onset of illness. The registry is also voluntary which might result in inclusion bias resulting in lower suicide rates, as noted in a recent publication (Isometsä, 2020). Due to multiple versions of the questionnaire used in BipoläR, there was a lot of missing information on several variables. Additionally, even though BipoläR contains a wide variety of potential risk factors, it lacks factors that would have been of interest such as somatic status, early life adversities, and polarity of the first episode.

Finally, awareness of potential risk factors for suicide is valuable for clinicians treating patients. Yet relying on single risk factors is not advisable in individual cases. Recently, the performance of suicide risk assessment scales was evaluated with unsatisfactory results (Runeson *et al.*, 2017). There is thus a need for a predictive model that could either triage or predict completed suicides in bipolar disorder, but this was beyond the scope of our paper. Recent attempts have shown some progress in the ability to predict suicides (Fazel *et al.*, 2019, Gradus *et al.*, 2019, Walsh *et al.*, 2017), but there is still a lively debate on the usefulness of these models (Belsher *et al.*, 2019).

5.4. Study *IV*: Psychoeducation for bipolar disorder and risk of recurrence and hospitalization–a within-individual analysis using registry data.

Using a sample of 2,819 patients with bipolar disorder, we investigated the effect of psychoeducation. Our analyses showed an effect of psychoeducation on episode recurrences, both overall and for depressive and manic episodes analysed separately, and for psychiatric hospital admission and involuntary sectioning.

The results are generally in line with the combined evidence of previous clinical trials (Bond and Anderson, 2015). However, a well-designed recent study

of the replication of the Barcelona program showed an effect of psychoeducation only in patients with few previous episodes, questioning the general effectiveness of psychoeducation (Morriss *et al.*, 2016). There are notable differences between RCTs and our study. Some RCTs were designed with an active control, something that is not possible in an observational study (Colom *et al.*, 2003, Morriss *et al.*, 2016). In the registry questionnaire, there was also no formal definition of psychoeducation. However, a recent master thesis for registered nurses, found that most Swedish programs were typically six two-hour sessions, and the professions most often responsible for the programs were psychiatric nurses, psychiatrists, and psychologists, in that order (Askland and Ahmad Sadik, 2016). Programs of similar lengths have been shown to be as effective as cognitive behavioural therapy (Parikh *et al.*, 2012). Thus, our study gives further corroborative evidence in the effectiveness of short-term psychoeducational programs. These programs are important, because the long-term programs require commitment, time, and resources that many smaller clinics do not have. Recently, evidence of the effectiveness of web-based applications of psychological interventions has increased greatly (Andersson *et al.*, 2015). Online psychoeducational programs are gaining ground (Hidalgo-Mazzei *et al.*, 2018). An online psychoeducational program has also been designed here in Gothenburg[1]. Such programs might cost-effectively extend the reach of psychoeducation outside specialized clinics.

There are several limitations to the current study. It is an observational study and direct causal conclusions are not possible. Using within-individual analysis, we have attempted to limit the influence of confounding, but time-varying confounding might still influence the result even though we adjusted for age, treatment, and GAF. Our division of the follow-up time into different intervals was done using the annual follow-ups and our results might be influenced by overlap between the administration of psychoeducation and outcome of the previous time-interval and time-varying confounding related to the initiation of psychoeducation. Therefore, we conducted a sensitivity analysis where the time-interval just before psychoeducation was removed. In this

[1] In the video material for the online psychoeducational program created in Gothenburg "psychiatric care staff number 1" is played by the author of this thesis.

analysis, psychoeducation was only associated with lower odds of receiving inpatient care. Although loss of power is also a possible explanation, as many time-intervals were removed in this analysis, the effect of time-varying confounding cannot be excluded.

In summary, this study suggests an effect of those psychoeducational programs that are used in clinical practice. This is encouraging news as those psychoeducational programs that have shown results in clinical trials are often not those used in clinical practice.

