Bipolar Disorders

Subtypes, treatments, and health inequalities

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UNIVERSITY OF GOTHENBURG

Gothenburg 2020

To my family

CONTENTS

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ABSTRACT

This thesis comprises five studies based on prospective, longitudinal data from the Swedish national quality register BipoläR. *Study I* examined the differences between bipolar subtype I and II with respect to clinical features, course of illness, comorbidity, and socioeconomic factors. *Study II* investigated temporal changes in drug prescription patterns in bipolar disorder. *Study III* examined the effectiveness of psychoeducation for bipolar disorder. *Study IV and V* examined health inequalities in the management of bipolar disorder with respect to sex and patients' educational level, respectively.

Results showed noticeable phenomenological differences between the BDI and BDII, where BDII has a different and more complex clinical presentation in terms of illness course and comorbidity (*Study I*). This supports the validity of separating BDI and BDII. Concerning pharmacological treatment, we found that lithium use decreased during the study period, while lamotrigine and quetiapine increased. The use of antidepressants remained unchanged in BDII but increased somewhat in BDI (*Study II*). We found that psychoeducation decreased the risk for depressive and manic episodes as well as inpatient care in routine clinical practice (*Study III*). Lastly, we found differences in the management of bipolar disorder without apparent medical rationale. Whereas women were more likely to receive psychotherapy, antidepressants, benzodiazepines, antipsychotics, lamotrigine, and electroconvulsive therapy, men were more likely to use lithium (*Study IV*). Further, higher education in patients increased the likelihood of receiving psychotherapy and psychoeducation, but decreased likelihood of receiving first-generation antipsychotics, tricyclic antidepressants, and compulsory inpatient care (*Study V*).

SAMMANFATTNING PÅ SVENSKA

Bipolär sjukdom karaktäriseras av återkommande kraftiga förskjutningar i stämningsläge och aktivitetsnivå. Depressiva, hypomana eller maniska sjukdomsskov varvas med symptomfria perioder. Uppdelningen i bipolärt syndrom typ I (BDI) och II (BDII) är etablerad men ej oomtvistad. Sjukdomsförloppet varierar avsevärt mellan individer. Medan en del är fria från skov i flera år, drabbas andra av frekventa och långdragna affektiva skov. Behandling syftar inte bara till att lindra akuta skov utan främst till att förhindra nya skov. Nya läkemedel för bipolär sjukdom har introducerats under 2000-talet och har marknadsförts intensivt. Förutom läkemedelsterapi är psykologisk behandling och patientutbildning viktiga kompletterande åtgärder. Enligt hälso-och sjukvårdslagen är jämlik vård ett övergripande mål vilket innebär att individer ska få lika vård oavsett grupptillhörighet såsom kön, ålder, utbildningsnivå och socialt status.

Denna avhandling bygger på fem delstudier med longitudinella data från det nationella kvalitetsregistret BipoläR. I *studie I* undersöktes skillnader mellan BDI och BDII avseende kliniska egenskaper, sjukdomsförlopp, samsjuklighet och socioekonomiska faktorer. I *studie II* undersöktes förändringar i farmakologisk behandling hos personer med bipolär sjukdom under 2007–2013. I *studie III* undersöktes effekten av patientutbildning för bipolär sjukdom i klinisk praxis. I *studierna IV och V* utforskades om vården vid bipolär sjukdom skiljer sig beroende på patientens kön och utbildningsnivå.

Resultaten i *studie I* visade signifikanta fenomenologiska skillnader mellan BDI och BDII vilket stödjer validiteten av dessa diagnostiska undergrupper. BDII uppvisade ett annat och mer komplext sjukdomsförlopp och mer psykiatrisk samsjuklighet. *Studie II* visade att litiumförskrivning minskade stadigt i bägge bipolära subtyperna, medan lamotrigin och quetiapin ökade under samma period. Behandling med antidepressiva förändrades inte i BDII-gruppen men ökade något i BDI-gruppen. *Studie III* visade att patientutbildning minskade risken för depressiva och maniska skov samt för inneliggande vård. Resultaten från *studierna IV och V* visar att vården vid bipolär sjukdom skiljer sig beroende på kön och utbildning på ett sätt som inte är medicinskt motiverat, eller som kan förklaras av andra faktorer. I *studie IV* fann vi att antidepressiva, lamotrigin, benzodiazepiner, elektrokonvulsiv behandling och psykoterapi var vanligare hos kvinnor, medan litium var vanligare hos män. I *studie V* fann vi att högre utbildning hos patienten var associerat med större sannolikhet att erhålla psykoterapi och patientutbildning, men med mindre sannolikhet att behandlas med första generationens antipsykotika, tricykliska antidepressiva och att få inneliggande tvångsvård.

ACKNOWLEDGEMENTS

Timea Sparding, Head of the Bipolar Outpatient Clinic, Sahlgrenska University Hospital. I thank you for listening, encouraging, understanding, helping, backing me up in clinic issues, representing me in meetings I could not attend, giving practical guidance and being there during the last three years with humour, strength, and warmth offering me support and a deep friendship that I carry with thankfulness.

I thank **my friends** who have stayed at my side despite all our postponed dates, after works, dinners, travels, and phone calls due to work. I promise to catch up.

Lastly, I thank **my mother** for believing in me and offering wings to my dreams, and **my family** for supporting me and giving meaning in my life!

LIST OF PAPERS

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

I. Karanti, A., Kardell, M., Joas, E., Runeson, B., Pålsson, E., Landén, M. Characteristics of bipolar I and II disorder: a study of 8,766 individuals. *Bipolar Disorders.* 2019 November 14.
    doi:10.1111/bdi.12867

II. Karanti, A., Kardell, M., Lundberg, U., Landén, M. Changes in mood stabilizer prescription patterns. *Journal of Affective Disorders,* 2016 May; 195: 50-6.
    doi:10.1016/j.jad.2016.01.043

III. Joas, E., Bäckman, K., Karanti, A., Sparding, T., Colom, F., Pålsson, E., Landén, M. Psychoeducation for bipolar disorder and risk of recurrence and hospitalization – a within-individual analysis using registry data. *Psychological Medicine,* 2019 May 6:1-7.
    doi:10.1017/S0033291719001053

IV. Karanti, A., Bobeck, C., Osterman, M., Kardell, M., Tidemalm, D., Runeson, B., Lichtenstein, P., Landén, M. Gender differences in the treatment of patients with bipolar disorder: a study of 7354 patients. *Journal of Affective Disorders,* 2015 Mar 15; 174: 303-9.
    doi:10.1016/j.jad.2014.11.058

V. Karanti, A., Bublik, L., Kardell, M., Annerbrink, K., Runeson, B., Lichtenstein, P., Pålsson, E., Landén, M. Patients' educational level and management of bipolar disorder. *(submitted)*

ABBREVIATIONS

ADHD	Attention-deficit Hyperactivity disorder
BDI	Bipolar disorder type I
BDII	Bipolar disorder type II
BD NOS	Bipolar disorder not otherwise specified
BipoläR	Swedish national quality register for bipolar disorders
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive therapy
FGA	First-generation antipsychotics
GAF	Global Assessment of Functioning
ICD	International Statistical Classification of Diseases and Related Health Problems
NPR	National Patient Register
PDR	Prescribed Drug Register
RCT	Randomized Controlled Trial
TCA	Tricyclic antidepressants

1 INTRODUCTION

Bipolar disorder, also known as manic-depressive illness, is a recurrent chronic condition characterized by extreme fluctuations in mood state and activity level.

1.1 Bipolar disorder

1.1.1 Historical aspects

About 400 BC, Hippocrates used the terms *mania* and *melancholia* (from Greek *melan* [black] and *chole* [bile]) to describe disturbances in mental health. In 1854, Jean-Pierre Falret described a condition he called *folie circulaire*, in which patients suffered from alternating mood states of depression and mania. And in 1882, the German psychiatrist Karl Kahlbaum used the term *cyclothymia* to describe mania and depression as stages of the same illness.

But it was not until the beginning of the twentieth century that Emil Kraepelin coined the term *manic-depressive psychosis* and differentiated it from *dementia praecox* (later called schizophrenia) by the absence of a dementing and deteriorating course (1). Kraepelin is therefore considered the father of the diagnosis "manic-depressive illness" and its description is close to what nowadays is diagnosed as bipolar disorder type I.

1.1.2 States of bipolar disorder: mania, hypomania, and depression

Bipolar disorder features distinct periods with altered mood states that are referred to as affective episodes, or mood episodes, and defined by specific diagnostic criteria. The criteria have been changing during the years, which is a challenge when contemporary and earlier research findings are compared. In this thesis, we have used the criteria for affective episodes and bipolar disorder according to DSM-IV-TR (2). The criteria has been slightly modified in the latest version of DSM, DSM-5 (3). The most important difference is that while previous editions focused on the mood states, the diagnostic criteria in DSM-5 require that elated mood alterations occur in combination with changes in activity and energy.

Figure 1. *Mood episodes*
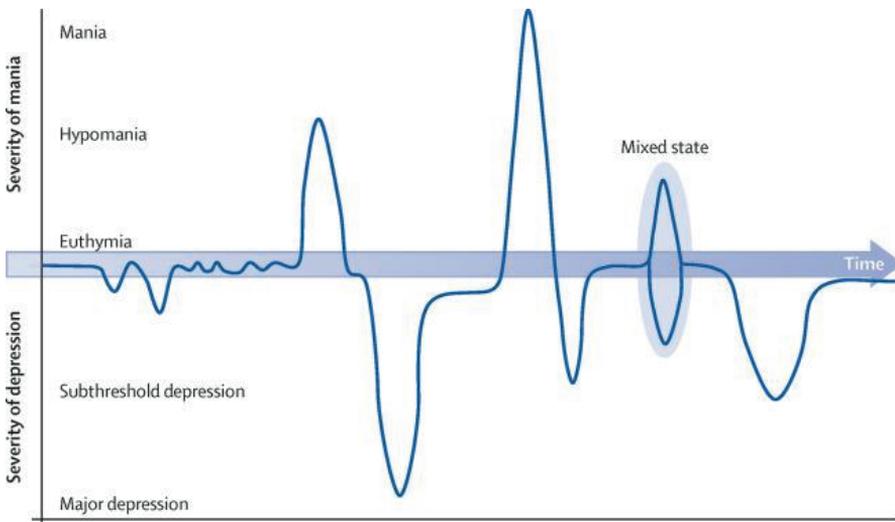
Illustration from "Bipolar Disorder" Grande I. et al. Lancet 2016 (4). Reused with licence (licence number 4718091411484).

A *major depressive episode* must last at least 2 weeks and typically includes depressed mood or loss of interest or pleasure as well as at least four additional symptoms (changes in appetite and weight, changes in sleep and activity, lack

of energy, feelings of guilt, problems thinking and making decisions, and recurring thoughts of death or suicide).

A *manic episode* is a distinct period of abnormally and persistently elevated, expansive, or irritable mood state lasting for at least 1 week, or less if the patient must be hospitalized. The condition is associated with inflated self-esteem, decreased need to sleep, distractibility, excessive physical and mental activity, and overinvolvement in pleasurable behaviour. A manic episode might also encompass psychotic symptoms. According to one estimate, about 75% of patients with an acute manic episode present with psychotic symptoms (5). The delusions are typically mood-congruent with grandiosity and megalomania, but mood-incongruent psychotic symptoms with persecutory delusions are not uncommon (5).

A *hypomanic episode* should last at least 4 days and features similar but less severe symptoms as a manic episode and cannot present with psychotic symptoms. A hypomania should neither cause marked impairment in social or occupational functioning, nor require hospital admission. But the disturbance should be observable by others.

A *mixed episode* should last at least 1 week during which both manic and depressive symptoms occur. In DSM-5, the classification of mixed episode has been removed and instead it has been introduced as a specifier "with mixed features" that can be applied to depressive, hypomanic or manic episodes (3).

1.1.3   Etiology of bipolar disorder

As is true for most mental disorders, the exact etiology and physiopathology underlying bipolar disorder remain obscure. It is known, however, that bipolar disorders are highly heritable. The heritability, i.e., the variance explained by genetic factors, has been estimated to range between 59% to 85% (6, 7). Research has also demonstrated shared common genetic determinants between schizophrenia and bipolar disorders (6) as well as between attention-deficit hyperactivity disorder (ADHD) and bipolar disorders (8). Given that the heritability is less than 100%, there are also environmental factors to consider. A commonly used model to conceptualize why a disorder emerges is the *stress-vulnerability model,* where genetic and environmental factors /life experiences interact with each other.

1.1.4 Subtypes of bipolar disorders

There are yet no biomarkers for the diagnosis of bipolar disorder, and clinical criteria endure (9). In order to diagnose bipolar disorders, it is crucial to follow the course of illness and determine the polarity of affective episodes that the patient has suffered. Cross-sectional diagnosing might be challenging, and the use of life-chart is a useful tool to give an overview of the previous affective episodes and the longitudinal course of the illness.

The different clinical presentations of bipolar disorders are complex and heterogenous. Several ways to subclassify the disorder have been put forward to capture the many phenomenological nuances of bipolar disorders. In principal, the phenomenological discussions have revolved around lumping or splitting. The lumping position suggests that there is a spectrum of bipolar disorder that includes all conditions with fluctuating mood states, but which differ with respect to duration and severity of symptoms. The splitting position postulates that bipolar disorder can be subdivided into multiple separate diagnostic entities. During the late 1990s to early 2000s, as many as eight different subtypes were proposed, a paradigm mainly propelled by Akiskal (10, 11). These subtypes included bipolar type I, I½, II, II½, III, III½, IV, and V. Even if there are still a few supporters of this extensive subclassification scheme, it has proven difficult to distinguish between all these subtypes and diagnose them in a reliable way in a clinical setting and that approach has lost traction. Instead, there are currently four established and broadly accepted subtypes of bipolar disorders that were introduced in DSM-IV (12) and which essentially remain in the latest DSM-5 version (3).

Bipolar disorder type I (BDI) is defined as a clinical course of one or more manic episodes usually accompanied by major depressive episodes. Mixed episodes can also be present in BDI.

