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Factors affecting the pharmacological treatment of bipolar disorder

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To Agnes, Alfred and Sixten

"Ring the bells that still can ring
Forget your perfect offering
There is a crack in everything
That's how the light gets in"
Leonard Cohen

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ABSTRACT

Background

In patients with bipolar disorder, long-term treatment with mood-stabilisers is often required to prevent manic and depressive episodes. At present, our knowledge remains limited regarding factors that influence the outcomes of mood-stabiliser treatment.

Lithium is a first-line treatment of bipolar disorder, thought to be superior regarding the prevention of acute relapse, self-harm and suicide. But despite its therapeutic superiority, patients may find lithium difficult to take long-term. The reasons why patients discontinue lithium treatment remain largely unknown. Neither do we know whether lithium is equally effective in patients with bipolar I and bipolar II disorder. Finally, there is only little evidence on how patients with a dual diagnosis of bipolar disorder and adult attention-deficit hyperactivity disorder (ADHD) should be treated. In this patient group, central stimulant treatment may be of benefit, as long as mood-stabilisers are given simultaneously to prevent manic relapses. However, there are no studies that have explored the impact of central stimulants on suicidal and non-suicidal self-injurious behaviour in patients with such a dual diagnosis.

Aim

The overall aim of this thesis was to study three factors that may modify treatment outcomes in patients with bipolar disorder or schizoaffective disorder; (1) adherence to lithium and reasons for lithium discontinuation, (2) impact of lithium discontinuation on clinical course in different bipolar disorder subtypes, and (3) impact of central stimulants on suicidal and non-suicidal self-injurious behaviour in patients with a dual diagnosis of bipolar disorder and ADHD.

Method shared by *all* studies

All three studies were part of LiSIE (Lithium – Study into Effects and Side Effects), a retrospective cohort study in the regions of Norrbotten and Västerbotten, exploring effects and side-effects of lithium and other mood-stabilisers. For our studies, we identified 1566 individuals who had been diagnosed with bipolar disorder or schizoaffective disorder. Study II and III are based on 1564 patients due to consent withdrawal in one patient and diagnosis reassessment in another. For the respective study included in this thesis, we extracted routine clinical data from the medical records.

Study I identified and assessed the reasons for lithium discontinuation in 468 patients with bipolar disorder or schizoaffective disorder in relation to (a) type of underlying disorder, bipolar I or schizoaffective disorder versus bipolar II or other bipolar disorder, (b) gender, and (c) person taking the initiative to discontinue lithium (doctor or patient).

Study II applied a mirror-image design to examine the clinical course and need for hospital admissions in 194 patients with either bipolar I or schizoaffective disorder or bipolar II or other bipolar disorder within two years before and after lithium discontinuation.

Study III assessed occurrence of suicidal or non-suicidal self-injurious behaviour in 206 patients with a dual diagnosis of bipolar disorder or schizoaffective disorder and ADHD. This study also used a mirror-image design, comparing the number of suicide attempts and non-suicidal self-injury events within six months and two years before and after central stimulant initiation.

Results

Study I: More than half of all patients discontinued lithium at some point. Lithium discontinuation mainly occurred because of adverse effects. More patients with bipolar II or other bipolar disorder than patients with bipolar I or schizoaffective disorder discontinued lithium because of a perceived lack of effect. Men were more likely to discontinue lithium when feeling well. They were also less likely to consult with a doctor prior discontinuation.

Study II: The number of hospital admissions and bed-days doubled after lithium discontinuation. This increase was exclusively attributable to patients with bipolar I or schizoaffective disorder. Not having consulted with a doctor prior to lithium discontinuation or no treatment with an alternative mood-stabiliser at the time of lithium discontinuation led to more admissions.

Study III: In patients with a dual diagnosis of bipolar or schizoaffective disorder and ADHD, central stimulant treatment reduced the number of suicide attempts and non-suicidal self-injury events. There was no increase in number of hospital admissions.

Conclusion

Lithium discontinuation in patients with bipolar disorder or schizoaffective disorder is common and mainly occurs because of adverse effects. It is important that patients who may benefit from lithium can continue their treatment. Therefore, clinicians should discuss and manage potential adverse effects of lithium treatment with patients before initiation and continuously during treatment. Particularly men may require proactive follow-up since they may be more likely to discontinue their treatment without consulting a doctor.

Lithium discontinuation in patients with bipolar I or schizoaffective disorder comes at a cost of deteriorated mental health and increased hospital utilisation. In patients with bipolar II or other bipolar disorder, judged on the impact of discontinuation alone, lithium did not appear to prevent more severe depressive episodes requiring hospital admissions. The higher relapse risk in patients with bipolar I or schizoaffective disorder points towards a need to apply a higher threshold for lithium discontinuation in this group.

In patients with both bipolar disorder and ADHD, addition of central stimulant treatment may reduce the risk of suicide attempts and non-suicidal self-injury events. This suggests that central stimulants can be safely given in this patient group, as long mood-stabiliser treatment are given concomitantly.

Keywords

Lithium, Bipolar Disorder, Schizoaffective Disorder, Physical Health, Compliance, Medication Adherence, Side Effects, Long Term Adverse Effects, Mood Stabiliser, Admission, Hospitalisation, Attention Deficit Disorder with Hyperactivity, Central Nervous System Stimulants, Self-Injurious Behaviour, Non-Suicidal Self Injury, Suicide Attempted, Suicide.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Bipolär sjukdom är en svår psykiatrisk sjukdom. Sjukdomen kännetecknas av episodiska förskjutningar av stämningsläge och aktivitetsnivå vilket ger upphov till perioder av depression, hypomani och mani. Hypomani och mani kännetecknas av ett ihållande förhöjt stämningsläge med hög energi och aktivitetsnivå. Depressiva episoder kännetecknas framförallt av sänkt stämningsläge med brist på intresse och glädje. Enligt den klassiska synen efterföljdes depressiva och maniska episoder av perioder med ”normalt” stämningsläge och ”normal” funktion. Senare forskning har visat att en betydande andel patienter med bipolär sjukdom är drabbade av kvarvarande långdragna depressiva symptom och nedsatt funktionsförmåga även under perioder där man inte uppfyller kriterier för en depression. Risken att under sin livstid insjukna i bipolär sjukdom är cirka en till två procent och kvinnor och män drabbas i lika stor utsträckning. Sjukdomen debuterar vanligtvis i ung vuxenålder, där den genomsnittliga åldern för insjuknande är cirka 25 år. Patienter med bipolär sjukdom kan vara svårt drabbade av sin sjukdom, där nya episoder kan leda till slutenvård och ökad risk för självmord. Risken för självmord är tio till femton gånger högre jämfört med den allmänna befolkningen.

Med rätt behandling kan många patienter med bipolär sjukdom bli symptomfria och återfå funktionsförmåga. För att minska risken för att patienter skall drabbas av en ny episod krävs ofta förebyggande långtidsbehandling med så kallade stämningsstabiliserande läkemedel, där litium sedan mer än 50 år tillbaka har varit förstahandsbehandling i många delar av världen.

Rådande riktlinjer förespråkar en alltmer individualiserad läkemedelsbehandling, där man bör väga in aspekter såsom dominerande sjukdomssymptom (depression eller mani), kvinnor i barnfödande ålder och olika psykiatriska samsjukligheter. Vår kunskap är idag begränsad vad gäller hur sådana faktorer påverkar läkemedelsbehandlingen och behandlingssvar vid bipolär sjukdom.

I den här avhandlingen har vi i tre olika delstudier undersökt faktorer som kan påverka läkemedelsbehandlingen vid bipolär sjukdom. I den första studien frågade vi oss hur vanligt det är att patienter med bipolär sjukdom avslutar sin litiumbehandling och vad de bakomliggande orsakerna till avslutad behandling är. I den andra studien undersökte vi sjukdomsförloppet efter avslutad litiumbehandling bland olika undergrupper av patienter med bipolär sjukdom. I den tredje studien frågade vi oss om centralstimulerande läkemedel (läkemedel som används vid behandling av ADHD) kan påverka förekomsten av avsiktlig självskada och självmordsförsök bland patienter som är diagnosticerade med både bipolär sjukdom och ADHD.

I den första studien visade vi att mer än hälften av alla patienter avslutade sin litiumbehandling. Vid majoriteten av tillfällena utsattes litium på grund av biverkningar. Det var vanligare att patienter som var diagnosticerade med bipolär sjukdom typ II eller annan bipolär sjukdom avslutade sin litiumbehandling på grund av avsaknad av behandlingseffekt, jämfört med patienter med bipolär sjukdom typ I eller schizoaffektiv sjukdom. Dessutom avslutade män oftare än kvinnor sin behandling när de mådde bra. Män var även mindre benägna att rådfråga en läkare innan litiumutsättning.

I den andra studien visade vi att medelantalet av alla psykiatriska sjukhusinläggningar och vårddagar fördubblades efter litiumutsättning. Det var enbart patienter som tillhörde gruppen bipolär sjukdom typ I eller schizoaffektiv sjukdom som hade ett ökat behov av slutenvård efter avslutad litiumbehandling. Bland patienter med bipolär sjukdom typ II eller annan bipolär sjukdom ökade inte antalet sjukhusinläggningar.

I den tredje studien visade vi att antalet avsiktliga självskadehandlingar och självmordsförsök minskade bland patienter diagnosticerade med både bipolär sjukdom och ADHD efter insättning av centralstimulerande läkemedel.