5.5. Study *V*: Effect of *CYP2C19* polymorphisms on antidepressant prescription patterns and treatment emergent mania in bipolar disorder

We studied a large sample of genotyped bipolar disorder individuals to test whether treatment patterns and the risk of treatment-emergent mania were associated with *CYP2C19* polymorphisms in bipolar disorder patients treated with citalopram, escitalopram, sertraline, amitriptyline, or clomipramine. We failed to find a substantial influence of *CYP2C19* metabolic phenotypes on treatment discontinuation, switch to another antidepressant, or the risk of treatment-emergent mania.

Previous large-scale attempts investigations of *CYP2C19* metabolic phenotypes and citalopram or escitalopram treatment show conflicting results. A recent study showed better effect and more early side effects among poor CYP2C19 metabolizers compared with extensive metabolizers, but no effect on drop-out, which would be the outcome that is most comparable to our results (Fabbri *et al.*, 2018). In contrast, another recent study utilizing electronic health records (Jukić *et al.*, 2018) found that both ultra-rapid and poor CYP2C19 metabolizers had a higher odds of treatment failure compared with extensive metabolizers. In that study, treatment failure was defined as switching to another antidepressant within one year of the last therapeutic drug monitoring. We could not replicate these results. However, we cannot rule

out that lack of statistical power limited the analyses of switching to another antidepressant treatment in our study.

We noted an association with a higher rate of discontinuation of the tricyclic antidepressants in ultra-rapid CYP2C19 metabolizers compared with extensive metabolizers. We have not seen this association described in the literature, but it conforms nicely with previous guidelines (Hicks *et al.*, 2017) as discontinuation could indicate adverse events. This association did not survive correction for multiple testing but a post hoc analysis showed that the association was concentrated to the first couple of months. Both amitriptyline and clomipramine have active metabolites. If the ratio between drug and metabolite is altered, it could lead to differences in side-effect profile or antidepressant effect that could increase the risk of treatment discontinuation (Hicks *et al.*, 2017).

We also report an association between the *CYP2C19* metabolic phenotypes and treatment-emergent mania, when analysing *CYP2C19* metabolic phenotypes as a continuous variable, with poorer metabolism being associated with a higher risk of treatment-emergent mania. This stands to reason as poorer metabolism would lead to higher plasma concentrations. Notably, this association did not withstand correction for multiple testing.

Aside from the registry related limitations, discussed at the end of this section, it should be noted that we combined the two tricyclic antidepressants clomipramine and amitriptyline despite that most previous research regarding *CYP2C19* metabolic phenotypes and tricyclics are done on amitriptyline; guidelines pertaining to clomipramine are mainly extrapolated from results on amitriptyline (Hicks *et al.*, 2017). We also used treatment discontinuation as an outcome. We assumed that higher rates of treatment discontinuation would be due to lack of efficacy or adverse events. However, successful treatment with antidepressants is also a reason to discontinue antidepressant treatment. We limited the follow-up to twelve months in the main analysis and also used switching to another antidepressant as an alternative outcome to test the robustness of our results. Notably, the suggestive effect seen in the

first analysis regarding tricyclic antidepressants was not replicated when using this second outcome.

To summarize, we report mainly negative results suggesting that pharmacogenetic testing for *CYP2C19* metabolic phenotypes have limited value in clinical practice. The findings suggesting that ultra-rapid CYP2C19 metabolizer might be associated with higher discontinuation rate of tricyclic antidepressant therapy, and that poorer metabolism might be associated with treatment-emergent mania, needs to be replicated in independent samples as they did not withstand correction for multiple testing.

5.6. Limitations

These studies are all registry-based, such studies come with a long list of limitations. Some of these are relevant to several of the studies in this thesis and are therefore disseminated thematically below.