Bipolar disorder type II (BDII) is characterized by one or more episodes of major depression and at least one episode of hypomania. No manic or mixed episodes should have occurred in BDII according to DSM-IV (12). In DSM-5, a specifier "with mixed features" is allowed for depressive, hypomanic, and manic episodes (3).

Cyclothymia is a condition with chronic fluctuating subthreshold hypomanic or depressive symptoms for at least two years.

Bipolar disorder not otherwise specified (BD NOS) includes any bipolar disorder that does not meet criteria for any specific bipolar disorder.

Figure 2. Summary of DSM-IV-TR classification of bipolar disorders

Bipolar I	Bipolar II	Cyclothymia	Bipolar Disorder Not Otherwise Specified
One or more manic or mixed episodes, usually accompanied by major depressive episodes	One or more major depressive episodes accompanied by at least one hypomanic episode	At least 2 years of numerous periods of hypomanic and depressive symptoms that do not meet the criteria for depressive or hypomanic episode	Bipolar features that do not meet criteria for any specific bipolar disorder

First, ed. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Edition. Text Rev. Washington, DC. American Psychiatric Association; 2000:345-428

1.1.5   Courses of bipolar disorder

Bipolar disorder constitutes one of the main causes of disability among young people, leading to cognitive and functional impairment and increased mortality, particularly death by suicide (13). A high prevalence of psychiatric and medical comorbidities is typical of affected individuals.

The natural history of bipolar disorder often includes periods of remission, during which the person experience less or no symptoms. Some patients have long periods of remission that can last a decade or more, other patients may suffer from very frequent or long-lasting affective episodes. Even though the course of illness hence is highly variable across individuals, the hallmark of the disorder is *recurrence*, particularly if adherence to treatment is poor. The polarity of the index episode can predict the polarity of subsequent episodes (14). If a patient has two-thirds or more of lifetime episodes being either depressive or manic, then the condition is classified as having a predominant polarity, i.e., depressive or manic dominant polarity (15). Patients with a depressive predominant polarity have been found to be more likely to attempt suicide, have a depressive onset, be diagnosed with bipolar II disorder, and to follow a seasonal pattern (15). Conversely, patients with a predominant manic polarity, have higher risk of substance disorder, present commonly at a young age with a manic episode, and are more likely diagnosed with bipolar I disorder (16).

In a 15-year follow-up study, patients with BDI (17) and BDII (18) were in a euthymic (neutral mood state) for only half of the study period. Depression was the most prevalent mood state, reported during 32% and 52% of the study, respectively. Mixed episodes, hypomania, or mania were recorded during 15%

and 10% of the study period, respectively. Importantly, subsyndromal states were three times more common than full syndromal episodes (17, 18).

Finally, the risk of death due to suicide is very high in bipolar disorder. It has been estimated to be about 20 times higher than that of the general population (19-21).

> In *study I*, we examined the differences between the two main subtypes BDI and BDII with respect to clinical features, course of illness, comorbidity, and socioeconomic factors.

1.1.6   Epidemiology

In a worldwide mental health survey (22), the aggregate lifetime prevalence of bipolar disorder was 0.6% for BDI, 0.4% for BDII, and 2.4% for the bipolar disorder spectrum corresponding to BD NOS. There is some variance in prevalence across countries where US and Colombia had higher prevalence while other parts of the world as India and Japan had lower prevalence of bipolar disorder.

In Figure 3, data from Institute for Health Metrics and Evaluation (IHME) shows the age-standardized prevalence of bipolar disorder worldwide by age. It appears that bipolar diagnosis is more common in younger age groups.

Figure 3. *Prevalence of bipolar disorder by age, Worldwide*
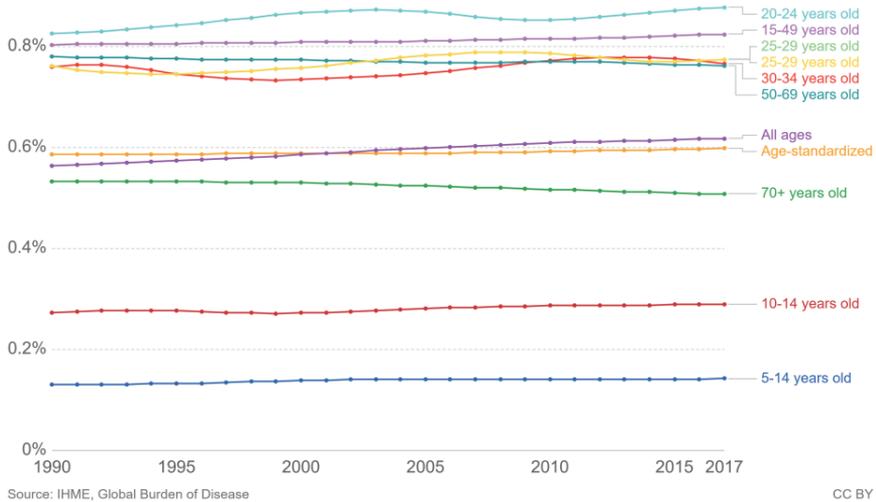
Figure 4. *Prevalence of bipolar disorder by age in Sweden*
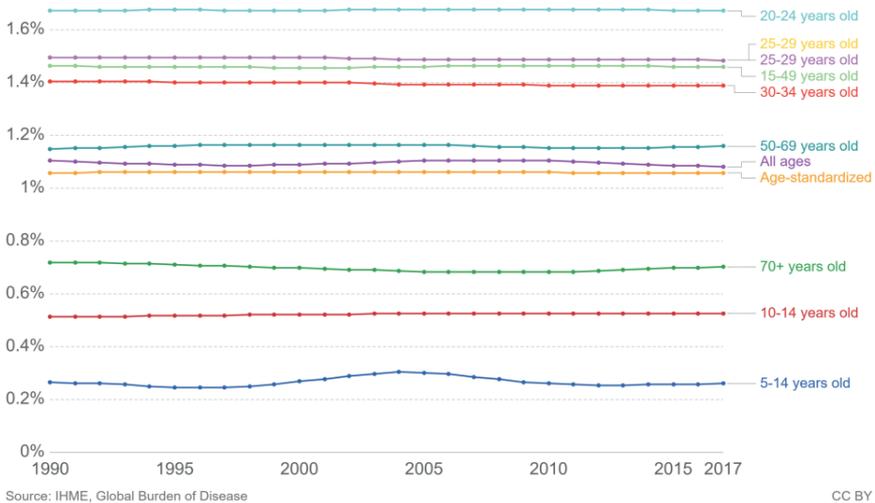
Data from Sweden show a similar picture (Figure 4), with slightly higher overall prevalence compared with the world mean prevalence, but lower prevalence than some countries such as US. Given that bipolar disorder is a life-long disorder, this would on the one hand suggest that the prevalence of bipolar disorder is increasing. But on the other hand, there has been no discernible increase in the prevalence of bipolar disorder diagnoses in Sweden during the latest 20-30 years. One explanation for this apparent inconsistency is that the disease activity might be lower in older age, which would give the impression of lower prevalence in older age.

1.1.7 The societal cost of bipolar disorder

Bipolar disorder can often result in functional and cognitive impairment and a reduction in quality of life (23, 24). In World Health Organization's (WHO) World Mental Health survey (13), bipolar disorder was ranked as the illness with the second greatest effect on days out of role. Bipolar disorder is in fact responsible for the loss of more disability-adjusted life years than all forms of cancer, or major neurologic conditions such as epilepsy and Alzheimer disease (25). This is because bipolar disorder is usually diagnosed in young adulthood.

That the disorder afflicts people in working age also results in high costs for the society (26). In Sweden, the average annual cost per patient was estimated to €28,011 in 2008 (27). Although focus is often on the cost of pharmacological treatments, the high societal costs of bipolar disorder were mainly due to sick leave and early retirement. Such 'indirect costs' accounted for almost 75% of the total costs, followed by cost for inpatient care (13%), and outpatient care (8%). In fact, pharmacotherapy only contributed with 2% of the total societal costs (27). This stresses the importance of optimal treatment of bipolar disorder in order not only to decrease patients' suffering but also to reduce the societal cost.

1.2 Treatment

Because of the recurrence and chronicity of bipolar disorder, it is fundamental not only to treat the acute affective episodes but also to use pharmacological maintenance treatment and psychological interventions to prevent further episodes.

1.2.1   Pharmacological treatment

The main goal for maintenance treatment in bipolar disorders is to stabilize mood and thus prevent new episodes. Mood stabilizers are drugs that are effective against mania and/or depression without risk of increasing the incidence of episodes with opposite polarity.

Novel pharmacological agents for the management of bipolar disorder were introduced in the 2000s that have been approved for treatment of acute episodes as well as maintenance therapy. The treatment armamentarium currently includes antiepileptic drugs (valproate, lamotrigine, carbamazepine) and some atypical antipsychotic drugs (quetiapine, olanzapine, aripiprazole). However, lithium still remains the first line treatment for prophylaxis in bipolar disorder according to international treatment guidelines (5, 12, 28-32).

But what is actually prescribed in routine psychiatric care often differ from the established clinical guidelines (33), and the concordance rate between actual prescriptions and the guidelines is particularly low in bipolar disorder (34-37). The few prior studies that have been conducted in the field include selected populations of patients with bipolar disorder. For example, they included only those treated in primary care (38), only patients with health insurance and thus underrepresenting severely ill or disabled individuals (37) or contrary, only patients from public mental health systems excluding those from private health care with higher income and milder forms of bipolar disorder (39), or only patients treated in tertiary bipolar disorder units (40).

> In *study II*, we investigated changes in drug prescription patterns in bipolar disorder during recent years.

In fact, up to the publication of our study (Study II), there was no representative study of prescribing patterns in bipolar disorder. It was therefore unknown if the launching of the new pharmacological treatments had affected the prescription patterns.

Lithium

The first publication on the prophylactic effect of lithium appeared already in 1963 (41), approximately ten years after the original observations by Cade in Australia (42) and Schou in Denmark (43) on lithium's effect in acute mania. Lithium has been estimated to reduce the risk for manic relapses by 38% and for depressive relapse by 28% (44). We recently estimated that lithium decreased the risk for hospitalization with 34%, the risk for hospitalization due to manic or mixed episodes with 44%, and the risk for hospitalization due to depressive episodes with 39% (45). Importantly, lithium has also been shown

to have an anti-suicidal effect, which is believed to be separate of its mood stabilizing effect (46-50).

Despite the availability of newer treatments, lithium is still considered the most effective treatment for reducing recurrence of episodes (45, 51) and is universally recommended as the first-choice mood-stabilizer for maintenance treatment of bipolar disorder in all international therapeutic guidelines (29, 52, 53). Including data from non-enriched studies, it is argued that lithium should be the single preferred first-line treatment for bipolar disorder (54). Regarding side effects, the most concerning ones have been lithium nephropathy, teratogenicity, and thyroid involvement, and from a patient's perspective also weight gain and tremor. However, recent studies have shown that the risk to the foetus of intrauterine exposure to lithium as well as the long-term risk of renal failure in people treated with lithium are lower than previously reported (55, 56).

The use of lithium in bipolar disorder varies across countries, where Scandinavia and the Netherlands traditionally have higher lithium prescription rate than other countries. In Denmark, 34% of individuals with bipolar diagnosis were prescribed lithium, in the Netherlands 70% (57), while in US lithium was prescribed as the initial drug for only 7.5% of patients compared with 10.1% for atypical neuroleptics and 17.1% for antiepileptics (37).

In Sweden, the rate of lithium prescriptions is considered a quality measure for the care of patients with bipolar disorder with the goal that 70% of patients with BDI should be prescribed lithium (58). Data on quality measures for management of bipolar disorder are followed up annually in the national quality register for bipolar disorder: BipoläR.

1.2.2 Psychological treatment

Although pharmacological treatment is the cornerstone in the management of bipolar disorder, the relapse rates are still relatively high (59). Psychological interventions are therefore recommended as adjunctive treatment in bipolar disorder.

Psychotherapy

There is growing evidence for a range of structured psychological interventions (individual, group, or family) that have been designed for bipolar disorders and are recommended by most current international guidelines. These include cognitive-behavioural therapy, family-focused therapy,

interpersonal, and social rhythm therapy (60). Cognitive-behavioural therapy assists patients in modifying dysfunctional cognitions and behaviours that may aggravate the course of bipolar disorder. Family-focused therapy aims to reduce stress and conflicts in the families of bipolar patients, which may impact on the patient's illness course. Social rhythm therapy aims to balance daily and nightly routines of bipolar patients. Interpersonal therapy provides strategies for solving interpersonal problems. The evidence base varies for different psychotherapies, where cognitive behavioural therapy probably has the best evidence base with impact on symptoms, social functioning, and risk of relapse (61), at least for patients with few previous affective episodes (fewer than twelve episodes) (62).

In this context, one should also keep in mind that patients with bipolar disorders often have comorbid psychiatric disorders, such as anxiety disorders or personality disorders, that might warrant complementary psychotherapeutic approaches.

In Sweden, the public health sector has struggled to meet the demands and needs for psychological treatments, which has resulted in waiting lists for psychotherapy in many psychiatric outpatient clinics, or strict selection of the patients that can be offered psychotherapy. Unavoidably, this has stimulated a market for psychotherapeutic treatments in the private sector, which is not covered by the welfare health system.

Psychoeducation

Psychoeducation, most commonly given in group setting, provides a supportive and interactive intervention in which patients learn about the bipolar disorder and how to cope with it including improved positive attitude to medication (60). The aim of psychoeducation in bipolar disorder is to reduce illness burden and recurrence as well as to improve treatment adherence. Psychoeducational programs offer knowledge about the risk of recurrence, treatment options, risks of drugs and alcohol use, as well as the importance of sleep, routines, and healthy habits in everyday life. The interventions also contain training in identifying the individual early warning signs of emerging mood episodes and early strategies to manage the symptoms.