Sammanfattningsvis pekar våra resultat på vikten av att hantera biverkningar och att samtala kring biverkningar kontinuerligt under litiumbehandling. Gentemot män kan man behöva använda sig av ett mer proaktivt förhållningssätt då de oftare tycks avsluta sin behandling när de mår bra samt utan att rådfråga läkare innan. Eftersom patienter med bipolär sjukdom typ I eller schizoaffektiv sjukdom löper större risk för försämring efter litiumutsättning, bör tröskeln vara högre för att avsluta behandlingen för patienter i denna grupp. Det krävs dock alltid en individuell bedömning där nyttan med behandlingen skall vägas mot risken. Att centralstimulerande läkemedel tycks minska förekomsten av avsiktlig självskada och självmordsförsök bland patienter med bipolär sjukdom och ADHD ger stöd för att centralstimulerande läkemedelsbehandling kan förskrivas till denna grupp. Så länge stämningsstabiliserande läkemedel används samtidigt.

ABBREVIATIONS

AC: Anticonvulsant

ADD: Attention Deficit Disorder

ADHD: Attention Deficit Hyperactivity disorder

APA: American Psychiatric Association

BAP: British Association for Psychopharmacology

BD: Bipolar Disorder

BD-I: Bipolar Disorder type I

BD-II: Bipolar Disorder type II

CANMAT: Canadian Network for Mood and Anxiety Treatments

CKD: Chronic Kidney Disease

CS: Central Stimulants

DSM: Diagnostic and Statistical Manual of Mental Disorders

FoL-enheten: Enheten för Forskning och Lärande (Research and Learning Department)

ICD: International Classification of Diseases

ICD-10 CM: ICD-10 Clinical Modification

ISBD: International Society for Bipolar Disorder

LAI: Long Acting Injectable

LiSIE: Lithium – Study into Effects and Side effects

LiSIE-N: Lithium – Study into Effects and Side Effects / Norrbotten

NICE: National Institute for Health and Care Excellence

NPR: National Patient Register

NSSI: Non-suicidal Self Injury

RCT: Randomised Controlled Trial

SCB: Statistiska Centralbyrån (Swedish Central Bureau of Statistics)

SGA: Second Generation Antipsychotic

SPA: Swedish Psychiatric Association

STROBE: Strenthening the Reporting of Observational Studies in Epidemiology

SZD: Schizoaffective Disorder

TSH: Thyroid Stimulating Hormone

WHO: World Health Organisation

ORIGINAL PAPERS

Paper I Öhlund L, Ott M, Oja S, Bergqvist M, Lundqvist R, Sandlund M, Salander Renberg E, Werneke U. Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study. *BMC Psychiatry*, 2018; 18:37.

Paper II Öhlund L, Ott, M, Bergqvist M, Oja S, Lundqvist R, Sandlund M, Salander Renberg E, Werneke U. Clinical course and need for hospital admission after lithium discontinuation in patients with bipolar disorder type I or II: mirror-image study based on the LiSIE retrospective cohort. *BJPsych* Open, 2019; 5:e101.

Paper III Öhlund L, Ott, M, Lundqvist R, Sandlund M, Salander Renberg E, Werneke U. Suicidal and other deliberate self-injurious behaviour in patients with bipolar disorder and comorbid attention-deficit hyperactivity disorder after initiation of central stimulant treatment – a mirror-image study based on the LiSIE retrospective cohort. *Submitted*.

1 INTRODUCTION

Bipolar disorder (BD), previously called manic-depressive illness, is a severe and chronic mental disorder characterised by extreme changes in mood. The disorder is relapsing and remitting in nature, with episodic severe moods swings ranging from depressed to hypomanic or manic. Patients may not always recover completely between episodes but experience residual symptoms and impaired functioning even during euthymic periods (1-3). Such residual symptoms increase the risk of relapse into further acute episodes (3). BD has a lifetime prevalence between 1% and 2% (4-7). Because of the relapsing and remitting character of the condition, most people will require long-term maintenance treatment with mood-stabilisers (8). Maintenance treatment with mood-stabilisers is not only necessary to prevent relapses into acute affective episodes but also to decrease the risk of suicide attempts and suicide (9). Commonly used mood-stabilisers include lithium, some anticonvulsants (AC), such as lamotrigine or valproate, and selected second-generation antipsychotics (SGAs). Currently, lithium remains first choice for the maintenance treatment of BD (10). Lithium has been considered superior to other mood-stabilisers in its ability to prevent suicide and severe affective episodes (11-14). But knowledge regarding lithium's comparative safety to other mood-stabilisers remains limited. Neither is it clear whether all patients do equally well on each mood-stabiliser (one size fits all), or whether effectiveness varies according to type of BD or psychiatric comorbidities. Evidence is also limited regarding treatment of patients with a dual diagnosis of BD and attention-deficit hyperactivity disorder (ADHD) in general and use of central stimulants (CS) in particular.

1.1 Classification systems

The most widely acknowledged diagnostic classifications system tools are the Diagnostic and Statistical Manual of Mental Disorders (DSM) (15) and the International Classification of Diseases (ICD) (16). Whereas DSM concerns mental disorders only (15), ICD concerns all medical conditions and dedicates one chapter to mental and behavioural disorders (chapter V) (16). DSM was created by the American Psychiatric Association (APA) with the first version (DSM-I) published in 1952. Subsequent versions included DSM-II (1968), DSM-III (1980), DSM-III-R (1987), DSM-IV (1994) and DSM-IV-TR (2000). The latest and current version is DSM-5, published in 2013 (17). ICD was developed under the auspices of the International Statistical Institute at the end of the 19th century. The first version was published as the International List of Causes of Diseases in 1893. The World Health Organisation (WHO) took over ICD in 1948. The revisions most relevant to this thesis are ICD-9, in use from 1974 to 1995, and ICD-10, in use from 1995 (18). The next revision, ICD-11, is expected to come into use from 2022 (19). Thus, diagnostic classification systems are

constantly changing (20). BD and other diagnoses relevant to this thesis are discussed here in the context of the diagnostic criteria systems that were most commonly used in the research work underlying this thesis. These are DSM-5 (15), DSM-IV-TR (21) and ICD-10 (16). ICD-10 Clinical Modification (CM) (22), which has been developed in the United States for use in health care systems, is not considered here.

1.1.1 Diagnostic criteria and classification of bipolar disorder

Mood fluctuations are common in life and a natural part of most people's lives. However, when mood swings become so tangible that they interfere with functioning in everyday life, then symptoms may be associated with BD. BD can manifest itself in three different mood states, (a) manic, (b) hypomanic, and (c) depressive episodes. Manic episodes are characterised by symptoms of abnormally elevated mood, high energy, racing thoughts, and excessive involvement in pleasurable and goal-directed activities. Hypomanic episodes run with the same diagnostic criteria as manic episodes, albeit with less severe symptoms and fewer days of mood disturbance. During hypomanic episodes mood and behavioural changes are clearly noticeable to others. Yet, such episodes do not cause such a pronounced functional impairment for the individual. Therefore, people seldom seek help during hypomania and the condition may remain unrecognized (23). At the other pole of the mood spectrum are depressive episodes. Such are characterized by clinical symptoms of profound low mood, low energy and loss of pleasure, motivation and interest in daily activities (*Table 1*) (cf. Appedix I, p. 96: Diagnostic criteria of manic, hypomanic and depressive episodes according to DSM-5, DSM-IV-TR and ICD-10).

Mixed features

Additionally, all types of episodes can carry symptoms of the opposite pole, "mixed features". In DSM-IV-TR, a "mixed episode" was considered a mood episode in itself. To meet the criteria, sufficient symptoms of both affective poles had to be present simultaneously or appear in close temporal succession. In the DSM-5, "mixed episode" was removed as a diagnostic entity and replaced with a "mixed specifier" (24). In DSM-5, this specifier can be applied to any affective episode that (a) fulfils the criteria for a hypomanic/manic or depressive episode, and (b) has three symptoms of opposite pole present at the same time. Approximately 40% of patients with BD experience episodes with mixed features (25). There are even other specifiers that can be added to a mood episode, such as "anxiety", "rapid cycling" and "mood-congruent psychotic features". By definition, psychotic symptoms are never present during hypomania; such would automatically qualify for a manic episode (15). Psychotic features are common in BD with a lifetime prevalence of up to 74% (26).

Table 1. Diagnostic Criteria of Manic, Hypomanic or Major depressive episodes according to DSM-5 (abridged) (15)

Manic episode
Essential
A distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy, for at least *one week*
Other
At least three symptoms, or four if mood has only been irritable, (1) Inflated self-esteem or grandiosity (2) Decreased need for sleep (3) More talkative than usual or pressure to keep talking (4) Flight of ideas of subjective experience of racing thoughts (5) Distractibility (6) Increase of goal-directed activity or psychomotor agitation (7) Excessive involvement in pleasurable activities with a high potential for painful consequences
Functioning
Marked impairment in functioning or need for hospitalisation or psychotic features
Hypomanic episode
Essential
A distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy, for at least *four days*
Other
Same as for manic episode
Functioning
Not severe enough to cause marked impairment or to necessitate hospitalisation, no psychotic symptoms
Major depressive episode
At least five symptoms present during a *two-week period*
Essential
(1) Depressed mood or (2) Loss of interest or pleasure
Other
(3) Significant weight loss (4) Insomnia or hypersomnia (5) Psychomotor agitation or retardation (6) Fatigue or loss of energy (7) Feelings of worthlessness or excessive or inappropriate guilt (8) Diminished ability to think or concentrate or indecisiveness (9) Recurrent thoughts of suicidal ideation, suicide attempt or specific plan to commit suicide
Functioning: Significant distress or impairment in functioning

Bipolar disorder subtypes
BD is further classified into different subtypes in all classification systems (cf. Appendix I, p. 98: Classification of bipolar subtypes according to DSM-5, DSM-IV-TR and ICD-10). Whereas ICD-10 requires occurrence of at least one episode of either pole for the diagnosis of BD (16), DSM-5 (15) and DSM IV-TR (21) only require occurrence of at least one manic episode for the diagnosis of bipolar disorder type I (BD-I). Major depressive episodes usually occur but are not required for the diagnosis of BD-I. In DSM-5 (15) and DSM IV-TR (21), bipolar disorder type II (BD-II) requires occurrence of both a hypomanic and a depressive episode. In both classification systems, cyclothymic disorder is characterized by prolonged recurrent symptoms of hypomania and depression, but symptoms do not fulfil criteria for either episode completely (15,21). Individuals with other subtypes "other specified/unspecified and related disorders" do not fully meet the criteria for manic or depressive episodes. For instance, duration of symptoms may be too short (15). DSM-5 has been criticized for adding increased energy/activity as a gate criterion for hypomania/mania. This addition and the strict duration criteria for hypomania and mania may lead to underdiagnosis of BD in depressed patients (20). DSM-5 has further been criticized for automatically allocating a patient to the BD-I category on grounds of a manic status only (27).