Treatment exposure in register studies must be defined based on a set of assumptions. In three studies (study *I, II, & V*) treatment exposure was determined through a series of dispense dates from the Prescribed Drug Register. Although it seems unlikely that patients would buy a drug twice without using it, actual data on treatment adherence is lacking. Additionally, if certain drugs have lower adherence that impacts the drug's effectiveness in routine clinical practice this should logically be included in the effectiveness estimates. Thus, it could be seen as a feature and not a flaw of the study design. However, the cut-off for treatment discontinuation of three months between drugs dispense dates, used in study *I & II,* is also arguably very conservative, perhaps classifying too many time-periods as non-treated. It does not consider possible stockpiling, differing treatment dosages or prescriptions for "as needed" use. Although this would likely bias the findings towards a false negative (Hayes *et al.*, 2019). We also analysed the data with four (study *I & II*) and six months (study *I & V*) as cut-offs with predominantly similar results. In study *V*, four months was used as a primary cut-off as this is probably a better fit based on Swedish prescription regulations. Another possible bias in these

studies is that the treatment exposure might also measure the effect of being in contact with health care providers and caregivers. However, if this was the case in study *II,* valproate treatment and the negative control, thyroid hormone medication, would show effects on suicide-related behaviour. Importantly, however, lithium does require regular checks of serum levels, and periods of lithium treatment might be associated with more frequent contact with caregivers.

The way in which diagnoses are set in clinical care is not standardized. Thus, the validity of registered diagnoses is often evaluated in painstaking, but very important, validation studies (Kessing, 1998, Rück *et al.*, 2015). In study *I & II,* we defined the patient population based on an algorithm from a previous validation study. The original diagnostic algorithm used two diagnoses of bipolar disorder in inpatient care (Sellgren *et al.*, 2011). We also included outpatient diagnoses which could potentially lead to lower the diagnostic validity of those included. In addition, we could not determine bipolar type 1 or 2 from the National Patient Register, as this is not possible in ICD-10. Yet in study *II,* we had a large subgroup of patients who also had information from BipoläR. Thus, in study *II* bipolar disorder subtype could be determined in at least a subset of patients.

Outcomes, like treatment exposures, can be determined with varying degrees of assuredness in registers. Hospital admission, used in study *I*, is a hard outcome. Very short admissions likely differ from longer ones with respect to disease severity. We used one overnight stay as a lower limit, but we also did a sensitivity analysis where we used three days instead. Suicide-related behaviour including completed suicides, used as outcome study *II & III*, can be sub-divided into determined and undetermined intent. In study *II*, we tested whether there was a difference between these two subgroups and although point estimates were similar the outcome was only significant in the sample using only determined intent.

Two studies used (study *II & IV*) BipoläR. Although this national register includes a large section of the Swedish bipolar patients, coverage is far from

complete and is estimated to be 29%. It is voluntary for both clinics and patients. When compared to the National Patient Register there were no differences in either sex or age distribution (Pålsson and Landén, 2018), however, we cannot exclude inclusion biases.

We used within-individual designs in study *I, II, & IV*. A range of different methods have been developed to reduce confounding in studies of treatment effects. In psychiatric epidemiology, several different strategies have been employed, e.g., propensity score matching (Erlangsen *et al.*, 2015), covariate adjustment (Kessing *et al.*, 2012, Kessing *et al.*, 2011), and within-individual models (Fazel *et al.*, 2014). The primary strength of the within-individual design is that it adjusts for all between-individual confounders, even those that are not measured directly. However, there are also several shortcomings. First and foremost, time-varying confounding can still influence the results. In all the studies we attempted to remedy this in part by adjusting for different confounders such as age, GAF, and length of previous periods of hospital admission. Another route of analyses in all of the three studies was specific sensitivity analyses using either the order of medication, as in study *I & II*, or removing specific time-intervals to observe if the effect of psychoeducation is similar across time (study *IV*). Furthermore, within-individual models are limited insofar that they can only gain information from individuals who have variation in the outcome. This means that individuals who never experiences a hospital admission during follow-up (study *I*) or never experiences a suicide related event (study *II*) cannot contribute information. Thus, the sample contributing information is a high-risk group for the event studied. Patients contributing information in study *I*, where the outcome event was psychiatric hospital admission, are however probably similar to patients eligible in relapse prevention studies. In such studies individuals are randomized after an acute episode, both groups thus have a high risk of affective episodes that require acute interventions. Additionally, the use of only within-individual variation, which also extends to covariates, often results in wider confidence intervals compared to analyses that use both within- and between-individual variation (Allison, 2005).