There is a variety of psychoeducational programs worldwide with both long — up to 6 months (63) — and briefer 6 weeks versions (64). Despite this diversity, all psychoeducational programs include similar key ingredients as described above. Previous studies have demonstrated psychoeducation's positive effect on social functioning (65) and adherence to pharmacological treatment (66, 67). Psychoeducation is recommended in many international

management guidelines for bipolar disorder (29, 32, 68) and its cost-effectiveness make it an appealing strategy. However, the effect of psychoeducation on relapse prevention (63, 69, 70) has recently been questioned; a recent study failed to show an effect on relapse except for patients with few previous mood episodes (71). Moreover, the evidence for psychoeducation is based on studies from academic centres (64) and have excluded patients with comorbidities (63, 72), which makes the study populations less representative for the patients physicians meet in routine clinical setting. Therefore, evidence needs to be completed with observational studies to evaluate the effect of psychoeducational programs in routine clinical practice.

In Sweden, psychoeducation for bipolar disorder is offered by the public health sector in most outpatient psychiatric units. Even within Sweden, there is a variety of psychoeducational programs and there was prior to our study no research studying the effect of the Swedish variants of psychoeducation in a clinical context.

> In *study III*, we examined the effectiveness of psychoeducation in routine clinical practice.

1.3   Inequality in treatment

Equal care is a fundamental tenet in Swedish healthcare and protected by the health- and healthcare act ("Hälso- och sjukvårdslagen" HSL, 1982:763) (73). The goal is that all inhabitants should be offered health care on equal terms regardless of sex, age, ethnicity, socioeconomic status, sexual orientation, or area of residence. There are several forms of treatment disparities and one should not a priori consider all disparities as unwanted or unwarranted. However, when differences in health and health care cannot be explained or justified by medical rationales, then disparities might signal unjustified inequality that we should pay attention to and counteract.

In an international perspective, patients' access to mental health systems differs substantially across countries. Treatment inequalities have generally received more attention in somatic care (74-77) than in mental health care.

Sweden is a welfare state with relatively low health inequality (78, 79). Sweden provides a tax-funded health care system that covers the entire population. Cost for drug treatment is subsidized; cost maximization is set at 2,300 SEK per

year for medication (80). Outpatient health care fees are also highly subsided; after an initial cost of 1,150 SEK, patients qualify for cost free care for the remainder of a 12-month period through the social welfare system. Nevertheless, inequalities in mental health and health care have been reported in Sweden (81, 82), but the situation when it comes to bipolar disorder is unknown.

1.3.1   Gender inequalities

Sex and gender are closely related concepts. Sex is based on biological factors such as reproductive function, concentrations of sexual hormones, the expression of genes on X and Y chromosomes and their effects (83). By contrast, gender is associated with behaviour, lifestyle, and life experience. The use of the terms sex and gender are, however, overlapping in medical literature. Sex and/or gender might influence access to health care, use of the health care system, and behavioural attitudes of medical personnel. Typical gender differences in health care include differences in the use of preventive measures, the prescription of drugs, health insurance and referral for or acceptance of particular therapies (83). Several gender-based differences in medicine have been recognized due to conscious or unconscious perceptions, i.e., gender bias. Gender bias may consist of recognizing differences between men and women when no such differences exist or ignoring gender-specific needs or differences when they do exist (84).

The lifetime prevalence of bipolar disorder appears equal between women and men (85-88). But there are studies suggesting sex differences in clinical presentation where women are more likely than men to suffer from subsyndromal depressive symptoms (89-92), to be diagnosed with BDII subtype, and to suffer from hypomanic (22, 85, 90, 93-95) and mixed episodes (88, 90, 96-98).

When it comes to treatment of bipolar disorder, there is no suggestion that patients' sex should be considered when choosing therapy with the exception of valproic acid (and carbamazepine) due to its high teratogenic risk as well as risk for menstrual abnormities and polycystic ovarian syndrome (99-101). Baldassano et al (102) reported no difference in the use of antidepressants between women and men with bipolar disorder, but there is paucity of data concerning treatment with lithium, mood stabilizers, ECT, and psychotherapy in routine clinical practice. Gender inequalities in treatment have been more studied in somatic care (103-108) than in mental healthcare. As an example,

unjustified gender differences have been found in the treatment of coronary artery disease which has led to adjustments in clinical recommendations (76, 77). The literature is as yet sparse regarding potential treatment inequalities due to gender in psychiatry, let alone bipolar disorder.

> In *study IV*, we investigated whether the treatment of bipolar disorder differs between women and men.

1.3.2 Educational inequalities

Inequality in health care can also stem from bias due to socioeconomic status such as income, education, and occupation. We used education as a proxy measure of socioeconomic status as it has high reliability and validity (109), is generable stable after early adulthood (110), and shapes future occupational opportunities and income potential (111, 112). Interestingly, people with bipolar disorder have been historically shown to have a higher socioeconomic status (5, 113, 114), and also higher likelihood of excellence school performance (115) or higher education (116) compared with the general population.

But the educational level, besides its association to the bipolar diagnosis, might also impact the treatment patients receive. Somatic care has shown examples of such inequality in treatment for myocardial infarctions (75), stroke (117), and osteoporosis (118). Concerning mental health care in general and bipolar disorder, there is a paucity of research on whether socioeconomic status influence the treatment.

> In *study V*, we examined whether the management of bipolar disorder differs between the patients with higher versus lower education.

2 AIM

The overall aim of the thesis was to increase our understanding of the presentation and clinical management of bipolar disorder using a large clinical representative sample of bipolar patients.

The specific study aims were to:

    I.   Study the clinical phenotypes of bipolar disorder type I and II with respect to:
        a. Clinical features and course of illness
        b. Comorbidity with other psychiatric disorders and physical illnesses
        c. Pharmacological and psychological treatment
        d. Socioeconomic factors

    II.   Investigate temporal changes in prescription patterns in bipolar disorder during 2007-2013

    III.   Study the effectiveness of psychoeducation for bipolar disorder

    IV.   Study if management of bipolar disorder is associated with patients' sex

    V.   Study if management of bipolar disorder is associated with patients' educational attainment

3 METHODS

The studies included in this thesis are based on data derived from the Swedish national health quality register for bipolar disorder (BipoläR). In Study II, we complemented with data from the Prescribed Drug Register and the Swedish National Patient register.

3.1 Description of data sources

3.1.1 BipoläR (Studies I-V)

BipoläR is a national Swedish quality assurance register for bipolar disorder management. It was established in 2004 with the main aim to improve the overall quality of care of bipolar patients in Sweden. The register captures individualized clinical data on the disorder, functioning, comorbidity, treatments, and outcomes. Patients are supposed to be followed-up annually yielding a longitudinal dataset on the natural history and clinical course of the disease.

The baseline data includes the primary psychiatric diagnosis [BDI, BDII, bipolar disorder not otherwise specified (BD NOS), cyclothymia, or schizoaffective disorder of bipolar type] as well as comorbid psychiatric axis I disorders and axis II disorders according to DSM-IV (119). It also captures data on somatic comorbidity (axis III in DSM-IV) according to ICD-10 categories (120). Further, psychosocial functioning (axis IV in DSM-IV) is captured along with a Global assessment of functioning (GAF, axis V in DSM-IV). The present severity of the disorder is assessed by Clinical Global Impression Severity Scale (CGI-S). The illness course is captured by documenting the number of depressive, hypomanic, manic and mixed episodes along with psychiatric hospital admissions, sick leave days, compulsory institutional care, criminal convictions, and suicide attempts or self-harm. Educational level, occupation, housing, household composition, and sick benefits are registered. Treatment variables include current psychotropic drugs, electroconvulsive therapy (ECT), and psychological treatments including psychoeducation. Weight and height as well as family history of mood disorder or suicide are also documented.

The first registration can occur at any point during the course of illness, at which a baseline registration is completed. The individuals are then followed up annually collecting data about the last twelve months. Data are entered into a web-based application. The information is collected by the treating

physician, or other staff trained in the diagnosis and treatment of bipolar disorder who have access to clinical data for the patient. Diagnoses in BipoläR are made by the treating clinician according to DSM-IV-TR (2). The formal use of structured psychiatric diagnostic instruments (e.g., SCID or M.I.N.I psychiatric interview) for the new registrations has increased from approximately one third of new registrations in 2015 to 52% in 2018 (121). In order to further increase the validity and quality of data, BipoläR continuously performs logic controls of input data.

Even if BipoläR includes more than 20,000 unique individuals with bipolar disorder in Sweden, it still does not cover the whole population of individuals with bipolar disorder in the country. The coverage of BipoläR is assessed yearly by linking BipoläR with the Swedish National Patient Register. The number of registered unique individuals in BipoläR are divided by the number of unique individuals that have been diagnosed with bipolar disorder at least once during the same year in National Patient Register's outpatient data *plus* the number of unique individuals in BipoläR. The reason for including BipoläR registrations in the denominator is that National Patient Register do not have full coverage either; there are individuals registered in BipoläR who are not registered in National Patient Register. For 2017, the coverage of BipoläR was estimated to 23.1 % of the total number of bipolar disorder patients receiving outpatient care for bipolar disorder in Sweden (121). It should be noted that this coverage estimate is based on the number of individuals registered in a particular year, e.g., 2017, and may fluctuate from year to year. The number of unique individuals with *any* registration in BipoläR is much larger (currently N=23,482) than the number that are followed up every year (N= 4,758 follow-ups and a total of 6,160 entries during 2017). Even though the BipoläR coverage of the total bipolar disorder population is less than the National Patient Register, it has the advantage of containing more fine-grained information about clinical variables and subtypes of bipolar disorder allowing for in-depth analysis not possible in National Patient Register. For example, *Study I* would not have been possible to do using National Patient Register because the ICD-10 does not reliably differentiate between bipolar I and II disorder.

The inclusion in BipoläR is voluntary both for the physician as well as for the patient. Registering units include both private and public psychiatric outpatient health care units and cover most health care regions in Sweden. By 2019, more than 240 psychiatric outpatient units and more than 2,400 registered users across Sweden were joined to BipoläR. In total, there are 23,482 unique baseline registrations and 46,010 follow-up registrations yielding 69,500 accumulated registrations in BipoläR (Figure 5) (121).

Figure 5. *Number of accumulated baseline-and follow-up registrations during the period 2004-2018*
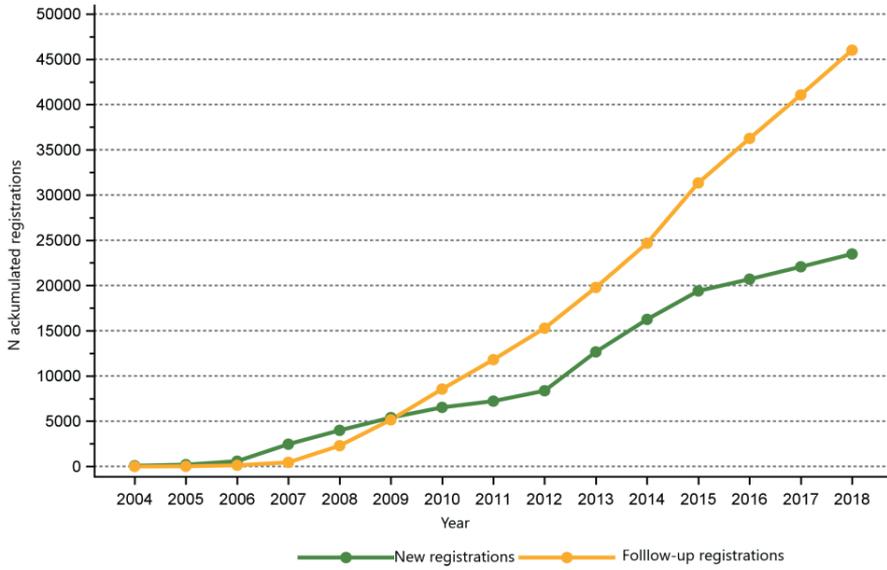
Figure 6. *Distribution of age and sex in BipoläR in 2018*
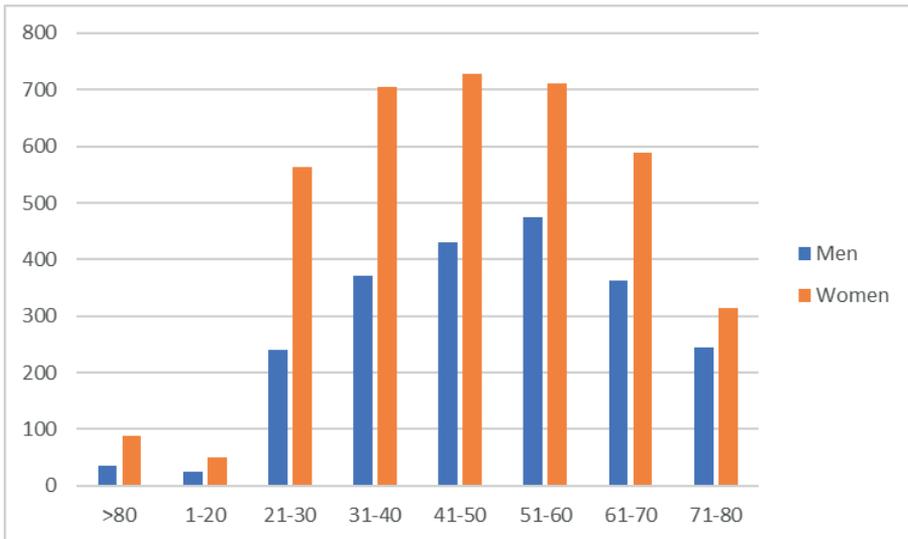
Figure 7. *Comparing the percentage of women during period 2007-2017 in BipoläR and National Board of Health and Welfare (Socialstyrelsen)*
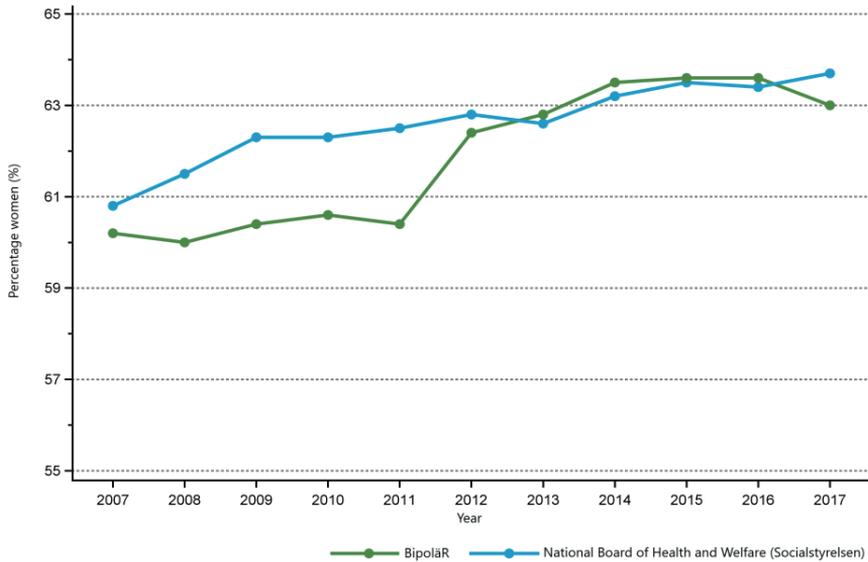
The sex distribution in BipoläR is uneven with an overrepresentation of women (63% of the registered individuals) and the same distribution remains in 2018 (Figure 6) (121).