1.1.2 Schizoaffective disorder
In 1899, the German psychiatrist Emil Kraepelin suggested a classification that demarcated "manic-depressive insanity" from "dementia precox", the latter being later renamed schizophrenia. The DSM and ICD classifications roughly follow this dichotomy of bipolar and psychotic disorders. However, already Kraepelin noted that there were intermediate states that did not fall clearly into either category. For these, the term "schizoaffective disorder" (SZD) was coined in 1933. Schizoaffective disorders related to a "subgroup of schizophreniform psychoses with a good prognosis and a simultaneous presence of schizophrenic and affective syndromes". Already Kraepelin recognised that overlapping symptoms put into question his diagnostic dichotomy of affective disorders on the one hand and psychotic disorders on the other. Affective and psychotic symptoms might after all occur on a continuum (28). The dichotomy/continuum question remains unresolved. SZD is listed in both, DSM (*Table 2*) and ICD (cf. Appendix I, p. 100: Diagnostic criteria and classification of schizoaffective disorder according to DSM-5, DSM-IV and ICD-10). SZD is mentioned here because patients with this diagnosis were included in the research work underlying this thesis.

Table 2. Diagnostic criteria of schizoaffective disorder according to DSM-5 (abridged) (15)

• An uninterrupted period of illness during which, at some time, there is a major mood episode (major depressive or manic) concurrent with criterion A for schizophrenia. • Delusions or hallucinations for two or more weeks in the absence of a major mood episode (major depressive or manic) during the lifetime duration of the illness. • Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of illness.
Specifiers Bipolar type (episodes of mania and sometimes major depression) Depressive type (includes only major depressive episodes)

1.2 Aetiology

The exact cause of BD is unknown. As for most other mental disorders, the aetiology may involve biological, psychological and social factors. BD is highly heritable, and several risk genes have been identified (29-31). Twin-studies have consistently shown that BD aggregates in families. Genes may account for familial aggregation in 60-85% (32). Individuals with a first-degree relative with BD have a 9% risk for also developing BD. This corresponds to a ten-fold increased risk compared to relatives of unaffected controls (31,32). However, monozygotic twin concordance is about 40-45%, indicating that genes cannot explain the complete picture (31). Beyond the well-established factor of heritability, little is known about the other aetiologic factors of bipolar disorder. Other biological factors include structural and functional brain changes and altered immune-inflammatory mechanisms (29,33). Ultimately, findings are diverse and difficult to integrate (29).

1.3 Epidemiology

1.3.1 Prevalence

Bipolar disorder affects about 1 to 2% of the world population (4-7), irrespective of gender (34), nationality, culture, ethnic group (35) or socioeconomic status (4). In a worldwide standardised mental health survey based on community adults (World Mental Health Survey Initiative), the aggregated estimated lifetime prevalence of bipolar spectrum disorder was 2.4%. When divided into subgroups, BD-I accounted for 0.6%, BD-II for 0.4%, and "subthreshold BD" for 1.4%. There was a substantial cross-national variation regarding rates of bipolar spectrum disorders. The lowest prevalence was observed in India (0.1%) and the highest in the United States (4.4%). This variation of prevalence rates may have been due to "true" differences, underreporting due to perceived stigma or

difference in access to mental health services. However, the authors also identified variations in the way the study instruments were applied, including variation in translation, implementation and quality control. Such method-related factors may have led to higher proportion of false negatives in some countries (5).

1.3.2 Clinical course and prognosis

BD is among the leading causes of disability worldwide (5,36), leading to impaired psychosocial functioning (2,37), impaired quality of life (38), and a dramatic reduction in life-expectancy compared to the general population (39).

The clinical course of BD is heterogeneous. Yet, the risk of relapse increases with the number of previous mood episodes (8). Individuals with bipolar disorder may be severely affected by their illness. Relapses may lead to severe mood episodes with increased risk of hospitalisation (12) and suicide (40). During episodes-free intervals, individuals may be relatively symptom-free. However, subsyndromal symptoms and functional impairment are common (1-3). Functional recovery may take a year after recovery from a mood episode (not fulfilling formal criteria for an active episode any longer). This delay is mainly due to residual depressive symptoms (1).

Patients with BD spend about half of their time symptomatically ill. Depressive symptoms predominate the picture in both BD-I and BD-II (41-43). In a prospective long-term naturalistic study, patients with BD-I disorder were followed-up for about 13 years on average. They were symptomatically ill for about 47% of the follow-up period. During the periods of active illness, depressive symptoms accounted for 32%, hypomanic/manic for 9% and cycling/mixed symptoms for 6% (41). A comparable study followed patients with BD-II disorder also for an average of 13 years. In that study, patients were symptomatically ill during 54% of the follow-up time. During the periods of active illness, depressive symptoms accounted for 50%, hypomanic symptoms for 1% and cycling/mixed symptoms for 2% (42).

During lifetime, most patients with BD are also diagnosed with at least one comorbid psychiatric disorder (5,8,35). Commonly reported comorbid conditions are anxiety disorders (5,35,44,45) ADHD (46), personality disorders (47) and alcohol (48,49) and other substance use disorders (49). Comorbidity affects the clinical course in patients with BD with poorer treatment response, more severe symptoms, more time spent ill and increased risk for suicide (44,46,47,50,51).

1.3.3 Life-expectancy

The average life expectancy of patients with BD may substantially be decreased by 9 to 20 years (39,52-54). There is an excess mortality rate of about two times than that of the general population (39,53,55). In a large meta-analysis of 31 studies, the all-cause standardized mortality rate (SMR; the ratio of observed

deaths in the study group compared to expected deaths in the general population) was two-fold. The SMR was increased for all causes of death under study, including deaths from circulatory diseases, respiratory diseases, infections, neoplasms and unnatural deaths (suicide, other violent deaths) (55).

Associated somatic morbidity

The causes for the reduced life expectancy in patients with BD are complex and multifactorial. Firstly, patients with BD have higher occurrence of some common chronic diseases, such as cardiovascular diseases (56), respiratory diseases (57) and type-2 diabetes (58,59). They also have more risk factors for other conditions, such as metabolic syndrome (59,60), obesity (61), unhealthy diet (62), smoking (57) and excessive alcohol use (48). Use of pharmacological treatments with unfavourable metabolic outcomes increase the risk even further (63). At the same time, patients with BD generally have poorer access to physical health care, including suboptimal care, treatment delay (64) and under-diagnosis (65). This unacceptable physical health disparity (66) does not seem to be improving. To the contrary, the mortality gap between individuals with BD and the general population is widening (67).

Suicidal behaviour and suicide

Finally, patients with BD experience higher mortality rates due to unnatural causes, including suicide, accidental and violent death (55). Patients with BD are at great risk for self-injurious and suicidal behaviour. Estimated lifetime prevalence of attempted suicide varies between 25 to 50% (50,68,69). In a Danish national register study of participants born between 1955 to 1991, a total of 176 347 individuals who came into contact with secondary mental health services for the first time were each matched with 5 control individuals. They were followed prospectively for a maximum of 36 years (median follow-up, 18 years). In this study, the absolute risk for death by suicide was 8% for men with BD and 5% for women (70). In a cohort study of 406 patients with mood disorders, 220 patients with BD previously admitted for psychiatric care, were followed prospectively for 40 to 44 years. By the last follow-up, 80% of patients with BD had died. Of these 10.2% had committed suicide (71).

Estimates of suicide risk vary widely. The risk may be eight to 30 times higher in patients with BD than in the general population (39,40,72-75). Schaffer et al. examined suicide attempts and suicide in patients with BD in a systematic review. This review included studies published from 1 January 1980 to 30 May 2014. To calculate the overall suicide rate, previously reported rates were pooled by sample size and exposure years.The review highlighted the heterogeneity of existing literature on suicide attempts and suicides in patients with BD. Addition of more recent studies lowered previously reported pooled estimated suicide rates. The review concluded that 23 to 26% of individuals with BD would attempt suicide. The overall estimated suicide rate was 164 per 100 000 person-years; a 10-fold

greater risk than that of the general population. The estimated male/female suicide rate ratio was 1.7:1 (50). The study by Hayes et. al. showed similar estimates, with the SMR for suicide being 14-fold in individuals with BD (55).