6. General Discussion

Bipolar is a devastating disorder, and its treatment is a multifaceted endeavour. Several new treatments have been introduced since Johns Cades remarkable discovery of lithium's efficacy in 1949 (Cade, 1949). But the design of clinical trials including exclusion criteria and selective study designs hampers generalizability to the larger group of patients seen by psychiatrists in clinical practise. In 2015, Guy Goodwin, then the president of the European College of Neuropsychopharmacology, compared the mega trial of simvastatin (Collins *et al.*, 2004) to his and his co-workers' study comparing the effectiveness of valproate and lithium in the BALANCE trial (Geddes *et al.*, 2010), n=20,000 versus n= 331. The disparaging conclusion was that the resources needed to conduct large conclusive studies regarding bipolar disorder treatments are absent. However, he also noted that observational studies, especially from large scale national registries, are potentially vast sources of knowledge if confounding can be minimized (Goodwin, 2015). The studies in this thesis are attempts at utilizing the power of observational studies to answer questions relevant to patients treated for bipolar disorder.

In a climate of scarce resources real-world evidence of effectiveness from observational studies has an important role to play as complementary evidence. As observational studies from national registers often contain an unprecedented number of patients the sample sizes are large. They are also non-exclusionary, meaning that they do not remove individuals based on pre-existing conditions; instead they contain all those diagnosed in the population. Notably, the Swedish quality registers, like BipoläR, are voluntary and patients and clinics can choose not to participate, which means that these registers do not cover the whole population. In contrast, most RCTs are done with selected samples that exclude many, or even most, of the patients that appear in routine clinical practice (Wong *et al.*, 2018). Generalizability of such findings are naturally questioned. The issue of generalisability is specifically questioned in enriched trial designs where patients are selected based on their treatment response in the acute phase (Ghaemi and Selker, 2017). Yet, obser-

vational studies have several drawbacks. The foremost is lack of randomization. Randomization removes any selection bias associated with allocation of treatment, eliminating confounding-by-indication. For observational studies, confounding-by-indication can seem like an insurmountable obstruction towards drawing reliable conclusions on treatment effects. some authors argue that the ability to make reliable conclusions from observational studies, or *Real World Evidence*, is a 'myth' due to the inherent lack of certainty regarding potential biases (Collins *et al.*, 2020). Perhaps the most famous example of observational studies drawing false conclusion is the case of postmenopausal oestrogen plus progestin therapy. Large-scale observational studies (Grodstein *et al.*, 1996) showed promising results suggesting that postmenopausal oestrogen plus progestin therapy was a safe treatment that reduced the risk of coronary heart disease. A few years thereafter, randomized clinical trials showed opposite results (Manson *et al.*, 2003). The conflicting results have served as a cautionary tale on the perils of relying on observational evidence (Vandenbroucke, 2004). Three of the studies in this thesis used a within-individual approach (study *I, II & IV*) to limit confounding-by-indication by controlling for all time-stationary confounders. This is an important step as it removes the influence of such factors such as genetic makeup and early life factors. Time-varying factors can still influence the results and control of such factors is important. In addition, the robustness of treatment exposure and outcome definitions should be tested in sensitivity analyses as these definitions are based upon several assumptions.