This is somewhat surprising given that recent international studies have not shown differences in the prevalence of bipolar disorder between women and men (5, 22, 122). A comparison, though, with the general populations as well as to other large bipolar study samples (123-125) shows similar sex distribution as in BipoläR (Figure 7). The National Patient Register also shows that more women than men are diagnosed with bipolar disorder in Sweden. BDII, BD NOS and schizoaffective syndrome of bipolar type have the highest rate of women in BipoläR.

The mean age of the registered individuals in BipoläR is 49 years (121). The mean age of individuals with BDI, BD NOS and schizoaffective disorder of bipolar type is higher than individuals with BDII and cyclothymia.

Concerning the distribution of bipolar subdiagnoses in BipoläR, it is worth noticing that until 2012, BDI was the most frequent in BipoläR. However, BDII has been continuously increasing during the recent years, and in 2018

BDII is the most frequent subdiagnosis in BipoläR (Figure 8) (121). The National Patient Register (NPR) shows that the diagnosis of bipolar disorder has been increasing in recent years in Sweden, but the NPR does not contain accurate information about bipolar subtypes. Therefore, we do not have data to confirm the increase of BDII in other registers in Sweden, but the trend with increasing prevalence of BDII is not surprising given the attention that bipolar disorder has been given the last years.

Figure 8. Distribution of bipolar subdiagnoses in BipoläR during 2008-2018
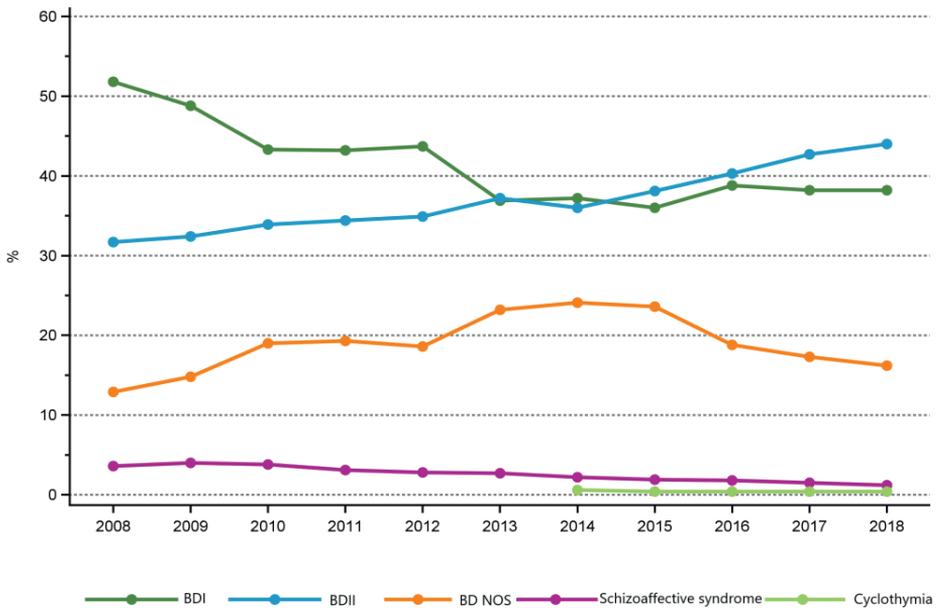
3.1.2   Prescribed drug register (Study II)

The Prescribed Drug Register contains individualized data for all prescriptions dispensed in Sweden since July 2005 (126), based on mandatory reporting from the state-owned National Corporation of Swedish Pharmacies.

3.1.3   Swedish National Patient Register (Study II)

The Swedish National Patient Register includes diagnosis for all psychiatric inpatient admissions since 1973, and all outpatient psychiatric outpatient admissions, excluding primary care, since 2001 (127, 128). The register contains discharge date, main diagnosis and secondary diagnoses based on the International Classifications of Diseases (ICD). The coverage for the inpatient care is full since 1973 and >90% of admissions have a registered main diagnosis. For the outpatient part, the coverage has increased gradually from 18.2% in 2001 to 87.3% in 2012 (129). As mentioned above, there are no data on subtypes of bipolar disorder, as ICD does not have a reliable classification system in place to distinguish the different bipolar subtypes.

3.2   Ethical considerations

According to Swedish law, registration in Swedish quality registers follows an opt-out procedure where patients must be informed that data are recorded. Patients may decline to participate ('opt-out'), in which case data cannot be recorded. Patient can also at any time have their data deleted. De-identified data may be used for research purposes provided that the research project has been approved by an ethical review board.

The Regional Ethics Committee in Gothenburg, Sweden (Dnr 294-11) has approved the studies included in this thesis. All analyses were conducted on a de-identified dataset where neither individual patients nor physicians can be identified or traced in the dataset.

3.3   Statistics

3.3.1   Study I

We used baseline registrations from BipoläR for the period 2004–2013. We restricted data analysis to this period because definition and wording of some variables changed from 2014, which would obfuscate data analyses. We excluded cases where the registered affective episodes were incompatible with the bipolar subdiagnosis, i.e., patients with BDI with no recorded manic episodes, or patients with BDII with recorded manic episodes. The remaining

study cohort was 8,766 individuals whereof 4,806 with BDI and 3,960 with BDII.

We performed two logistic regression analyses for each variable, one unadjusted and one adjusted for sex and age. For the analysis of occupational status and self-sustainability, we only included individuals younger than 66 years old, since 65 is the most common age for retirement in Sweden. Concerning the lifetime number of affective episodes, we additionally adjusted for the duration of illness. The duration of illness was estimated by subtracting the 'age at first contact with caregiver due to mental health problems' from the age at registration. We excluded individuals who had their first contact with a caregiver before 8 years of age, because this is likely to indicate child-onset psychiatric disorders rather than the onset of bipolar disorder. We performed a logistic regression analysis for the lifetime number of depressive episodes by dividing the sample into three groups: i) no episode, ii) 1-3 episodes, and iii) >3 episodes. By definition, BDII patients must have had at least one hypomanic episode and BDI patients must have at least one manic episode why we used two groups in the logistic regression: i) 1-3 and ii) >3 elated (manic and hypomanic) episodes.

3.3.2   Study II

We used data from 32,019 registrations (baseline and annual follow-ups) for BDI and BDII during the period 2007-2013. We performed three logistic regression models: In the first, we used mood stabilizers and antidepressants as outcome and adjusted for confounding factors such as sex, age, and bipolar type. In the second, we stratified for sex and adjusted for bipolar type and age as confounders. In the third, we used changes in drug prescription as outcome and adjusted for sex and age.

We performed sensitivity analyses using data from with NPR and PDR for the same period in order to get complete coverage of the Swedish population. We performed chi2 test to determine if changes that occurred between 2007 and 2013 were statistically significant.

3.3.3   Study III

We used baseline data from 12,850 individuals with 31,470 unique visits (baseline registrations and annual follow-ups) entered in BipoläR until late of

2013 when the extraction of data for this study took place. The number of individual follow-ups varied between 1 and 10. The baseline registration captures if a patient ever has received psychoeducation, and the annual follow-up captures psychoeducation during the last 12 months.

We divided the data into time periods, each one consisting of a baseline measurement indicating whether the person had or had not received psychoeducation, followed by the subsequent measurement indicating the outcome (i.e., if the person had suffered from affective episodes, been hospitalized or made suicide attempt during the last 12 months). As treatment periods, we included all periods after the registration at which it was first documented that the patient had received psychoeducation.

We excluded follow-ups that occurred earlier than 9 months or later than 2 years after the preceding registration in order to decrease variability in time between the visits. We also excluded patients who have received psychoeducation already in the baseline registration, which means that subjects were psychoeducation-naïve when entering the study. Furthermore, the first 3 registrations for each person had to include information on psychoeducation in order to be able to construct at least two time-intervals. We performed analyses in the remaining sample consisting of 2,819 individuals. Of them, 402 subjects had registered psychoeducation at any follow-up and therefore could contribute data for studying effectiveness of psychoeducation. For a schematic view of the sample selection, see Appendix.

We performed conditional logistic regression stratified on individuals. To circumvent confounding by indication, we used a within-individual design in which the individual serves as his/her own control. The outcome variables were: any affective episode, depressive episode, elated or mixed episode, inpatient care, involuntary hospitalization, and self-harm or suicide attempts. Covariates in the model were: GAF-symptom score, age, and treatment with mood stabilizers (lithium or antiepileptics). We performed a supplementary between-group model analysis adjusted for the same covariates and we used logistic generalized estimating equation model (GEE) to account for the correlation between observations on the same individual.

Finally, we performed four sensitivity analyses. First, we used only the first interval with psychoeducation to eliminate attenuation of the effect of psychoeducation over time. Second, we excluded the time segment immediately before psychoeducation to eliminate the bias of patient's status on the indication for receiving psychoeducation. Third, we computed time intervals where we used measure of psychoeducation and outcomes form the

same visits in order to exclude that psychoeducation occurring early in a time segment might influence the outcome in the same time segment. Finally, in the above-mentioned computed time intervals, we excluded ambiguous observations where outcome might have occurred before psychoeducation.

3.3.4   Study IV

We analysed baseline registrations for 7,354 individuals in BipoläR for the period 2004-2011. The association between sex and treatment modalities was analysed using logistic regressions where female sex was chosen as reference category. We adjusted for age, bipolar subtype, GAF-symptom level, comorbid anxiety disorders, comorbid substance disorder, previous suicide attempts, and number of depressive, manic, and mixed episodes coded as "none", "1-3 episodes", and "4 or more episodes". We tested for multicollinearity using the variance inflation factor (VIF); no signs of multicollinearity were found. We performed separate analyses for BDI and BDII.

Additionally, we performed a subanalysis for patients in reproductive age (45 years old or younger), in order to elucidate sex differences in the use of valproate considering its significant teratogenicity. Finally, we conducted a sensitivity analysis excluding the 27 registrations that occurred during pregnancy since pregnancy can affect the choice of treatment; the results remained the same.

3.3.5   Study V

We included patients with bipolar disorder entered in BipoläR during the period 2004–2013. We did not include patients included after 2013 since BipoläR changed the registration form 2014 and the educational variable was excluded. We excluded patients with schizoaffective disorder or other comorbid psychotic syndrome to ensure that antipsychotics were prescribed for bipolar disorder. Furthermore, we excluded patients with autism spectrum or mental retardation as these conditions impact directly on educational level. Finally, we excluded individuals younger than 22 years of age and those with ongoing education as they might not have reached their highest level of education.

We analysed 10,065 patients with bipolar disorder, whereof 4,289 with BDI, 4,020 with BDII, and 1,756 with BD NOS (n=1,756) using binary logistic regression in order to investigate the association between patients' educational

level and pharmacological and psychological interventions. We calculated odds ratios after adjusting for age and functional level as measured by GAF-function score. We included additional covariates in the model adjusting for factors specific to treatment variables. For lithium and lamotrigine, we adjusted for bipolar subtype since lithium is more likely to be prescribed in BDI and lamotrigine in BDII. For antipsychotic treatment, we adjusted for number of elated and mixed episodes during the last 12 months, and for antidepressants and ECT, we adjusted for number of depressive episodes during the last 12 months as the likelihood to receive these treatments is higher for the respective mood states. We finally adjusted for comorbid anxiety disorders in respect to treatment with benzodiazepines and comorbid personality disorders in respect to psychotherapy.

We performed two sensitivity analyses. First, we excluded all individuals younger than 26 years of age to minimize the risk of ongoing education; the results remained the same and data are not shown. Second, we stratified the study population according to age to minimize the risk of an age cohort effect with different educational level across the generations by dividing the cohort into three groups: i) subjects between 22-44 years old, ii) 45-64 years old and iii) older than 64 years old.

4 STUDY I: BIPOLAR SUBTYPES I AND II – THE CLINICAL PHENOTYPES

4.1 Aim

The aim of this study was to investigate the phenotypic differences between BDI and BDII with respect to clinical features, illness course, comorbid conditions, suicidality, and socioeconomic factors in a large representative clinical sample of bipolar patients diagnosed according to recent diagnostic criteria according to DSM-IV.

4.2 Results

We found clear differences between BDI and BDII that do not inevitably follow from the operational diagnostic criteria.

4.2.1 Clinical features and course of illness

Subjects with BDII were more likely to have a family history of mood disorder (unipolar depression, bipolar disorder, dysthymia or suicide events in a 1st, 2nd, or 3rd degree relative) than persons with BDI. They had slightly higher GAF function score, but lower GAF symptom score than BDI, which indicates better function level but more symptom burden in BDII. The BDII group had higher prevalence of suicide attempts, whereas the likelihood of psychiatric inpatient care was half of that of BDI. BDII were older than BDI at first contact with caregiver due to mental health problem, but younger at first signs of mental illness. Subjects with BDII had higher prevalence of lifetime depressive episodes but had less lifetime elated episodes than BDI after adjusting for estimated duration of illness. We found no differences between the two subtypes regarding the total GAF score, sick leave days, sentence to prison or other legal sanction in the last 12 months prior to registration in BipoläR (Table 1).