1.3.4 Gender

In most studies, the lifetime prevalence of BD is about equal in both genders (5,34,76). There is little evidence of gender differences in prevalence rates overall (7). However, several studies point towards gender differences regarding bipolar subtypes, polarity, duration of symptoms and treatment patterns (77). BD-II (5,76,78), rapid cycling (76,79) and mixed episodes (76,80) have repeatedly been shown to be more common among women with BD. Moreover, evidence suggests that women have higher rates of depressive episodes (34,79,80). Other studies, however, report lack of relationship between gender and occurrence of rapid cycling (78,81) or depressive episodes (78). In the World Mental Health Survey Initiative, lifetime rates of BD-I and subthreshold bipolar disorder were greater in men than in women (5). In addition, a national U.S. epidemiologic survey found no difference in lifetime prevalence of BD-I between men and women although unipolar mania was more common among men (34).

Irrespective of whether occurrence of subtypes differs between men and women; clinical course, comorbidities and treatment may differ. Women with BD may have an increased risk for suicidal behaviour (80), eating disorders, anxiety, as well as metabolic and endocrine illnesses (80,82). Men, however, may run a higher risk of substance misuse (77,79) and neurodevelopmental disorders (79,80). A Swedish national register study based on 7354 patients identified several treatment differences between men and women with BD. Women were more frequently treated with antidepressants, lamotrigine, benzodiazepines, ECT and psychotherapy. Men were more likely to receive lithium. The authors concluded that gender differences in level of functioning, bipolar subtype or severity of illness could not explain these observed treatment differences. They suggested that clinicians' treatment decisions were influenced by gender to some extent (77).

1.3.5 Age of onset

BD frequently commences in young adulthood. Overall, the mean age of onset is around 25 years (8). Evidence of whether BD-I or BD-II manifest earlier in life is inconclusive. In a review of 17 studies of patients with BD-I and BD-II, mean age of onset varied between 18 to 34 years. Whereas eight of studies reported a significant difference of age of onset between patients with BD-I and BD-II, nine studies did not. Of the studies with significant differences, six studies suggested an earlier age of onset for BD-I. Two studies suggested an earlier age of onset in BD-II (83).

Although the majority of patients fall ill early in life (84), about 5 to 10% of individuals are 50 years or older at time of their first hypomanic or manic episode (85).

Earlier age of onset may impact long-term outcomes negatively (86). BD during early life has been associated with greater chronicity and severity, including higher levels of comorbidities (86-88), poorer response to treatment (87), higher frequency of mood episodes (88), greater severity of depression (86), more psychotic symptoms (87), more hospitalisations (89) and higher rates of suicide attempts (88,89). Whereas mean age of onset is early, mean age at diagnosis is much later. The delay between illness onset and start of prophylactic long-term treatment may lie between seven and eleven years (90).

1.4 Mood-stabilisers as maintenance treatment

Long-term treatment with mood-stabilising medicines are often required to prevent recurrence of major depressive and hypomanic or manic episodes, reduce residual symptoms and restore functioning in daily life. Such mood-stabilisers include, lithium, AC and some SGAs.

1.4.1 Lithium

Lithium remains a first-line agent in the maintenance treatment for bipolar disorder (8,10,91-93). The evidence-based guidelines from the British Association for Psychopharmacology (BAP) (93) and the National Institute for Health and Care Excellence (NICE) guidelines (10), recommend lithium as treatment of choice. With the exception of the Canadian Network for Mood and Anxiety Treatments (CANMAT), the International Society for Bipolar Disorders (ISBD) guidelines (8) and the Swedish Psychiatric Association (SPA) guideline (94), evidence of the treatment of BD-II is extrapolated from evidence for the treatment of BD-I. However, several guidelines point out the importance of individualised treatment, taking the predominant polarity into account (91-93,95). The evidence for lithium as a maintenance treatment for BD is strong and consistent both in clinical trials (91,96-100) and naturalistic settings (101).

In a systematic review and meta-analysis of randomised controlled trials concerning relapse prevention, lithium was compared with placebo and alternative mood-stabilisers (AC or SGAs). Results derived from seven trials showed that lithium was more effective than placebo for the prevention of overall mood and manic episodes. A further seven trials showed that lithium was also superior to AC in the prevention of manic episodes, but not for overall mood or depressive episodes (99). Data from long-term observational studies and large register studies have added further evidence for the superiority of lithium compared to other mood-stabilisers, concerning prevention of severe affective episodes and hospital admissions (12,14,101-103).

Additionally, lithium is the only mood-stabiliser with demonstrated suicidal behaviour-protective effect (11,13,104,105), but other mood-stabilisers have been rarely studied to this effect (50).

Adverse effects

Along with its desired effects, lithium may cause undesired adverse effects. Adverse effects are common during lithium treatment. Yet, estimates of adverse effects vary considerably across studies. Nausea, seen in 10% to 20% of lithium-treated patients, and diarrhoea, seen in 10% of patients, are generally considered early and transient. Other common adverse effects are tremor, primarily of the hands (30%), weight gain (20 to 77%) and fatigue/dullness (106). Excessive urination with secondary thirst (polyuria and polydipsia) may occur in up to 70% of patients. This effect occurs early in treatment and is often reversible. However, it may become irreversible after long-term therapy (106,107). Nephrogenic diabetes insipidus (defined as a reduced urine concentration capacity due to tubular renal insufficiency) may occur in 12% of patients treated with lithium for more than 15 years (108). Long-term use of lithium may lead to progressive chronic kidney disease (CKD) (109). Moderate CKD has been reported in 21 to 55% of patients treated with lithium long-term. End-stage renal disease has been reported in 1.5% (110). Thyroid stimulating hormone (TSH) may rise in 19 to 35 % of patients with a prevalence of lithium-induced hypothyroidism of 14 to 17% (111). Disturbances in calcium homeostasis have been reported in a quarter of lithium-treated patients (112) and the risk for lithium-induced hyperparathyroidism is approximately 10% (113). Lithium has a narrow therapeutic index that can give rise to intoxications. This may be one of the reasons for the decline in lithium use seen in some parts of the world (114). Most intoxications, however, can be managed safely, if recognised early (115).

1.4.2 Anticonvulsants

Several AC are used as maintenance treatment for BD. Valproate and lamotrigine are the most frequently used as mood-stabilisers.

Valproate

Valproate in its various formulations (sodium valproate or divalprolex sodium) is used widely (91). The CANMAT and ISBD guideline considers valproate a first-line agent for preventing relapses (8). It has been suggested that lithium in monotherapy is superior to valproate in monotherapy (97). One recent post-hoc analysis of a small randomised controlled trial (RCT) called into question the therapeutic superiority of lithium (116). Possibly, though, this trial was underpowered. Although valproate may be better tolerated than lithium (117), serious adverse effects can arise. The major concern for treatment with valproate is teratogenicity. Valproate use during pregnancy is highly associated with malformations, such as neural tube defects, cardiac and craniofacial/oro-facial

cleft malformations (118). Since November 2014, the European Medicines Agency (EMA) has advised doctors in the EU to "not to prescribe valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated" (119).

Lamotrigine

Lamotrigine is mainly effective for the prevention of depressive episodes in BD. Thus, lamotrigine is particularly suited for the treatment of BD-II (93,120). Due to the need of slow titration to prevent severe skin reactions (91), lamotrigine monotherapy may not be an option for patients who require fast relief from depressive symptoms (93). A recent Cochrane review did not find any increased risk for major malformations with lamotrigine during pregnancy. More data is needed though, before drawing firm conclusions (118). Lamotrigine is usually well tolerated and advantageous in terms of metabolic side effects (91).

Other anticonvulsants

Carbamazepine may be effective in preventing mania and "any" mood episode in non-enriched samples. However, the usefulness is clearly limited due to a relatively low therapeutic index and tolerability problems. Carbamazepine is a potent cytochrome P450 (CYP) 3A4 inductor. Hence it can interact with many other medicines including oral contraceptives. At the same time, carbamazepine runs an increased risk for congenital malformations (118). Yet another AC, topiramate, has been tested as a mood-stabiliser. However, treatment trials and maintenance studies have not favoured its use to prevent relapses (91,93).

1.4.3 Second-generation antipsychotics

Several SGAs are also useful as long-term treatment for BD. Quetiapine, olanzapine and aripiprazole are currently most commonly used in this context. There is firm evidence that quetiapine can prevent affective episodes at both poles, i.e. either mania or depression in enriched samples (91,93). Olanzapine can also prevent manic and depressive episodes with somewhat weaker evidence for its propensity to prevent depressive relapses. Aripiprazole can prevent subsequent manic episodes in patients who responded to initial aripiprazole-treatment during an acute manic episode. However, it remains unclear whether aripiprazole can prevent subsequent depressive episodes (91).

Other SGAs may also have mood-stabilising properties. Long acting injectable (LAI) risperidone preparations prevent manic but not depressive episodes. Paliperidone, an active metabolite of risperidone, may prevent mania (91,93). Lurasidone may be useful for preventing depressive relapses (93) and treating acute bipolar depression (121). As an add-on treatment, ziprasidone may prevent manic episodes (91,93).

SGAs have lower risk of extrapyramidal side effects and tardive dyskinesia compared with first-generation antipsychotics. Concerning metabolic adverse

effects, SGAs are heterogenous. Clozapine and olanzapine have the worst metabolic profile and aripipazole, bexiprazole, cariprazine, lurasidone and ziprasidone the best metabolic profile (122). Quetiapin may also lead to substantial weight gain. SGAs with adverse metabolic profiles and higher risk for weight gain may be downgraded in the hierarchy of recommended maintenance treatments (91).

1.5 Factors associated with pharmacological treatment response

At present, treatment guidelines stress the importance of individualized treatment, taking factors such as predominate polarity, comorbidities and peri- and postnatal factors into account. However, our knowledge remains limited regarding such factors that may modify the pharmacological treatment outcome. BD subgroup, gender, adherence, age, comorbidities such as substance use disorder or ADHD may all influence treatment effects both in short and long-term. Such factors may not be sufficiently taken into account in daily practice.