Our results in study *I* strongly suggest that the effect of atypical antipsychotics is biased by the design in previous relapse prevention studies. This finding was later replicated in a study with a similar design (Lähteenvuo *et al.*, 2018), and in a small but important clinical trial (Berk *et al.*, 2017). The importance of observational studies is even greater when the outcomes or the modifiers of drug effects are scarce and individual with a high risk of the outcome are systematically excluded, like with suicide-related behaviour (Wong *et al.*, 2018, Zimmerman *et al.*, 2016); making even post-hoc analyses of existing trials hard to perform. The specific methodology used in study *I & II* in this thesis was first developed at the Karolinska Institutet and used to assess the impact of ADHD medication on rare outcomes such as criminality (Lichtenstein *et al.*,

2012) and traffic accidents (Chang *et al.*, 2014), where it would be unfeasible and possibly unethical to conduct a randomized trial. Although, trials to examine the efficacy of lithium treatment on suicide prevention exists, they are small and efficacy estimates therefore come with wide confidence intervals (Cipriani et al., 2013a). Similarly, results from meta-analyses can depend upon inclusion or exclusion of very small studies (Roberts *et al.*, 2017). Recently, the trial "NCT01928446: Lithium for Suicidal Behavior in Mood Disorders (Li+)" was cancelled, recruiting only 528 out of the goal of 1862 participants (Katz and Crescenz, 2020) and there is still no definitive trial on the efficacy of lithium in suicide prevention. Our findings from study *II* agree with previous smaller studies suggesting that lithium has a unique anti-suicidal effect. Likewise, actual psychoeducation programs vary widely from those tested in controlled trials (Askland and Ahmad Sadik, 2016). Our observational findings in study *IV* therefore provide key evidence suggesting that the intervention provides beneficial effects also when delivered in clinical practice. Both study *I & II* have been used as corroborative evidence on treatment effects in guidelines for bipolar disorder treatment (Fountoulakis *et al.*, 2016, Goodwin *et al.*, 2016, Grunze *et al.*, 2018, Sakurai *et al.*, 2020). However, the weight of evidence given to large scale register studies with modern methods of confounder adjustment are not clearly defined and there is no consensus as to how such data shall be interpreted when in conflict with trial evidence (Leucht and Davis, 2018).

The study on risk factors for completed suicides in this thesis is a more traditional territory for observational studies. Apart from advancing knowledge of risk factors of completed suicides, it could potentially also serve as a guide for confounder adjustment in observational studies on treatments for suicidal behaviour in bipolar disorder. It could moreover be used to enrich studies on suicidal behaviour with high risk patients for suicide as this type of enrichment might lead to less costly trials and potentially more personalized treatment. The recently cancelled trial of lithium's effect on suicidal behaviour used a high-risk group of veterans with recent suicidal behaviour (Katz and Crescenz, 2020). The lack of clinical trials regarding specific outcomes in bipolar disorder extends to antidepressant treatment where there is limited evidence of efficacy (Fountoulakis *et al.*, 2016) even though the use of

antidepressants in bipolar disorder is widespread, even as monotherapy (Karanti *et al.*, 2016, Rhee *et al.*, 2020). Since there are few detailed treatment studies on antidepressants in bipolar disorder, the possibility of using treatment studies to explore the effects of different *CYP2C19* polymorphisms on antidepressant treatment for bipolar disorder seems unlikely. Therefore, large scale genetic studies with register linkages could provide a valuable alternative to address these research topics, even though we could not show convincing results in this study. In the future, pharmacogenomic testing holds the promise of giving rise to personalized treatment that go beyond the rather crude groupings that our diagnostic groups represent today.

In conclusion, the five studies presented in this thesis have attempted to extend the current knowledge on bipolar disorder treatments and risk factors of completed suicides in bipolar disorder patients. The studies presented in this largely corroborates previous results regarding effects of bipolar disorder treatments. The results suggest effectiveness of several commonly used treatments, both pharmacological and psychoeducational, in reducing risk of psychiatric hospital admission and affective episodes. They also add confirmatory evidence to long held suspicions that previous efficacy estimates of atypical antipsychotics are overstated. We could not show convincing evidence of an influence of polymorphisms of *CYP2C19* on antidepressant treatment patterns and antidepressant treatment emergent mania. Finally, the results from this thesis extend current knowledge on risk factors of completed suicides in bipolar disorder.