Table 1. Clinical features and course of illness

	N	BDI	BDII	aOR[a)b)]	95% CI
Family history of affective disorder (% within bipolar type)	5098	1664 (58.6)	1496 (66.2)	1.34	1.19-1.50
GAF-function level, mean (SD)	8489	66.4 (13.9)	66.6 (12.6)	1.003	1.000-1.007
GAF-symptom level, mean (SD)	8488	66.5 (13)	65.4 (11.8)	0.996	0.993-1.000
GAF-total, mean (SD)	4914	63.4 (13.6)	63.4 (11.8)	1.00	0.998-1.007
History of suicide attempts (% within bipolar type)	8364	1613 (35.3)	1552 (40.9)	1.12	1.02-1.23
Sick leave days in the last 12 months, mean (SD)	8735	119 (152)	118 (147)	1.00	0.999-1.000
Hospitalization in the last 12 months (% within bipolar type)	3656	405 (8.4)	219 (5.5)	0.52	0.43-0.63
Age at first contact with caregiver due to mental health problem, mean (SD)	4692	27.6 (11.8)	27.4 (12.2)	1.019	1.013-1.025
Age at first signs of mental disorder/illness	4802				
18-24 years old (% within bipolar type)		741 (28.0)	471 (21.9)	0.57	0.49-0.66
>25 years old (% within bipolar type)		1054 (39.8)	609 (28.3)	0.58	0.50-0.67
<18 years old (% within bipolar type)	Reference category	856 (32.3)	1071 (49.8)		

Sentenced to prison, youth custody or other legal sanction in the last 12 months (% within bipolar type)	4910	29 (1.1)	25 (1.1)	1.03	0.60-1.78
Number of depressive episodes [c]	8766				
None (% within bipolar type)	Reference category	280 (5.8)	38 (1.0)		
A few 1-3 (% within bipolar type)		1351 (28.1)	563 (14.2)	3.1	1.8-5.3
More than 3 (% within bipolar type)		3175 (66.1)	3359 (84.8)	11.4	6.7-19.2
More than 3 manic or hypomanic episodes[c]	8766	3941 (82.0)	2498 (63.1)	0.374	0.34-0.41

[a] *aOR >1 indicates that the variable is more frequent in BDII than BDI*
[b] *The results are adjusted for sex and age*
[c] *The results are adjusted for sex, age and duration of illness.*

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4.2.2 Comorbidity

The cross-sectional rate of comorbid disorders differed significantly between the two subtypes (Table 2).

Our findings show that BDII had higher prevalence of overall psychiatric comorbid disorder as well as higher prevalence of specific psychiatric disorders, i.e., anxiety disorders, eating disorders, ADHD, and personality disorders, but not substance use disorders. BDI had on the other hand higher body mass index (BMI) and higher rate of endocrine, nutritional, and metabolic diseases.

Table 2. Comorbid conditions

	N	BDI	BDII	aOR[a),b)]	95% CI
Psychiatric comorbidity (% within bipolar type)	8463	1024 (22.1)	1195 (31.3)	1.41	1.28-1.56
Substance use disorder (% within bipolar type)	8463	257 (5.5)	190 (5.0)	0.93	0.76-1.13
Anxiety disorder (% within bipolar type)	8463	440 (9.5)	586 (15.3)	1.54	1.35-1.76
Eating disorder (% within bipolar type)	8463	57 (1.2)	129 (3.4)	2.07	1.51-2.85
ADHD (% within bipolar type)	8463	129 (2.8)	180 (4.7)	1.41	1.11-1.78
Personality disorder (% within bipolar type)	8463	121 (2.6)	170 (4.5)	1.44	1.13-1.83
Somatic comorbidity (% within bipolar type)	8558	1555 (33.1)	1208 (31.3)	1.03	0.94-1.13
Thyroid involvement over the last 12 months under treatment with lithium (% within bipolar type)	2350	324 (6.7)	167 (4.2)	0.84	0.68-1.04
BMI, mean (SD)	8503	27.1 (5.0)	26.6 (5.2)	0.99	0.98-0.995
Hyperglycaemia over the last 12 months (% within bipolar type)	3656	166 (3.5)	104 (2.6)	0.87	0.67-1.13
Diseases of the circulatory system (% within bipolar type)	8475	311 (6.7)	175 (4.6)	0.90	0.74-1.10
Endocrine, nutritional and metabolic diseases (% within bipolar type)	8490	611 (13.1)	408 (10.6)	0.85	0.74-0.97

[a)] *aOR >1 indicates that the variable is more frequent in BDII than BDI*
[b)] *The results are adjusted for sex and age*

4.2.3   Treatment

We found no differences in the rate of polytherapy (two or more medications) between the two bipolar disorder subtypes (BDI 70.4%, BDII 71.3%) or the number of medications they received [median value was 2 for both subtypes and mean value was 2.46 (BDI) and 2.45 (BDII)]. Neither did the rate of persons without medication differ between the two subtypes (3%).

However, subjects with BDII were more likely to receive antidepressants, lamotrigine, and psychotherapy. BDI patients were more likely to receive ECT, treatment with any antipsychotic as a group (especially olanzapine), treatment with any mood stabilizers (especially lithium and valproate). The use of benzodiazepines or quetiapine did not differ between the two subtypes. Finally, BDI patients were more likely to receive psychoeducation, while BDII patients were more likely to have received psychotherapy (Table 3).

Table 3. Treatment

Treatment (% within bipolar type)	N	BDI	BDII	aOR[a), b)]	95% CI
Antidepressant drug	8766	1644 (34.2)	2175 (54.9)	2.37	2.17-2.59
Benzodiazepine	5110	1142 (23.8)	900 (22.7)	1.01	0.90-1.13
Any antipsychotic drug	8766	2053 (42.7)	1061 (26.8)	0.47	0.43-0.52
Olanzapine	8766	727 (15.1)	275 (6.9)	0.43	0.37-0.50
Quetiapine	8766	543 (11.3)	521 (13.2)	1.07	0.94-1.22
Any mood stabilizer	8766	4207 (87.5)	3311 (83.6)	0.77	0.68-0.87
Lithium	8766	3297 (68.6)	1771 (44.7)	0.40	0.37-0.44
Lamotrigine	8766	743 (15.5)	1452 (36.7)	2.88	2.60-3.20
Valproate	8766	626 (13)	327 (8.3)	0.61	0.53-0.70
Psychotherapy (>10 sessions)	8766	2845 (59.2)	2794 (70.6)	1.47	1.34-1.61
Psychoeducation	8766	1246 (25.9)	906 (22.9)	0.77	0.69-0.85
ECT	8498	1104 (23.9)	598 (15.4)	0.66	0.59-0.74

[a)] *aOR >1 indicates that the variable is more frequent in BDII than BDI*
[b)] *The results are adjusted for sex and age*

4.2.4   Socioeconomic factors

BDII subjects were more likely to have children, do well in ordinary housing, working or study, be self-sustained, and have a post-secondary education. The rate of single-person household versus shared household as well as the occurrence of psychosocial factors did not differ between the subtypes (Table 4).

Table 4. Socioeconomic factors

Socioeconomic factors (% within bipolar type)	N	BDI	BDII	aOR[a), b)]	95% CI
Own children	5043	1758 (62.6)	1352 (60.5)	1.29	1.12-1.47
Ordinary housing	5096	2657 (93.6)	2178 (96.5)	1.80	1.37-2.36
Psychosocial factors	8569	1390 (29.5)	1234 (32)	1.004	0.91-1.10
Educational level	8205				
Not completed elementary school		300 (6.7)	177 (4.7)	0.66	0.54-0.80
Completed elementary school		879 (19.7)	634 (17.0)	0.83	0.73-0.94
Completed high school		1610 (36.0)	1429 (38.3)	0.90	0.81-0.995
Education higher than high school (at least 2 years)	Reference category	1683 (37.6)	1493 (40.0)		
Occupation (> 50%)	7014	1864 (49.9)	1934 (59.1)	1.38	1.25-1.52
Self-sustainability vs social assistance/disability pension	8195	2643 (58.6)	2213 (60.1)	1.16	1.06-1.27
Household composition (% within bipolar type)	8195	1309 (47.5)	991 (45.3)	0.92	0.82-1.03

[a)] *aOR >1 indicates that the variable is more frequent in BDII than BDI*
[b)] *The results are adjusted for sex and age*

4.3 Discussion

Although BDI and BDII are well established subtypes and included in DSM-IV (2) as well as in its latest version of DSM-5 (3), voices have recently been raised suggesting that separating the two subtypes is unjustified since it is a matter of severity grade of the same disorder (130-132). As late as in 2019, researchers argued that BDII has served its purpose—which was to acknowledge that bipolar disorder is a heterogenous illness demanding closer clinical examination of the various manifestations—and therefore should be abandoned. Some researchers have gone so far as to suggest that BDII is a myth and the category does not exist as a separate subtype (132). In the light of these scientific concerns—and that previous literature have been partly contradictory and partly out-of-date—our study adds importantly to the differences between BDI and BDII in a current, large, and representative study population of bipolar disorder diagnosed with modern criteria.

Our findings confirm previous literature that BDII has more often a family history. This has previously also been used as an indicium for including BDII as a separate subdiagnosis in DSM-IV (133). Regarding age at onset, the literature has been contradictory with some studies showing younger age at onset of BDII (134), some showing the opposite (135-137), and some showing no differences between the subtypes (138-143). Our study suggests these inconsistencies can be reconciliated by considering how age at onset is defined. We showed that BDII was younger at age of first signs of mental illness, but in fact older at age of first contact with caregiver due to mental health problem. A possible explanation for the early age of symptom onset in BDII is early onset of comorbid conditions such as ADHD, which is more frequent in the BDII group.

Our results on prevalence of affective episodes are in line with previous literature that showed higher rate of depressive episodes in BDII (137, 138, 141, 144, 145) and higher rate of elated episodes in BDI. Given the fact that elated episodes and specifically manic episodes are more likely to warrant inpatient care, our finding that BDI had higher risk for inpatient care than BDII is rational. This is also in concordance with previous studies (137, 142, 146). BDI is more common among men and BDII more common among women as proposed also by earlier literature (136, 147).

Furthermore, our study strengthens the evidence that BDI has worse psychosocial functioning than BDII (142, 148) despite that BDII has higher burden of symptom. The latter likely mirrors more subthreshold symptoms (137, 141, 144, 149) or higher comorbidity in this group. In our study, persons

with BDII had on average higher education than persons with BDI. We did not find differences with respect to criminal behaviour, but the events were few and analyses hampered by low statistical power.

Finally, we showed a clearly increased comorbidity with psychiatric disorders as anxiety disorders, personality disorders, ADHD, eating disorders in BDII compared to BDI with odds ratios ranging from 1.4 to 2.1. Our findings are in accordance with most previous studies (138, 141, 143, 150-153) and mirrors similar rates with the European studies while the American studies show even higher comorbidity rates. Interestingly, the rates of substance use disorder did not differ between subtypes. A possible explanation for this is that in Sweden patients suffering from both substance use disorder and bipolar disorder are treated often by addiction outpatient clinics and therefore may be not adequately represented in our study material derived from BipoläR.

The differences in treatment between the two subtypes were significant. Approximately half of patients with BDII received antidepressants compared with one third of patients with BDI. Lamotrigine was also more common in BDII groups. These differences are expected given that BDII has more depressive episodes and lamotrigine is used to prevent depressive episodes (154, 155). In the same way, antipsychotics and mood stabilizers were more common in BDI which is also understandable given their antimanic effect (44, 155). The use of quetiapine was equal between the groups probably due to its balanced effect on both manic and depressive conditions. Surprisingly, the use of benzodiazepines did not differ between BDI and BDII despite the higher rate of comorbid anxiety disorders in BDII. Finally, BDII received more psychotherapy than BDI which might reflect the higher rate of psychiatric comorbidity, especially personality disorders in BDII.

4.4   Conclusion and significance

So, to Malhi's (130) question "what the hype about the subtype? It is all the same", the answer is no in my view. Our study, the largest to date with a clinical representative patient population of almost 9,000 subjects with bipolar disorder diagnosed by current diagnostic criteria suggests that the two subtypes represent different clinical phenotypes. BDI shows more hospitalizations, lower psychosocial functioning, and lower educational attainment while BDII groups features a more complex picture with early debut of symptoms, more frequent comorbid psychiatric conditions, more frequent depressive episodes and suicide attempts. I would argue that our study lends support to the validity

of BDII as a distinct separate subtype of bipolar disorder. Some of the findings presented herein might also guide diagnostic decisions early in the course of illness. For example, early onset of mental health problems with a history of eating disorders, anxiety disorders, ADHD, or personality syndromes and frequent depressive episodes might herald BDII.

It is also known that BDII has lower rate of switching to antidepressants than BDI (156, 157) and that individuals with BDII are more likely to have a positive effect of monotherapy with antidepressants (158, 159). The different pharmacological response between the subtypes supports further the distinguishing of the two subtypes from a clinical point of view.

Adding to the merit of separating the two bipolar subtypes is growing evidence from recent neuroimaging studies suggesting that BDI and BDII differ structurally in several brain areas with partly unique neurobiological characteristics for the subtypes (160-164). Even recent genetic studies point to partly unique differences between the subtypes and suggest a distinction in etiology between BDI and BDII. BDI appears closer genetic to schizophrenia (165, 166) while BDII closer to unipolar major depression (166), or anxiety disorders (165).

In conclusion, our standpoint aligns with that of Post's (167), that the advantages for keeping the separation between the two subtypes supersedes the arguments for dropping it. To cite Post, "if you cannot name it, you cannot study it". If BDII disappears, we will not know how future studies relate to the older literature where the subtypes were studied separately. And studies on genetic, pathophysiological and drug response differences between BDI and BDII would of course not be possible (167).

5 STUDY II: CHANGES IN THE PRESCRIPTION PATTERNS IN BIPOLAR DISORDER

5.1 Aim

The aim of this paper was to investigate possible changes in the prescription of mood stabilizers and antidepressants for bipolar disorder during the recent years in a representative study population for individuals with bipolar disorder.

5.2 Results

We showed (Figure 9) that lithium decreased steadily in both BDI and BDII during the study period, while the use of lamotrigine and quetiapine increased. The use of antidepressant remained principally unchanged but increased somewhat in BDI. The use of valproate decreased in BDII and the use of olanzapine decreased somewhat among women.