1.5.1 Non-adherence to lithium

Adherence to prescribed medication is a major challenge in medicine in general (123,124). However, non-adherence seems even more common among patients with psychiatric disorders (123). For patients with severe psychiatric disorders, adherence to medicine is crucial; non-adherence often causes exacerbation of illness with potentially serious consequences. Lack of insight, substance misuse, limited access to health care, lack of social support and adverse effects are some of the factors associated with non-adherence in patients with severe psychiatric disorders. For patients with BD, non-adherence to psychotropic medication has been estimated to 44% (125).

In patients with BD, lack of adherence to lithium is a frequent cause of relapse (126). In a large longitudinal cohort study, the median duration of continuous adherence to first-time lithium treatment was only 76 days (127). Reported non-adherence rates for lithium vary widely, from 6 to 61% (128-131).

Despite the robust evidence for lithium as maintenance treatment and guideline recommendations to choose lithium as first-line agent (10,93), tolerability issues may limit long-term use. In patients with BD, lithium is underutilised (114,132). The reasons are multifactorial. Introduction and marketing of other mood-stablisers, concerns about serious adverse effects such as renal impairment and lithium intoxication and lack of understanding of lithium's mechanism of action may all play a role (132-135).

Little is known about reasons for stopping lithium treatment in patients with BD. Patients and clinicians may discontinue for different reasons (106). Reasons for lithium discontinuation have been explored in only few small studies from the 80s and 90s (128,136-138). A first step towards improvement of adherence is understanding why women and men with BD discontinue lithium maintenance treatment.

1.5.2 Consequences of non-adherence to lithium

Patients who discontinue lithium treatment have a high risk of recurrence (139). Yet, little is known about the clinical course of BD after lithium discontinuation, considering subtypes of BD. BD I and II differ by degree in clinical features (140). Hence, mood-stabilisers could have a differential impact on both BD types. The evidence for mood-stabiliser treatment for BD II is limited. As mentioned previously, guidelines tend to extrapolate their treatment recommendations from the available evidence of BD-I (10,93). Both, clinical trials (91,99) and observational studies (101) mainly focus on BD-I. Register studies lack data at symptom level (141). This may make it difficult to distinguish between both types of disorders and give rise to misclassification.

1.5.3 ADHD as a factor that modifies treatment and clinical course of bipolar disorder

Classification and diagnostic criteria of ADHD

ADHD is a common comorbidity in patients with BD (46). Being a relatively recent psychiatric disorder, diagnostic classification is still evolving (142). Whereas DSM requires symptoms of inattention *or* hyperactivity/impulsivity (15,21), ICD requires symptoms of impaired attention *and* overactivity (16). ICD suggests an onset of symptoms before the age of six years (16) and DSM-IV-TR before the age of seven years (21) (cf. Appendix I, p.101: Diagnostic criteria and Classification of ADHD according to DSM-5, DSM-IV-TR and ICD-10). In DSM-5, the age limit is substantially raised to 12 years (*Table 3*) (15).

Table 3. Diagnostic Critera for ADHD in adults according to DSM-5 (abridged) (15)

A persistent pattern of inattention and/or hyperactivity/impulsivity that interferes with functioning or development, as characterised by inattention (at least five symptoms) and/or hyperactivity or impulsivity (at least five symptoms).
Inattentive or hyperactive-impulsive symptoms
•have persisted for at least six months.
•were present prior the age of 12 years.
•are present in at least two settings.

Epidemiology

Prevalence of a dual diagnosis of BD and ADHD

Due to overlapping symptoms of BD and ADHD, diagnostic differentiation might be challenging (143), Even more so when deciding whether the patient suffers from one or both conditions. This diagnostic overlap may in part explain the variation in prevalence estimates. For individuals with BD and comorbid ADHD, prevalence estimates range from 4% to 48% (120). For individuals with ADHD, comorbid BD prevalence estimates range from 5% to 47% (144).

Clinical course and prognosis

Co-occurrence of ADHD in patients with BD seems to increase the risk of unfavourable outcomes in terms of unemployment, lower socioeconomic status, unstable relationships, substance misuse, increased risk of hypomania (46) and suicide attempts (46,145). Both ADHD (146,147) and BD (50,55) *per se* already increase the suicide risk.

Central stimulant treatment in patients with bipolar disorder and ADHD

CS medications are mainstay as pharmacological treatment for ADHD. These include methylphenidates (MPH) in different formulations and amfetamines such as lisdexamfetamine, dexamfetamine and mixed amfetamine salts (148,149). The NICE guidelines (updated 2018) recommend lisdexamfetamine or methylphenidate as first-line treatments for adults with ADHD (150). A recently published meta-analysis of double-blind randomized controlled trials endorsed amphetamines (including lisdexamfetamine) as preferred first-line agents for adults (148).

Many clinicians may be reluctant to treat patients with BD and ADHD with CS for fear of inducing manic switches. Most evidence regarding the effects and adverse effects of CS in patients with BD has been gathered in the context of treatment for bipolar depression. In the majority of relevant trials and case reports, there was no association between CS treatment and subsequent switches to hypomania/mania. However, research of efficacy and safety of CS treatment in patients with BD and comorbid ADHD is limited (151,152). A large Swedish register study of adult patients with BD compared the rate of mania (defined as hospitalization for mania or a new dispensation of a mood-stabiliser) between those who had received CS and those who had not. They found no evidence for that methylphenidate would induce mania when mood-stabilisers were given concomitantly (153). The Updated European Consensus Statement considered this result additional support for the current recommendation to treat patients with BD and ADHD with stimulants as long as mood-stabilisers are taken concurrently (149).

Suicidal behaviour in patients with bipolar disorder and ADHD treated with central stimulants

As previously described, most studies point towards an increased risk of suicidal behaviour in patients with BD and comorbid ADHD. However, whether CS affect suicidal behaviour in this patient group has not been explored in the literature.

According to the national formularies in Sweden and in the UK, methylphenidate is contraindicated in patients with suicidal tendencies (154,155). For lisdexamfetamine, suicidal tendencies are not listed as a contraindication in the Swedish national formulary (154).

The impact of CS on suicidal behaviour has been explored to some extent in patients with ADHD *only*. A large Swedish register study showed a reduced within patient rate of suicide related events among CS users (156). Yet, the evidence is sparse and mainly concerns children and adolescents with ADHD. In a nationwide study of children and young adults, a reduction in suicide risk was seen with prolonged methylphenidate treatment (157). A further nationwide study based on adolescents and young adults found methylphenidate to be risk-neutral in regard to suicide attempts. For males, however, long-term methylphenidate treatment seemed to decrease the risk of suicide attempts (147). Yet another study that followed boys with ADHD into young adulthood, showed that those who had been treated with higher methylphenidate doses had significantly fewer suicide attempts during childhood (158). For patients with a dual diagnosis of BD and ADHD, the impact of CS on suicidal behaviour has not been explored.

1.6 The thesis in context

Lithium is a first-line treatment of bipolar disorder, thought to be superior regarding the prevention of acute relapse, suicide and self-harm. But despite this therapeutic superiority, patients may find it difficult to take lithium long-term. Discontinuation rates between 6 to 61% have been reported. There are only a few small naturalistic studies conducted in 1980s/90s that have explored reasons for lithium discontinuation. Also, there is some evidence concerning reasons for drop-out from clinical trials. **Study I** explored reasons for lithium discontinuation.

Although lithium remains the treatment of choice for bipolar disorder, it also remains unclear whether lithium works equally well in BD-I and BD-II. Guidelines commonly extrapolate recommendations for BD-II from available evidence for BD-I. Finally, our understanding of how pharmacological treatment works in special patient populations remains limited. **Study II** compared the clinical course after lithium discontinuation in patients with BD-I and BD-II.

ADHD has emerged as a clinically significant comorbidity in patients with bipolar disorder. Patients with bipolar disorder and comorbid ADHD may benefit from CS. Recent evidence suggests that methylphenidate could be safely used in adults with BD, as long as mood-stabilisers were given simultaneously to prevent manic episodes. However, there are no studies that have explored the impact of CS on suicidal behaviour. **Study III** examined the risk of suicidal and non-suicidal self-injury (NSSI) behaviour when starting CS in patients with a dual diagnosis of BD and ADHD.

2 AIMS

2.1 Overall aims

The overall aim of this thesis was to study three factors that may modify treatment outcomes in patients with BD or schizoaffective disorder (SZD), (1) adherence to lithium and reasons for lithium discontinuation, (2) impact of lithium discontinuation on clinical course in different BD subtypes, and (3) impact of CS on suicidal and NSSI behaviour in patients with a dual diagnosis of BD and ADHD.

2.2 Specific aims

The specific aims of the studies included in this thesis were:

Study I: To (a) test whether patients with BD or SZD treated with lithium maintenance therapy were more likely to discontinue lithium because of adverse effects than a lack of therapeutic effectiveness, (b) explore gender differences, (c) understand the role of diagnosis and (d) identify who, patient or doctor, took the initiative to stop lithium.

Study II: To compare the impact of lithium discontinuation on hospital admissions and suicidal and NSSI behaviour in patients with BD-I or SZD (BD-I/SZD) and patients with BD-II or other BD (BD-II/other BD).

Study III: To evaluate the impact of CS treatment on suicidal and NSSI behaviour in patients with a pre-existing diagnosis of BD or SZD. Specifically, we tested the hypothesis that CS treatment significantly decreased the number of suicide attempts and NSSI events.

2.3 Hypotheses to be tested

In study I, we hypothesized that patients with BD/SZD were more likely to discontinue lithium treatment due to adverse effects than lack of therapeutic effectiveness.