7. Future Perspectives

This thesis only approaches a few of the many unanswered questions relating to bipolar disorder treatments and outcomes. In study *V*, we studied the topic of antidepressants in bipolar disorder. However, we did not approach the central question on antidepressant treatment in bipolar disorder, i.e., are they effective in treating bipolar depression? The differences in treatment timing between antidepressant- and maintenance treatments in bipolar disorder makes it more susceptible to time-varying confounding-by-indication as the antidepressants are initiated when treating an acute depressive episode. This makes the within-individual approach less appealing. Using a between-individual approach does however come with its own major limitations. One common belief is that differences seen between RCT and observational studies on postmenopausal oestrogen plus progestin therapy was due to residual confounding and that those who received the treatment were better educated and less prone to cardiovascular outcome. However, this view has been challenged (Stampfer, 2004). An alternative explanation holds forth that the main culprit was study design and specifically the placement of the study-start. Previous studies had relied on medication history. Recalculations using an approach which attempted to mimic a randomized controlled trial, setting the study start at the actual point of treatment initiation, have shown remarkably similar results to those of randomized controlled trials (Hernán *et al.*, 2008). Similarly, the biggest challenge in a good register study of the effect on antidepressants in bipolar disorder would be to figure out a good way to set the initiation date in both the treated and untreated group. If this could be satisfactorily attained, the SWEBIC material offers unique possibilities to adjust for an extensive list of between individual baseline characteristics, as it contains both genetic and clinical information which could result in a very interesting study using, for example, propensity score matching.

The within-individuals analyses made in this thesis all share a vulnerability towards time-varying covariates. There exists an ongoing debate on disorder progression in bipolar disorder, on whether bipolar progression is represented by a subgroup or if bipolar disorder progression could be described in

several different stages (Kapczinski *et al.*, 2014). Using BipoläR, we have recently presented data that for two years of follow-up that show stability in groups estimated based on function and inter-episode remission (Joas *et al.*, 2019). This should be studied further as it could provide valuable information on the possibility of time-varying disease severity that might influence within-individual estimates of treatment effects.

Repurposing existing medications, such as anticonvulsants, have already proven to be useful in bipolar disorder treatment. Several newer studies have investigated other drugs, for example: calcium channel blockers and statins (Hayes *et al.*, 2019, Kessing *et al.*, 2019). However, these attempts still remain in the early stages and very robust sensitivity analyses remain key. Hopefully, new information from the large scale GWAS studies could lead to plausible targets for interventions (So *et al.*, 2016) as they have recently done in schizophrenia (Sellgren *et al.*, 2019). In such cases, register based studies on already existing medication could provide important early evidence. In a similar vein, it would be of interest to widen the range of outcomes studied, using these methods, given the large impact of bipolar disorder on outcomes not directly related to affective episodes. Such outcomes could include job loss and early retirement, outcomes that are relevant for the patients and incur large societal costs (Ekman *et al.*, 2013).

Finally, working with registers and attempting to use observational studies to draw conclusions, with extensive lists of limitations, one often becomes envious of the "magic of randomization" (Collins *et al.*, 2020). In Sweden, some registers have developed new innovative ways of merging the power of randomized controlled trials and national registers into register-based randomized controlled trials (James *et al.*, 2015). These massive undertakings make it possible to conduct randomized trials within routine clinical care, with follow-up done using national registers that can record clearly defined outcomes such as hospital admission and mortality. As far as I know, no such study has been done in psychiatry. One possible candidate would perhaps be the burgeoning field of internet psychiatry, and what better candidate for such a study than the internet-based psychoeducational program developed at the Sahlgrenska Academy.

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