Sensitivity analyses using the PDR and NPR confirmed our findings from BipoläR. Furthermore, results from PDR showed that the total number of lithium prescriptions in Sweden increased slightly during the same period but linking data to the NPR revealed that this slight increase was not proportional to the increased prevalence of patients with bipolar diagnosis. This therefore gives a relative decrease in lithium prescription for individuals with bipolar diagnosis.

Figure 9. *Prescriptions of mood stabilizers and antidepressants by bipolar subtype. A) Bipolar type I. B) Bipolar type II. Data from the quality register BipoläR.*
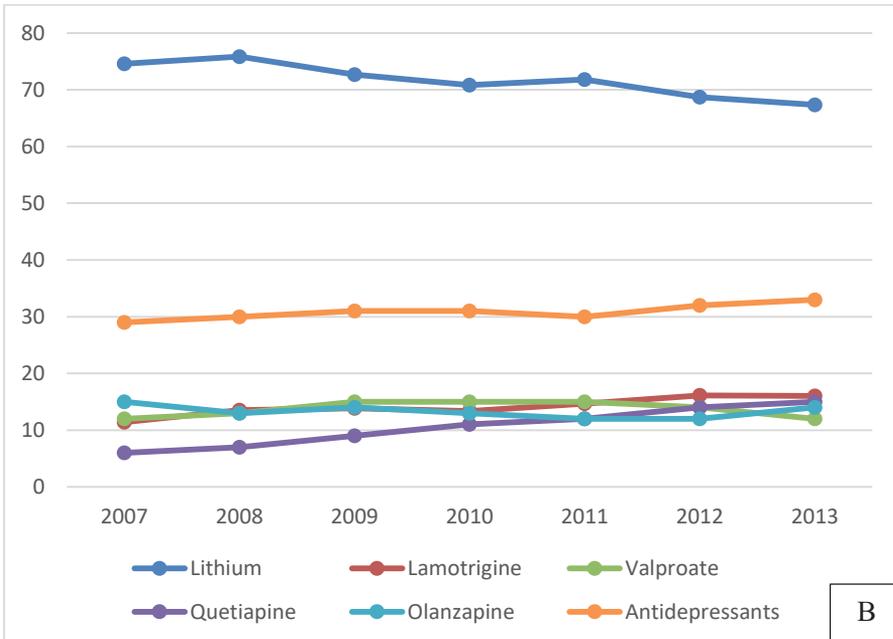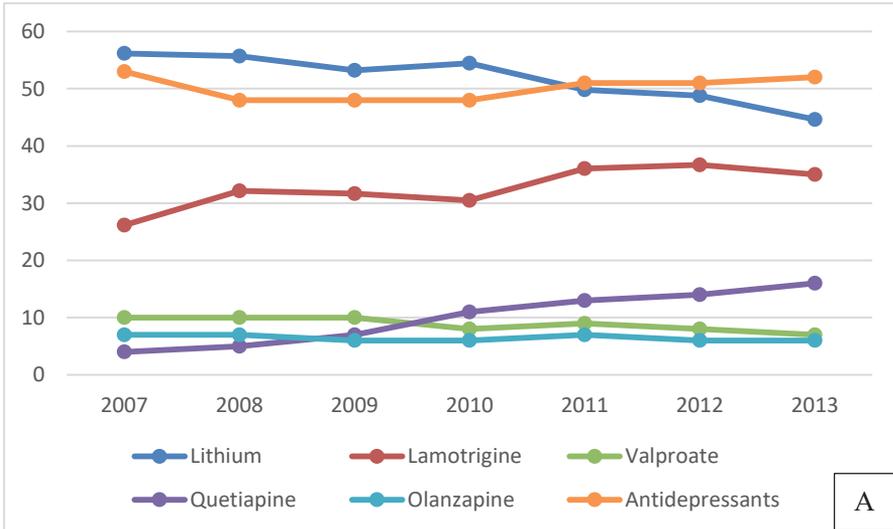
5.3   Discussion

A possible explanation for these prescription changes is that the patient population may have changed during the recent years so that relatively more patients with BDII were diagnosed. Our study, though, does not support this explanation as lithium decreased in both BDI and BDII. Likewise, lamotrigine and quetiapine increased in both bipolar subtypes.

One can also argue that the increase of lamotrigine and quetiapine might be balanced by the decreased use of antidepressants given the fact that the use of antidepressants in bipolar depression has been questioned and the evidence base is inconclusive (29, 168-170). Unfortunately, this is not the case as the prescription of antidepressants remained unchanged in BDII, and in fact increased somewhat in BDI.

The decrease in the prescription of lithium is surprising and not justified by recent evidence that rather has strengthened lithium's position as first line treatment option in bipolar disorder (54, 171, 172). Previous research from US and Germany have also shown a decreased use of lithium (173, 174). A possible explanation is that lithium has not been actively marketed by pharmaceutical companies because of the low cost and has never been patented in contrary to the newer medication such as lamotrigine and quetiapine that have been intensively marked to the clinicians.

One the other hand, we should take in account the importance of tolerability in the choice of pharmacological treatment. Lamotrigine has been recommended as first-line treatment of bipolar depression since 2002 (12, 28, 29) and there are studies supporting its efficacy in both acute bipolar depression (175, 176) as well as maintenance in bipolar disorder (177). But there are also studies questioning its efficacy (170, 178, 179). However, lamotrigine has shown relatively good tolerability with double-digit number needed to harm (NNH). Lithium, and other mood stabilizers have lower number to treat (NNT) than lamotrigine or antidepressants but are less tolerable. One might assume that clinicians would be more oriented towards efficacy whereas patients might be more concerned with side effects, but some data in fact suggest that physicians explain non-adherence to a higher extent by side effects than patients (180). However, in absence of treatments with both adequate efficacy and tolerability, the interventions with adequate tolerability but inadequate evidence of efficacy have been favoured (181). This could explain, at least partially, the favoured prescription of lamotrigine and antidepressants for bipolar depression. Interestingly, lamotrigine is in fact only indicated for BDI in Sweden.

It should also be noticed that drug treatment is highly subsidized in Sweden: after an initial cost of 2,300 Swedish kronor, patients are eligible for free prescribed drugs for the remainder of a 12-month period through the social welfare system (182). That means that affordability should not have a significant impact on the choice of the pharmacological treatment and therefore newer and more expensive drugs can be used broadly by patients regardless income.

Finally, the decrease of valproate among women is an encouraging finding indicating that clinicians have become more aware of the recommendations to avoid the use of valproate in fertile women due to teratogenic effect as well as risk for menstrual abnormalities and polycystic ovary syndrome (99-101, 183-185).

5.4   Conclusion and significance

This was the first nationwide representative study on prescription patterns in patients with bipolar disorder. Major changes in the prescription of drugs in the treatment of bipolar disorder have taken place in recent years in Sweden with decreased use of lithium and increased use of lamotrigine and quetiapine while antidepressants have been remained stable. The changes cannot be explained by changes in the international or national guidelines for treatment of bipolar disorder. The findings are concerning and confirmed by later published studies reflecting the same trends in other Scandinavian countries (186), in Scotland (187), in USA (37), and Korea (188) indicating that this is an international trend rather than a national one.

The observed changes in prescription patterns run contrary to current recommendations regarding the use of lithium and antidepressants in bipolar disorder and they do not align with recent studies that strength lithium's importance and superiority in the plethora of pharmacological treatment of bipolar disorder (45, 51, 189). Indeed, bipolar disorder has been identified as one of the areas of psychiatry with the widest gap between evidence-based treatment and clinical practice (55). This may alter the outcome for individuals with bipolar disorder and may be an important area for quality improvement. In light of these prescription changes, Post argued in 2018 (190) that lithium in underutilized and suggested an enhanced use of lithium given its multiple effect on mania, depression, prophylaxis, suicide prevention and neuroprotection. He also pointed out that reported side effects, specifically renal impairment, might be exaggerated in the past. It is important to keep

reminding psychiatrists about the unique properties of lithium as a part of the optimal management of bipolar disorder. Hopefully, the latest data from BipoläR show that the trend with decrease of lithium prescription in Sweden has now ceased. In fact, in 2018 lithium use increased somewhat. We would like to believe that our study has contributed to this change by alerting clinicians in Sweden to the decrease of lithium prescriptions and raising the awareness of lithium´s importance and evidence in the treatment of individuals with bipolar disorder.

6 STUDY III: PSYCHOEDUCATION IN BIPOLAR DISORDER AND RISK OF RECURRENCE AND HOSPITALIZATION

6.1 Aim

The aim of this study was to estimate the effectiveness of psychoeducation for bipolar disorder in routine clinical setting.

6.2 Results

We found that psychoeducation was significantly associated with a decreased likelihood of subsequent elated, mixed and depressive episode as well as any mood episode regardless polarity. Psychoeducation was also inverse associated with inpatient care (Table 5). We found no evidence for decreased likelihood of involuntary inpatient care or suicide attempts and self-harm.

Table 5. Effect of psychoeducation on different outcomes

Total number of individuals = 2819; individuals receiving psychoeducation (PE) during follow-up = 402; time intervals = 9161

Outcome	aOR[a]	95% CI	Missing[b]	N with change on outcome	N with change on outcome + PE
All relapses	0.57	(0.42-0.78)	591	1152	207
Elated or mixed episodes	0.54	(0.39-0.76)	634	917	183
Depressive episodes	0.63	(0.47-0.86)	634	1099	208
Suicide attempts or self-harm	1.22	(0.54-2.76)	635	146	32
Inpatient care	0.54	(0.33-0.86)	591	484	89
Involuntary sectioning	0.66	(0.34-1.30)	640	213	45

[a]*Adjusted for age, mood stabilizing treatment, and GAF-symptom*
[b]*The number of time intervals with missing data*

6.3   Discussion

Psychoeducation has been shown to have a protective effect on relapse on any kind of affective episode when psychoeducation was given in a group setting (69). However, a later randomized controlled trial (RCT) showed effect of psychoeducation only for patients with a low number of previous affective episodes (71). Our study provides additional information to previous RCTs regarding the effect of psychoeducation in clinical setting.

Most previous studies include extensive psychoeducational programs as standard as for example the Barcelona program which includes 20 sessions á 90 minutes with two psychologists lasting 6 months. Even though this program is well defined, structured and has been shown positive outcomes, it is often challenging to implement on large scale in clinical settings as it is time-

consuming and requires highly trained personal (psychologists). Most outpatient clinics do not have the resources to apply such programs in the real-world clinical practice but compromise with briefer programs. In Sweden, the most common psychoeducation program for bipolar disorder in outpatient clinics consist of six 2-hours sessions in group setting (191). Our findings give additional support for the effectiveness of short psychoeducational programs (64, 67) that makes them a cost-effective and broadly applicable alternative for the outpatient clinics.

Furthermore, in most prior RCTs the group of subjects with BDII was underrepresented which means that the results are applicable mainly to BDI. We had equal groups of the two bipolar subtypes adding important evidence for the effect of psychoeducation in both BDI and BDII.

Finally, we could not find evidence supporting that psychoeducation prevents suicide attempts and self-harm. This may be a result of limited statistical power, as the number of events were low, but it could also mean that psychoeducation does not have protective effect on these outcomes. These topics are not always addressed in the briefer psychoeducational programs given by outpatient clinics in Sweden.

6.4   Conclusion and significance

This large-scale observational study with within-individual design is an important complement to previous RCTs suggesting that psychoeducation is effective also in routine clinical settings and decreases the risk of new affective episodes and inpatient care in both BDI and BDII. The naturalistic design means that the findings can be generalized to the patients with bipolar disorder in real-world clinical practice.

An important feature of our study is that we used a within-individual design in order to limit potential confounding by indication, i.e., that patients offered psychoeducation have specific characteristics. Using this method, the individual serves as is his/her own control regarding sex, genetics, premorbid history, and lifetime severity of the disorder. It is interesting that our analysis with a between-individuals model failed to demonstrate an effect of psychoeducation, which might be due to confounding by indication. This shows that methodological limitations might not only contribute to Type I errors, false positive results, but also to type II errors where true findings are missed.

The field of psychoeducation in bipolar disorder is not well studied and we recommend that further studies investigate the active component of psychoeducation in order to acquire a deeper understanding of the mechanisms of psychoeducation and possible enabling an optimal and cost-effective customization of psychoeducational programs.

7 STUDY IV: GENDER DIFFERENCES IN THE TREATMENT OF BIPOLAR DISORDER

7.1 Aim

The aim of this study was to investigate if there are gender inequalities in the treatment of bipolar disorder.

7.2 Results

Women with bipolar disorder were more likely to be diagnosed with BDII and BD NOS while men were more likely to be diagnosed with BDI. Women had more depressive and mixed episodes, higher likelihood of comorbid anxiety disorder and previous suicide attempts and men had more manic episodes and higher likelihood of comorbid substance disorder. GAF function level was lower in women.

Women had higher likelihood of receiving ECT (in BDI), antidepressants, benzodiazepines, lamotrigine (in BDII), neuroleptics (in BDI) and psychotherapy after adjusting for age, bipolar subtype, GAF-symptom score, comorbid anxiety disorder, comorbid substance use disorder, previous suicide attempts, number of depressive, elated, and mixed episodes. Men were more likely to be treated with lithium. Men with BDI had also higher likelihood of receiving mood stabilizers. We found no differences between women and men regarding treatment with valproate, not even in a subanalysis focused on the reproductive age.

Table 6. Gender and odds ratios for interventions among 7,354 patients with any bipolar disorder recorded in BipoläR 2004-2011.

	N	OR (95%CI)	P	aOR (95%CI)	P
ECT	7,186	0.80 (0.71-0.90)	<0.001	0.80 (0.69-0.89)	<0.001
Antidepressants	7,354	0.72 (0.65-0.79)	<0.001	0.81 (0.73-0.91)	<0.001
Lithium	7,354	1.39 (1.26-1.53)	<0.001	1.25 (1.12-1.39)	<0.001
Valproate	7,354	1.21 (1.04-1.40)	0.015	1.15 (0.98-1.35)	0.086
Lamotrigine	7,354	0.69 (0.61-0.77)	<0.001	0.85 (0.75-0.97)	0.017
Mood stabilizers	7,354	1.15 (0.99-1.32)	0.060	1.14 (0.98-1.32)	0.098
Neuroleptics	7,354	0.97 (0.88-1.07)	0.561	0,93 (0.84-1.04)	0.220
Benzodiazepines	4,827	0.70 (0.62-0.79)	<0.001	0.72 (0.63-0.83)	<0.001
Psychotherapy	7,354	0.58 (0.53-0.64)	<0.001	0.67 (0.60-0.74)	<0.001

aOR: OR adjusted for age, bipolar subtype, GAF-symptom score, comorbid anxiety disorder, comorbid substance use disorder, previous suicide attempts, number of depressive, manic, and mixed episodes. OR< 1 indicates lower likelihood for men to receive the treatment.