In study II, we hypothesized that lithium maintenance treatment was less effective for patients with BD-II/other BD than for patients with BD-I/SZD.

In study III, we hypothesized that CS treatment significantly decreased the number of suicide attempts and NSSI events in patients with a dual diagnosis of BD/SZD and ADHD

3 MATERIALS AND METHODS

3.1 Method shared by all three studies

The methods for studies I, II and III are summarised in respective Strenthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (cf. Appendix II, p. 102: the STROBE statement). The STROBE initiative is an international collaboration that has developed "recommendations on what should be included in an accurate and complete report of an observational study" (159).

3.1.1 The LiSIE study

All studies of this thesis are part of LiSIE (Lithium – Study into effects and Side Effects). LiSIE is a research programme, set up to improve prophylactic long-term (maintenance) treatment of affective disorders. The programme takes form of a retrospective cohort study, exploring effects and side effects of lithium treatment compared to other mood-stabilisers.

3.1.2 Participant inclusion for the entire LiSIE cohort

For the entire LiSIE-cohort all patients in the two northernmost Swedish regions Norrbotten and Västerbotten, who were at least 18 years old and who had either received a diagnosis of BD (ICD F31), SZD (ICD F25) or had been treated with lithium between 1997 to 2011, were invited to participate. Patients were included if they consented. In accordance with the ethics approval granted (cf. section 3.1.3) deceased patients were also included. Exclusion criteria were then applied for study I, II and III.

3.1.3 Ethical approval

All studies were approved by the Regional Ethics Review Board at Umeå University, Sweden, dnrs: 2010-227-31M, 2011-228-32M and 2014-10-32M. For study III, there was an additional approval by the Regional Ethics Review Board at Umeå University, dnr: 2018-76-32M, with the request to extend the review period until 31 December 2017. The region of Norrbotten had approved the review of the electronic medical records for the purpose of research after appraisal by the Region Norrbotten Research and Learning Department, (Enheten för Forskning och Lärande, Region Norrbotten, FoL beredningsråd. Formerly called the Research and Development Department, Enheten för Forskning och Utveckling, Region Norrbotten, FoU beredningsråd). Ethical considerations are discussed in further detail in section 3.5.

3.1.4 Consent procedures

Participants were informed about the nature of the LiSIE-study in writing and provided verbal informed consent. The consent was documented in the research files, dated and signed by the research worker who obtained the consent. Consent procedures were concluded by the end of 2012. The cohort was locked at this point, and no new patients were included into the study thereafter. One patient subsequently withdrew from the study in accordance with the consent procedures. For deceased patients, in accordance with the ethics approval granted, no consent was obtained (cf. section 3.5).

3.1.5 Catchment area for participants of studies I, II and III

The studies included in this thesis are exclusively based on individuals from Norrbotten. Participants were identified through BD or SZD diagnoses recorded at health facitilities within the region. A uniform electronic medical record system is used within Norrbotten, enabling clinical information and laboratory test results to be available between disciplines.

Sweden is divided into 21 regions (previously county councils), with primarily responsibility of funding and provision of health care (160).

The region of Norrbotten is the northernmost region of Sweden. It covers about a quarter of Sweden´s total area with a population of around 250,000. Norrbotten region is mainly rural with some urban areas. Population density is 2.6 habitants per km^2. For comparision, the overall population density in Sweden is 25 habitants per km^2 (161).

Secondary mental health care within the region is almost exclusively public. Adult secondary mental health services are geographically divided into three areas: Sunderbyn, Piteå and Gällivare. There are three psychiatric in-patient facilties at hospitals located in the respective towns. There is also a region-wide forensic psychiatry medium-secure unit (in Öjebyn). Psychiatric outpatient clinics are located in the six most populated municipalities within the region (Luleå, Piteå, Kiruna, Boden, Gällivare and Kalix (162)) (*Figure 1*).

Figure 1. Adult secondary mental health care services within the region of Norrbotten

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3.1.6 Participant selection and inclusion criteria for studies I, II and II

From the entire LiSIE-cohort, participants from the region of Norrbotten were identified to form the Norrbotten LiSIE cohort (LiSIE-N). Of all 2239 invited patients in the region of Norrbotten, 1691 (75.5%) provided informed consent and 910 were deceased. Thus, the final LiSIE-N consisted of 2601 individuals. These were at least 18 years old and had either received a diagnosis of BD (ICD F31), SZD (ICD F25) or had been treated with lithium between 1997 and 2011. To further meet the inclusion criteria for respective studies of this thesis, patients had to have received a diagnosis of BD or SZD on at least two occasions, at least

six months apart any time between 1997 and 2013. In total, 1566 patients with BD or SZD were included for study I (*Figure 2*). Studies II and III are based on 1564 patients due to consent withdrawal in one patient (cf. section 3.1.4) and diagnosis reassessment in another. Baseline characteristics of the study sample at the end of the inclusion period are presented in *Table 4*.

3.1.7 Participants and exclusion criteria for studies I, II and III

For the studies I, II and III, patients were excluded in whom, after manual validation from the medical records, a diagnosis of schizophrenia was more likely than BD or SZD (*Figure 2*). Population data in Figure 2 are retrieved from the Statistics Sweden; Statistiska Centralbyrån, SCB (163).

3.1.8 Classification of diagnoses

Throughout the review period, clinicians had recorded diagnoses according to ICD or DSM in their various editions. For all three studies, the type of underlying affective disorder was recorded, BD-I, SZD, BD-II and other BD. For study I and II, patients were stratified into two groups according to underlying affective disorder. BD-I and SZD were allocated in one group (BD-I/ SZD) and BD-II, BD or otherwise specified BD (BD-II/BD other) in another group. The final diagnoses were validated from the medical case records.

Classification rules

A presence of a manic episode allocated a patient to the BD-I group by default. The category "other BD" was used for patients who (a) had an explicit BD diagnosis, (b) had not been given a diagnosis of BD-II, and (c) had not experienced any manic episode. This category included patients with a recorded diagnosis of BD not further specified and patients for whom a clinician had diagnosed a hypomanic episode in the context of having taken antidepressant medication (sometimes also referred as bipolar type IV disorder in the medical records). Additionally, for studies II and III, mixed features in a mood-disorder episode (mixed features) or rapid cycling were recorded.

3.1.9 Control for selection bias for studies I, II and III

Of all patients approached, 75.5% consented to inclusion into the LISIE study. In accordance with the ethical approval granted, selection bias was checked in the whole LiSIE study, comparing age, sex, maximum recorded lithium and creatinine level as key parameters, available in anonymized form. There was no significant difference between participating and non-participating patients.

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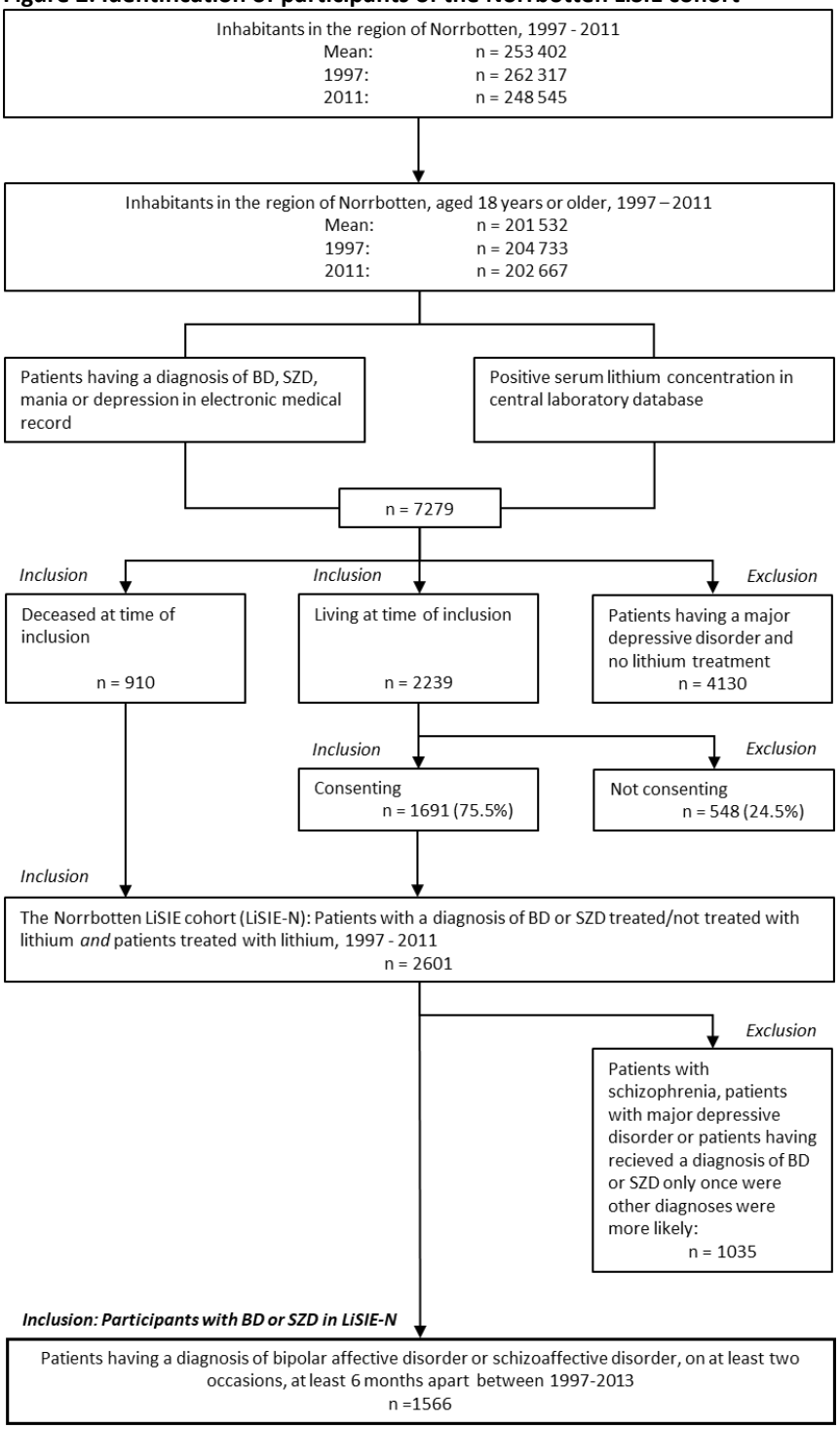
Table 4. Baseline characteristics of the study sample at the end of 2011

	Total sample			BD			SZD		
	Total	Female	Male	Total	Female	Male	Total	Female	Male
Study I, n (%)	1566	972 (62.1)	594 (37.9)	1333	843 (63.3)	490 (36.7)	594	129 (55.4)	104 (44.6)
Study II and III, n (%)	1564	971 (62.1)	593 (37.9)	1331	842 (63.3)	489 (36.7)	233	129 (55.4)	104 (44.6)
Living, n (%)	1346	844 (62.7)	502 (37.3)	1159	739 (63.8)	420 (36.2)	187	105 (56.1)	82 (43.9)
Age									
Mean (SD)	46.4 (16.1)	44.8 (16.2)	49.2 (15.5)	45.7 (16.4)	44.0 (16.5)	48.8 (15.7)	50.5 (13.5)	50.1 (12.9)	51.1 (14.2)
Min – Max	18 – 90	18 – 90	19 – 90	18 – 90	18 – 88	19 – 90	20 – 90	21 – 90	20 – 81
Deceased, n (%)	218	127 (58.3)	91 (41.7)	172	103 (59.9)	69 (40.1)	46	24 (52.2)	22 (47.8)
Age at death									
Mean (SD)	65.1 (15.8)	66.7 (16.4)	63.0 (14.8)	66.2 (16.7)	68.2 (17.0)	63.3 (15.9)	61.1 (11.1)	60.4 (11.6)	61.8 (10.6)
Min – Max	20 – 94	20 – 94	21 – 94	20 – 94	20 – 94	21 – 94	38 – 86	38 – 81	46 – 86

BD, bipolar disorder; SZD, schizoaffective disorder; n, number; SD, standard deviation.

Figure 2. Identification of participants of the Norrbotten LiSIE cohort

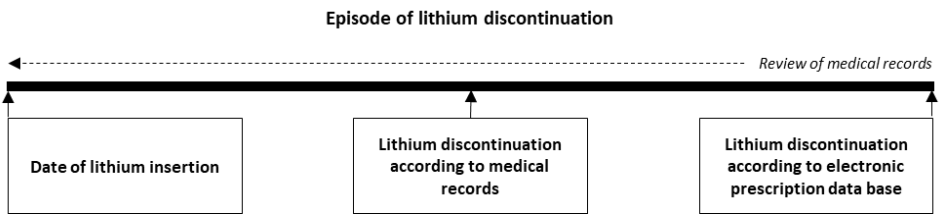


3.2 Specific method study I

3.2.1 Study design

Study I had a retrospective cohort design with lithium discontinuation as the index event (*Figure 3*). For study I, routine clinical data recorded was retrospectively examined until 31 December 2015. Data extraction, validation and analysis were performed 2016 and 2017.

Figure 3. Study design



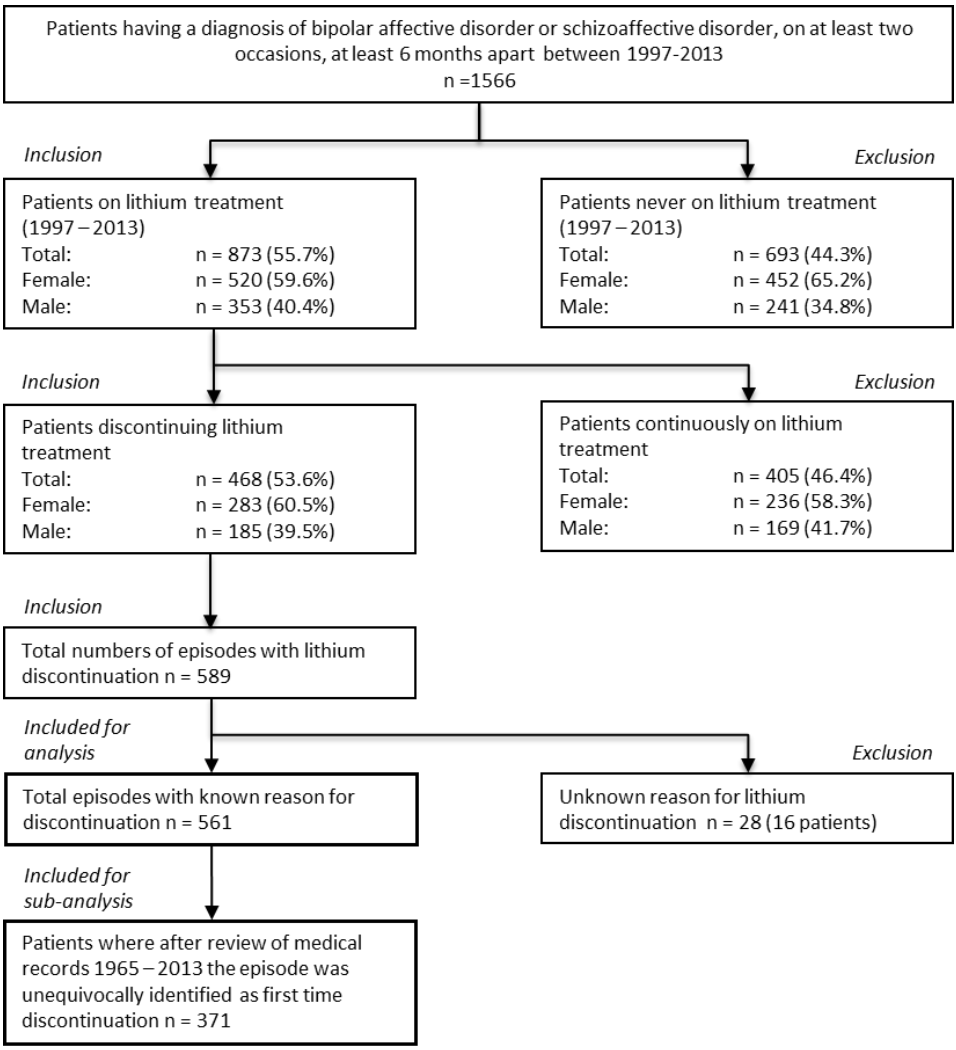
3.2.2 Participant selection and inclusion criteria

From the 1566 eligible patients in LiSIE-N, all patients with at least two lithium serum concentrations > 0.2 mmol/L recorded in the laboratory database at any time between 1997 and 2013 were included. This way, 873 patients were included since considered "truly" exposed to lithium. From these, all patients were identified with discontinuation of a lithium prescription at any time between 1997 and 2013 in the electronic prescription database. This way, 468 patients were identified who had first received and then discontinued lithium. Some patients had several attempts at lithium treatment. For the 468 patients included there were 589 episodes of lithium discontinuation recorded. Only episodes with recorded reason for lithium discontinuation were considered in the final analysis.

Exclusion

Twenty-eight episodes, corresponding to 16 patients, were excluded because reasons for lithium discontinuation had not been recorded (*Figure 4*).

Figure 4. Identification of study sample



3.2.3 Variable definitions

Exposure variables

Episodes of lithium discontinuation
Initially, all available encoded episodes of lithium discontinuation were identified from the patient database. Each such episode was manually validated according to information in medical records. This way, false positives were identified. Such arose when an electronic encoded prescription had been stopped or not been renewed because a new lithium prescription was issued instead. In some cases, lithium discontinuation preceded cancellation of the prescription. For such, the date of lithium discontinuation was determined from the documentation in the medical records as accurately as possible. An episode of lithium discontinuation was judged to be present when a patient had discontinued lithium treatment at least on one occasion for more than seven days, with the intention to stop for good. Temporary interruption of lithium was not counted as discontinuation (cf. section 3.2.3).

First episode of lithium discontinuation
In a sub-analysis, reasons for lithium discontinuation in relation to time on lithium treatment (lead-time) were explored. Here, only first episodes of lithium treatment were considered. This procedure was applied to avoid error estimates of the length of time a reason/problem/adverse event had persisted before lithium was stopped. For the sub-analysis, only episodes were included where it was certain that these were truly first episodes of lithium discontinuation. To identify previous lithium treatment episodes, which might have occurred prior to 1997, archived medical records were traced backwards to find each individual date of first lithium initiation. The earliest recorded date for start of first lithium treatment was 1965.

Exclusion
For the sub-analysis, ninety-seven patients were excluded, for whom it was unclear if the episode of lithium discontinuation during the study period really related to the very first lithium treatment episode (cf. section 3.2.2, *Figure 4*).

Diagnosis
This variable is described in detail in section 3.1.8. The diagnoses of the underlying BD or SZD were obtained at two time points, (a) at the date of first lithium start, or (b) at the date of each lithium start. All diagnoses were manually validated from the documentation in the medical records.