7.3 Discussion

Our findings show significant differences in treatment of bipolar disorder between women and men where women have higher likelihood of receiving most of drug treatment as well as ECT and psychotherapy while men receive more lithium.

In somatic health care, there have been indications that most common disparities occur in favour of men in a wide range of conditions from cardiology (vascular surgery, heart transplantation, coronary artery disease, hypertension) to orthopaedics (join arthroplasty) and other areas (renal transplantation, treatment of human immunodeficiency virus [HIV], pneumonia, psoriasis) (103-106, 108, 192, 193). There are very few reports on gender differences that favour women (193). Hence, it is believed that men are more likely to receive invasive, intensive, modern and expensive treatment than women.

In contrast to this stereotype, we found that women with bipolar disorder have higher likelihood of receiving almost all treatment except of lithium. This is in line with previous studies that women with alcohol problems were more likely to receive psychotropic medication than men (193) and with the general tendency in psychiatry where women receive more drug treatment than men (80). One of the most significant gender differences in our study was seen in psychotherapy where women had approximately 33% increased rate of receiving psychotherapy and in lithium where men had about 25% higher likelihood of being prescribed lithium than women.

This begs the question whether treatment of bipolar disorder is subject of bias where men are treated less favourably and receive less treatment in general. But gender differences can only be considered as biased if it can be demonstrated that the differences are unfair, in other words that health care is being provided independently of clinical need for such care. Whether that is the case is yet undecided. Summarizing the literature, we can conclude that our findings on gender differences in the treatment of bipolar disorder are not backed by medical evidence.

Concerning psychotherapy, the topic is not studied in bipolar disorder but in unipolar depression there are no evidence to suggest different response depending on sex (194, 195). The higher rate of psychotherapy in women than men in our study could not be explained by differences in age, bipolar subtype, GAF symptom level, comorbid anxiety disorder or substance use disorder, previous suicide attempts, and number of affective episodes. A possible reason for the higher likelihood of psychotherapy in women could be patient's choice, i.e., that women may prefer and request psychotherapy to greater extent than men, but that remains to be shown.

When it comes to other interventions, the literature has not shown clear sex differences in response to lithium (196-201), neuroleptics, antidepressants (194, 202-206), or ECT (207) that would motivate that women and men with bipolar disorder receive these treatments to different extent. We should notice, though, that bipolar disorder is scarcely studied and most evidence comes from either unipolar depression in the case of antidepressants, anxiolytics and ECT (207), or schizophrenia in the case of neuroleptics and ECT (208). For lithium, there is one study suggesting a tendency toward slight superiority in women in BDII (209) and furthermore a recent study (210) showing that women with bipolar disorder treated with lithium seem to have better and longer sleep as well as less use of night sedatives. This should rather indicate higher rate of lithium prescriptions to women, which is contrary to what we found. Our

findings on higher lithium prescription in men could not be explained either by differences in for bipolar subtype or the number of manic episodes.

If sex differences in the treatment of bipolar disorder cannot be explained by corresponding sex differences in the effectiveness of the interventions, one could argue that side effect differences or other factors might influence clinical decisions. But we fail to find support for that. Some studies point to pharmacokinetic sex differences—women might eliminate lithium (211) or neuroleptics (212, 213) less effectively—but these are subtle differences that can be managed with lower dosages or careful monitoring of blood concentration levels. Women may be at higher risk for hypothyroid adverse effects of long-term lithium treatment (211), but this side effect is easy to manage and should not be a reason to prescribe less lithium to women with bipolar disorder. Women with bipolar disorder are more likely to suffer from central obesity and metabolic syndrome (214) and are more worried about weight gain as side effect of medications (215), which would warrant less use of neuroleptics in women. But our findings are similar to those of Russo et al (216) who found that women with bipolar disorder were 27% more likely than males to receive neuroleptics. Regarding side effects from ECT's, women may have lower risk than men for cognitive impairment (217), but greater risk for depressive relapse, after ECT (218). Again, this is no medical rational for the higher use of ECT in women with bipolar disorder.

The higher prescription of antidepressants in women with bipolar disorder compared with men is in line with previous studies showing that women receive more often antidepressants (219). This might actually have a reasonable explanation. Women with bipolar disorder have a higher frequency of depressive episodes. Even though we adjusted for the number of depressive episodes in our analysis, we could not adjust for subsyndromal depressive symptoms, which is more prevalent in women than men (89, 90, 92). The same explanation might apply to lamotrigine given its antidepressant profile. In the same vein, although we have adjusted for comorbid anxiety disorders, anxiety can be a part symptom of subsyndromal depressive or mixed episodes which might explain the higher use of benzodiazepines in women.

We expected that women would use less valproate than men given the high teratogenic risk of valproate, as well as the risk for menstrual abnormalities and polycystic ovary syndrome (99-101, 183-185). Surprisingly though, we could not show less valproate use in women than men, not even among women of fertile age. Ignoring gender-specific needs or differences when they do exist is also a sign of treatment inequality (84).

7.4 Conclusion and significance

In Sweden, women with bipolar disorder are more likely to receive drug treatment, ECT, and psychotherapy, while men are more likely to receive lithium. These gender differences could not be explained by confounding factors.

It is difficult to know if these gender differences in the treatment of bipolar disorder arise on clinicians' level or on patients' level. In other words, is there a gender bias in physicians decision making, or do women and men have different treatment preferences? If the preferences differ across genders, the disparities we find might not be unwanted, but rather reflect clinical decisions that take patients' choices into account.

In the case of valproate, our findings together with other reports have contributed to the alerting of clinicians about the use of valproate in fertile women. In 2018, the Pharmacovigilance Risk Assessment Committee (PRAC), a part of European Medicines Agency (EMA), endorsed new measurements sending direct information to clinicians reminding them of the cautions/restrictions for valproate use in women and requiring companies marketing valproate to carry out additional studies to monitor valproate use. In Sweden, both the Medical Product Agency and regional medical guidelines of bipolar disorder emphasized the need of restricted use of valproate in women. This is a good example of how research results can directly interact with institutions and be implemented in clinical practice.

With respect to the other gender disparities, we failed to find medical evidence that could explain them, with the possible exception of antidepressants, lamotrigine, and anxiolytics as subsyndromal symptoms could be an explanation for the higher rate of prescription of these drugs. A later study in 2018 (220) confirmed our data showing that women with bipolar disorder were more likely to receive antidepressants than men.

One might argue that the lower rate of interventions in men with bipolar disorder reflects unfavourable bias against men. However, more treatment is not necessarily a good thing. We know for example that women suffer more from mixed episodes and rapid cycling (88, 90, 96-98), which can be triggered by the use of antidepressants. Strikingly, female sex is the only known risk factor for antidepressant-induced mania (221). It is therefore important to question the high prescription rate of antidepressants in women, since treatments may also have a negative impact on the course and outcome of bipolar disorder. Likewise, lithium is the most effective mood stabilizer and

the high rate of lithium use in men might be beneficial despite that men receive less than all other interventions.

In a welfare system where the goal is equality in treatment, it is important to shed light on gender differences in treatment of bipolar disorder not only to discourage practices with a negative impact or no scientific support, but also to keep strategies that are justified by evidence such as less use of valproate in women. We suggest therefore that future research report data stratified on sex as well as study if the current gender differences in treatment result in different outcome for patients with bipolar disorder. We would also like to see that future clinical guidelines address the role of sex in recommended treatment for bipolar disorder.

8 STUDY V: PATIENTS' EDUCATIONAL LEVEL AND MANAGEMENT OF BIPOLAR DISORDER

8.1 Aim

The aim of this study was to investigate if there is inequality in the management of bipolar disorder due to the educational level of the patients.

8.2 Results

We found that the educational level of patients was inversely associated with the use of first-generation antipsychotics (FGA), tricyclic antidepressants (TCA) and compulsive inpatient care, which means that individuals in lower education group had an increased likelihood of being treated with these interventions. By contrast, individuals with higher educational level had increased likelihood of receiving psychoeducation, psychoeducation for next-of-kin, and psychotherapy after adjusting for confounding variables (Table 7). We did not find any association between patients' educational level and treatment with mood stabilizers, antipsychotics, antidepressants, benzodiazepines, or ECT.

Table 7. Association between educational level and interventions for bipolar disorder

Intervention	Model 1[2]	Model 2[3]
	aOR[1] (95% CI)	aOR[1] (95% CI)
Mood stabilisers as a group	0.96 (0.86-1.07)	
Lithium	0.97 (0.89-1.05)	0.99[a] (0.91-1.08)
Lamotrigine	1.11 (1.01-1.22)	1.08[a] (0.98-1.19)
Divalproex	0.92 (0.81-1.06)	
Antipsychotics as a group	0.90 (0.83-0.99)	0.94[b] (0.86-1.03)
Quetiapine/aripiprazole/olanzapine	1.01 (0.92-1.11)	1.04[b] (0.94-1.14)
First generation antipsychotics	0.71 (0.58-0.88)	0.76[b] (0.62-0.94)
Antidepressants as a group	1.05 (0.96-1.14)	1.07[c] (0.98-1.17)
Tricyclic antidepressants	0.74 (0.58-0.96)	0.76[c] (0.59-0.97)
Benzodiazepines	0.97 (0.87-1.09)	0.99[d] (0.88-1.10)
ECT	0.94 (0.85-1.04)	0.9[c] (0.85-1.04)
Psychotherapy	1.31 (1.20-1.43)	1.34[e] (1.22-1.46)
Psychoeducation	1.18 (1.07-1.30)	
Psychoeducation for next-of-kin	1.24 (1.11-1.38)	
Compulsory inpatient care	0.79 (0.67-0.93)	

[1] aOR = Adjusted odds ratio for educational level vs intervention. An aOR>1 means that the intervention is more common in the group with higher education
[2] Model 1 adjusted for age and GAF-function
[3] Model 2 adjusted even for: [a] bipolar type; [b] number of manic, hypomanic and mixed episodes; [c] number of depressive episodes; [d] comorbid anxiety disorders; [e] comorbid personality disorders

8.3   Discussion

There are few previous studies on the impact of patients' educational level on the management of bipolar disorder. Treatment disparities are challenging to study as they may simultaneously depend on access, need, and demand without being able to adjust for each of them (222). Furthermore, disparities may arise on system, clinician, or patient level. Concerning psychological interventions, previous studies indicate in line with our findings that higher educational level is associated with higher likelihood of receiving psychotherapy (223-225). When it comes to drug therapy, one previous study did not found any association between pharmacological treatment and educational level in patients with BDI in US (226), while another study found that higher educated patients with BDI had lower likelihood of receiving second generation antipsychotics (227). Both studies are relatively small compared to ours and the contradictory findings might be due to varying healthcare organizations and access to welfare programs across countries. To our knowledge, there are no studies supporting that patients with higher education have greater need or better response to psychological treatments or that patients with lower education would have better response to FGA or TCA. Our findings cannot be explained by differences in the number of elated or mixed episodes during the last 12 months in respect to FGA or in the number of depressive episodes during the last 12 months in respect to TCA. With respect to psychotherapy, we adjusted for comorbid personality disorder given that it is an indication for psychotherapy.

8.3.1   Educational level as proxy for income differences

Both FGA and TCA are old drugs and therefore less expensive. As educational level reflects socioeconomic status, a conceivable explanation for our findings could therefore be differences in patients' income than educational level per se. New drugs are more expensive and have been shown to be more commonly prescribed among patients with higher socioeconomic status (228, 229). Patients with lower income might choose cheaper drug therapies due to restricted affordability. Although this might serve as an explanation in countries with less developed welfare systems, Swedish socioeconomic differences are modest in an international perspective and all citizens are covered by the same insurance program where the drug treatment is highly subsidized as described in the Introduction (see 1.3). Indeed, a previous Swedish study also found association between education and drug utilization

after controlling for income (230). Income differences across educational groups are therefore less likely to explain our findings.

However, when it comes to psychotherapy, income differences among the patients may play a significant role. Swedish public health sector currently does not meet the need and demand for psychological treatment. Patients with higher education might have better income and afford private psychotherapy. In our data, we cannot distinguish if psychotherapy was provided by private or public providers. Furthermore, on a system level, psychiatric units in a socio-economically disadvantaged geographical areas may lack access to psychotherapists which results in less possibility to offer psychotherapy regardless of patients' educational level.

Psychoeducation is, however, provided by publicly funded psychiatric outpatient units and the disparities cannot be explained by differences in income.

8.3.2 The role of patient

Patients with higher education has been shown to have higher health awareness and to demand better treatment (222, 231). People with higher education may have better access to drug information including side effects, and therefore demand other treatment than FGA and TCA. Interestingly, the same association between educational level and FGA has been demonstrated in elderly patients with and without dementia in Sweden (232), supporting a patient-mediated explanation.

On the other hand, a higher educational level may mirror patient's cognitive reserve. The cognitive reserve has been associated with the course and functional outcome of bipolar disorder (233, 234). Although we adjusted for GAF-function score, number of mood episodes, and comorbid personality disorder, we could not control for differences in cognitive function. Thus, patients' educational level may be associated with the severity of illness, which in turn might be associated with treatment. In that case, the disparities would be warranted and suited to clinical needs.

8.3.3   The role of clinicians

It is difficult to rule out the notion that clinicians might unintentionally make different decisions depending on patients' educational level. Patients' sociodemographic characteristics have previously been shown to impact on clinicians' behaviour during the medical assessment (235-238) and on the diagnoses and treatments patients receive (239, 240). Such influence cannot be explained by patients' income, insurance coverage, or disease severity (241, 242). It has been shown that patients with low and middle socioeconomic status were perceived more negatively by the clinicians than patients with higher socioeconomic status regarding personality, abilities, behavioural tendencies, and role demands (243). The discrepancy between physician belonging to the middle class and patient in lower social classes might influence physicians medical decisions (244). It has been shown that patients with lower social status are prescribed drugs regardless their health status, receive less information by the clinicians (238, 245-247) and are less likely to be listened by the clinicians(243). In a Swedish study (248), physicians appeared aware of the fact that patients' educational level affected their medical decisions, even though they considered this to be unfair.

8.4   Conclusion and significance

We found that patients' level of education is associated with differences in the management of bipolar disorder in Sweden. The lack of medical evidence to support such differences indicate inequality in treatment that can arise on multiple levels. Presumably, clinician-patient interactions play an important role (249). Patients ability to decision-making and demand of certain therapies may also explain that higher educated patients receive differential treatment.

The design of our study does not allow for causal inferences but shed light on the educational disparity and highlights the need of further research in order to investigate the mechanism underlying these differences. Further studies should include data on specific indications for pharmacotherapy, geographical differences in access to care, and deeper knowledge in patients' and clinicians' attitudes.

9 GENERAL DISCUSSION

9.1 Previous research

Achieving new knowledge requires reviewing prior research and identifying topics that are not well understood and hence in need for further investigation. The complexity of mental disorders, including bipolar disorder and its treatment, is mirrored by the extensive literature with tens of thousands of publications. Despite the intensively active research through the decades, there are unsettled issues needed to be addressed. Some topics, such as potential treatment inequality in bipolar disorder, have suffered from a striking paucity of data warranting further research. In other cases, such as differences between bipolar subtypes, there have been several studies through the years. But contradictory results or methodological limitations have nevertheless hampered firm conclusions and warranted additional studies.

Two main common issues that obfuscate conclusions from prior studied in the field of bipolar disorder are: i) limited sample size and differing study populations, and ii) a lack of evidence from representative clinical populations. These matters prompted us to conduct new studies on the topics and to apply different methodological approaches in order to arrive at a more complete understanding.

9.1.1 Sample size and differing study populations through the years

Most previous studies in the field of bipolar disorders and the characterization of their subtypes have been small, typically including 80-300 subjects. Depending on the research question, studies with limited sample size run the risk of being underpowered. Previous studies have also primarily focused on BDI (250-255) while BDII has been underrepresented. Many studies have been based on inpatient populations (253-256) and thus biased towards mania-prone patient populations. Moreover, most of the cohorts were sampled long before the current acute and maintenance psychopharmacological treatments were available. Furthermore, a large amount of previous studies was based on outdated criteria for defining bipolar disorder in general, and BDII in particular. Studies in the 1970s or earlier (257, 258) were conducted with varying diagnostic criteria because there were no generally accepted formal diagnostic criteria at that time. For example, some studies required

hospitalization for the diagnosis of BDII depression, which is not in concordance with current criteria. Later studies (141, 146, 150) used the Research Diagnostic Criteria (RDC) (259), which did not required hospitalization for neither depressive or hypomanic episodes, but had no duration requirement for hypomanic episodes, and depressive episodes could be shorter than 2 weeks. DSM-IV requires a minimum of 4 days for a hypomanic episode and 2 weeks for a depressive episode (2). The changing criteria over time resulted in different patient populations. That may explain conflicting results in the literature and limits conclusions that can be drawn. Prior findings might nor be generalizable to the current era of outpatient-centred psychiatric care. Therefore, I argue that there was a need for large-scale studies on patients with bipolar disorder diagnosed with current diagnostic criteria and managed in a modern context.

9.1.2 Real world evidence – what it is and why it is important in bipolar disorder

Randomized clinical trials (RCT) are the gold standard to access the *efficacy* and safety of new medicines (260). But many authors have pointed out the discrepancy between the conditions of these trials and the actual practice of treatment (261). A clinical trial is necessarily based on a limited sample of individuals selected by strict inclusion- and exclusion criteria in order to reduce the inter-individual variability. Typically, exclusion criteria encompass comorbid psychiatric or somatic disorders, significant suicidal ideation, older age *et cetera*. This means that RCTs often are restricted to low-risk populations. This leads to low external validity as they do not reflect the patient population we are seeing in clinical practice. Furthermore, it is common with high expectations in research patients, which is correlated with better outcomes (262). Even adherence has been shown to be better in clinical trials than in clinical setting (263). Not only patients but also clinicians may have a different approach and behaviour in research setting compared to clinical setting (264), which may interfere with the outcome. Therefore, findings from RCTs may not be generalizable and applicable to clinical practice.

To obtain better knowledge on the benefits and risks of treatments under real life conditions, we need to combine RCTs with real world evidence (observational data). The real-world naturalistic studies provide different insights. In RCTs, we get information about *efficacy* and main safety profile of treatments. Real-world studies provide information on the *effectiveness* of the treatment under routine clinical care conditions. RCTs have relatively

short-term duration, while observational studies can follow patients over many years.

Given that bipolar disorder is a lifelong disease, long-term studies are needed. The clinical patient population is varying and complex. Comorbidity with other psychiatric diseases is common.

The studying of the ultimate effect of medical care on the health and well-being of patients is often referred as *outcomes research*. The results from outcomes research contribute to important information about existing treatments and practices, improve the quality of health care and evaluate new treatments (265). One domain in outcome research is *register-based research,* which offers good opportunities to use clinically obtained data to study patient populations and outcomes. The availability of large databases as health quality registers is crucial and provide us unique opportunities to study representative patient populations independently of drug companies and economic interests. Sweden is one of few countries with a long-established tradition in national health quality registries. Sweden has more than 100 quality registers for various disorders and medical procedures (266). The Swedish health care quality registries are mainly developed to improve health care but can also be used for research purposes.

10 STRENGTHS AND LIMITATIONS OF THE DESIGN AND THE REGISTER BASED RESEARCH

There are several methodological facets to consider. An important first strength of this thesis is the large sample size of persons with bipolar disorders treated in natural clinical setting. The large data sets increase the statistical power to detect differences. The main advantages of using the Swedish register BipoläR is that results are population based and free of exclusion criteria. Results can therefore be expected to be generalisable to the bipolar disorder population at large and represent real-world management of bipolar disorder. As such, results are relevant for clinical care. The availability of outpatient diagnoses is an important strength because it allows the inclusion of outcomes that do not require hospitalization. This avoids bias that may potentially result from the sole use of inpatient data and enables more generalizable risk estimates. The clinical diagnoses in BipoläR are made according to current established DSM-IV diagnostic criteria. BipoläR has also the advantage compared with other national registries like the National Patient register that it offers high-resolution naturalistic data and more detailed phenotypic information giving opportunities to study varying aspects of course and outcome in bipolar disorders. Furthermore, register studies are relatively low-cost research since they use data that already exist for the improvement of health quality.

On the other hand, naturalistic observational studies have several challenges. With respect to limitations, it might be argued that the clinical diagnosis recorded in BipoläR do not follow a standardized research protocol. On the other hand, registry-based diagnoses in Sweden have been shown to have good validity overall (127). Psychiatrists who register patients in BipoläR are often specialized in the treatment of mood disorders in general and treatment of bipolar disorders in particular which provides conditions for god validity and high data quality. In order to further improve the validity of diagnoses in our study, we excluded cases where misclassification was present (Study I).

Another aspect is that even though BipoläR contains data from several thousand registrations, the subjects included in BipoläR still represent a subsample of patients with bipolar disorder in Sweden. We could not address possible selection bias due to preferential inclusion of subpopulation in the registry or unmeasured bias such as missing information for a covariate or outcome. When applicable, we conducted sensitivity analyses comparing the data with other registries (the National Patient Register and the Prescribed

Drug Register) that have more complete coverage of patients with bipolar disorder and drug prescription in Sweden (Study II). However, BipoläR has previously been found to be reasonably representative to the whole Swedish bipolar disorder population (58)

Finally, observational data does not allow casual inferences, but merely shed light on associations between the studied variables. A common problem with naturalistic studies is the indication bias because of lack of randomization. Confounding might occur because patients have been selected for a specific treatment based on a higher or lower propensity for a certain outcome. A way to minimize the risk for confounding bias is to use a within-individual study design as the one we used in Study III. With this method, the individual serves as his/her own control and we minimized confounding caused by differences in disorder severity, genetic, and early environmental factors.

Another important aspect is that register studies are limited by the data available in registries. We lacked, for example, information on the indication for drug prescriptions. To partially address this, we excluded individuals with psychotic disorders, and we adjusted for bipolar subtype, comorbid psychiatric conditions, and the number of depressive or elated episodes (Study V). Additionally, we do not have data on the dosages of drug therapies or information whether the prescription is daily or as needed. Finally, BipoläR does not provide symptom level data, specific mood rating scales, or subphenotype information on rapid cycling or psychosis and therefore cannot give information on specific affective symptoms. BipoläR also lacks information on the number of years of illness. We therefore estimated the duration of illness indirectly by subtracting the 'age at first contact with caregiver due to mental health problems' from the age at registration (Study I).

Another disadvantage with register studies is the variation in data quality caused by acquisition in busy clinics and recall bias which should be kept in mind when interpreting the findings.

Finally, BipoläR contains only psychiatric outpatient treatment data, and it is unknown whether these findings translate to inpatient care or to patients treated in primary care.

As is true in the whole of the scientific community, results must be replicated to show consistent convergent results across multiple datasets from different countries and continents.

11 KEY FINDINGS

- Bipolar type I and II represent different clinical phenotypes.

- Bipolar type II has more complex clinical presentation regarding course of illness and comorbidity.

- During the period of our study, lithium prescription decreased in both bipolar subtypes, while lamotrigine and quetiapine increased. The use of antidepressants remained unchanged in BDII, and in fact increased somewhat in BDII.

- Recent changes in prescription pattern do not align with recommendations from international guidelines regarding the use of lithium and antidepressants and may influence outcome of bipolar disorder.

- The use of valproic acid decreased, which is a positive trend given its teratogenic effect in fertile women.

- Psychoeducational programs, even the brief ones common in Sweden, are effective for preventing depressive and elated episodes as well as inpatient care.

- Even in a welfare state like Sweden, there are signs of inequality in the management of bipolar disorder due to gender and patients' educational level.

- Women with bipolar disorder have higher likelihood of receiving drug treatment (except lithium), ECT, and psychotherapy than men. These differences have no medical rationale.

- Men with bipolar disorder have higher likelihood of receiving lithium.

- Higher educated patients with bipolar disorder have increased likelihood of receiving psychotherapy and psychoeducation, but decreased likelihood of receiving first-generation antipsychotics, tricyclic antidepressants, and compulsory inpatient care than lower educated patients. We found no medical rationale behind these differences.

12 CONCLUSION AND FUTURE PERSPECTIVES

The rapid and continuing development of registers worldwide provide us with a large amount of information and accessible data than ever before. While the ability to generate data has increased, there are still several challenges in processing, analysing and interpreting information in a meaningful way. The quality registers are time consuming for the clinicians, which means that we need to critically appraise the burden of work they produce in relation to the benefit we get both in terms of improving quality of care and in terms of providing data for research. There is a need to focus on validating and considering the usability of such information.

On the other hand, many arguing for some research methods being superior to others. RCTs are typically regarded more valid, "true" thus easier to publish compared to register-based studies. I have been appealed by the clinical nearness of register data and the relatively immediate applicability in my work as psychiatrist. Occasionally, it has been frustrating in my work as researcher to be analytically restrained by pre-existing data in the registers. At the same time, being aware of the limitations of each method is a fundamental and necessary condition for a critical approach to own research and findings. In my opinion, the only way to proceed toward deeper knowledge and scientific truths is to combine different research methods where each one contributes with a piece in the puzzle of science that complements or replicates the investigated topic.

Future studies

Future studies should focus on varying aspects of bipolar disorder investigating at the same time both bipolar subtypes and gender and not only on one of them. It would be interesting to use registers to investigate the clinical phenotype of bipolar disorder not otherwise specified and schizoaffective disorder of bipolar type, which are to date not sufficiently understood, and to clarify the relationship between these subtypes of bipolar disorders. Finally, an emerging challenge for further studies is the linkage of population-based registers and biobanks (with a higher degree of information on, e.g., a genetic level) which would make it possible to examine environmental and genetic factors as well as their interactions.

13 EPILOGUE

Taking all together, the time I have been spent for this doctoral thesis research has been a great pleasure and given me unique opportunities to develop my critical thinking and to read and learn more about bipolar disorders. It has stimulated my curiosity for further potential research topics and made me humbler in relation to the "truth" and my clinical practice. I see the combination of research and clinical work as important. The research community needs more clinicians who have insight in the real-world clinical settings and can help to formulate relevant research topics and are able to interpret results in a contextual way. In parallel, clinics need more researchers that question the praxis and develop healthcare by updating and applying recent research findings. Last but not least, clinics need leaders with both clinical and research competence in order to drive healthcare in a novel and useful direction towards our prime goal that is improving patients' health and quality of life.

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APPENDIX
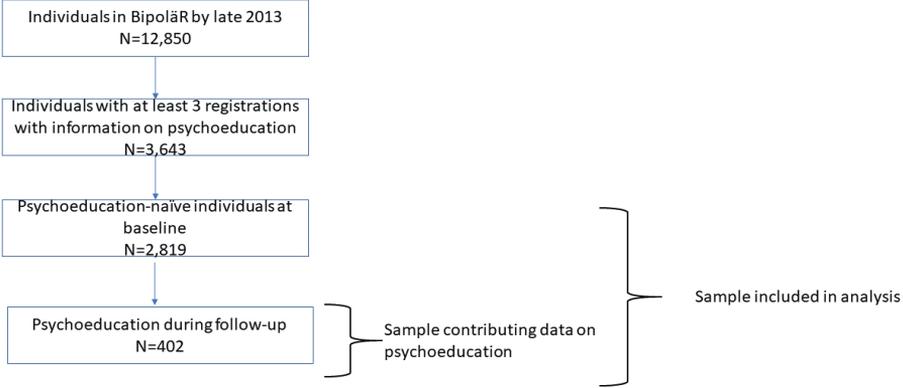
Figure Sample selection (Study III)