Outcome variables

Reasons for lithium discontinuation
The main outcome was reasons for lithium discontinuation. All recorded reasons for lithium discontinuation were divided into three main categories, (a) psychiatric reasons, related to the disorder itself or associated circumstances, i.e. non-adherence (feer for adverse effects, not agreeing with diagnosis, refusing medication, feeling subjectively well, not adhering to monitoring), perceived or actual lack of effectiveness, intentional lithium intoxication and other reasons, (b) physical health reasons or associated reasons that could interfere with lithium treatment, i.e. increase of lithium concentration, unintentional lithium intoxication, pregnancy or pregnancy-planning, physical health problem, and (c) adverse effects.

Lead-time to lithium discontinuation - first episodes only
This outcome explored how long a patient had coped with or a doctor had accepted a "reason" or an adverse event before lithium was discontinued.

Agent who took the initiative to discontinue lithium
A further outcome concerned the "agent who took the initiative to discontinue lithium", patient or doctor. For the decision process, it was explored whether or not patients had been in contact with and/or had consulted their doctor before discontinuation.

Stratification of outcomes
The reasons for lithium discontinuation were assessed further in relation to (a) type of underlying affective disorder, BD-I/SZD vs. BD-II/ other BD, (b) gender, and (c) person taking the initiative to discontinue lithium (doctor or patient).

3.2.4 Control for bias
All included episodes of lithium discontinuation were assessed separately by two reviewers in order to minimize observer and recording bias. Patients who had been excluded from the main analysis since reasons for lithium discontinuation were missing, had the same age and sex distribution as included patients. Regarding BD, the final diagnoses were validated by at least two researchers.

3.2.5 Statistical analysis
Descriptive statistics were used including frequencies and percentages for categorical data, means and standard deviations for continuous data, and when appropriate, median, ranges and minimum and maximum values. Pearson's chi-squared test was used to assess potential group differences for categorical data and independent t-test and one-way analysis of variance (ANOVA) for continuous data. ANOVA was used for comparison between the three groups,

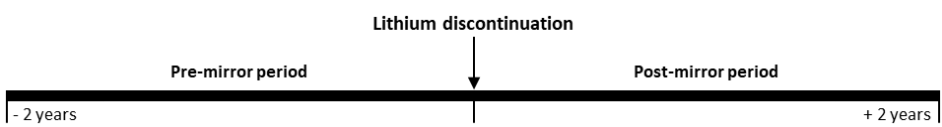
adverse effects, psychiatric reasons and physical health reasons. Throughout, statistical significance level was set to $p < 0.05$. For the statistical analysis, we used the IBM SPSS Statistics version 23 (Armonk, NY; IBM Corp).

3.3 Specific method study II

3.3.1 Study design

Study II had a mirror-image design in the framework of a retrospective cohort study. The index event for the mirror was lithium discontinuation. The mirror periods were the time within two years before lithium discontinuation (pre-mirror period) and the time within two years after lithium discontinuation (post-mirror period) (*Figure 5*). Both mirror-periods were then compared regarding to changes in outcome variables. For study II, routine clinical data recorded was retrospectively examined until 31 December 2015. Data extraction and validation were performed in 2016 and 2017. The data-analysis was performed in 2018. Study II followed partly the method of study I in regard to participant selection, exposure variable definitions and control for bias. Thus, where appropriate the method of study I is referred to.

Figure 5. Study design



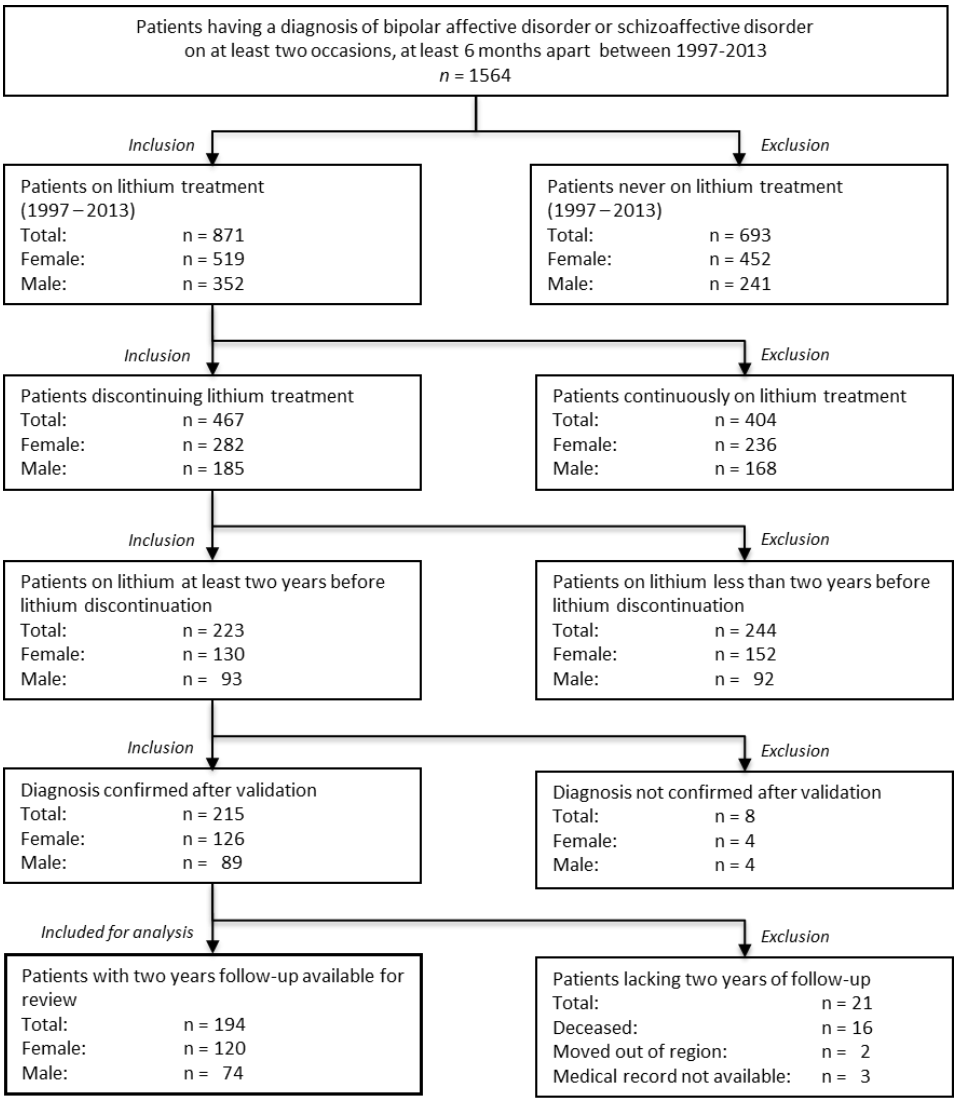
3.3.2 Participant selection and inclusion criteria

Study II used the same sampling procedure as in study I (cf. section 3.2.2). 467 patients were identified who had first received and then discontinued lithium. From this sample, 194 patients were identified who had (a) discontinued their lithium treatment, (b) been treated with lithium continuously for at least two years before discontinuation and, (c) had a two-year period available for follow-up. For this study, only the first episode of lithium discontinuation preceded by two years were considered.

Exclusion

For final analysis, eight patients were excluded for whom diagnosis of BD/SZD within the two-year pre-mirror period could not be confirmed. Additionally, a further 21 patients were excluded since their two-year follow-up fell short. This procedure was chosen to allow perfect mirror periods (*Figure 6*).

Figure 6. Identification of study sample



3.3.3 Variable definitions

Exposure variables

Episode of lithium discontinuation
Cf. section 3.2.3

Diagnosis
This variable is described in detail in section 3.1.8. The underlying affective disorder recorded prior to lithium discontinuation could vary. This was due to different assessments by different clinicians, use of various DSM- and ICD-editions and the long review period. The earliest recorded date for a BD was 1967. Hence, diagnoses from four different time points were abstracted to reach an approximation of the most likely diagnosis according to the DSM-5. Diagnoses were recorded (a) at the time of lithium initiation (b) before lithium discontinuation (c) at the end of the pre-mirror period, and (d) last recorded diagnosis at the last individual follow-up before 31 December 2015. Additionally, records were screened for diagnoses of hypomanic or manic episodes and for mood episodes with mixed features.

Lithium exposure
Patients needed to have been treated with lithium continuously for at least two years before stopping. This was validated from the medical records. All available electronic laboratory lithium serum concentration values within the two-year period before lithium discontinuation were abstracted. Mean lithium serum concentration values were adjusted for in the regression model. Archived medical records were traced backwards to identify the date of lithium initiation. The earliest recorded date for start of first lithium treatment was 1967.

Speed of lithium discontinuation
Here it was distinguished between "rapid" (0 to 14 days) or "gradual" discontinuation (more than 14 days).

Lithium reinstatement
Some patients reinstated lithium within the two-year post-mirror period. Information regarding lithium reinstatement was available from the medical records and the electronic prescriptions and the laboratory database.

Mood-stabiliser use after lithium discontinuation
Mood-stabiliser use after lithium discontinuation were considered as a potential confounding factor for our outcomes. Hence, the medical records were systematically abstracted for information regarding prescription and use of mood-stabilisers in the post mirror-period. There were three options, (a) no mood-stabiliser use after lithium discontinuation, (b) use of an alternative mood-

stabiliser, (c) lithium reinstatement. Alternative mood-stabilisers could fall into two categories, (a) AC, specifically valproate, lamotrigine, carbamazepine, and topiramate, or (b) SGAs, specifically olanzapine, quetiapine, aripiprazole, and risperidone. Such mood-stabiliser use was checked at the point of lithium discontinuation, and at three months and two years after lithium discontinuation.

Stable mood-stabiliser treatment
Treatment was defined as "stable", when a patient (as indicated by medical records) had been treated with the same alternative mood-stabiliser at three months and two years after lithium discontinuation.

Agent who took the initiative to discontinue lithium
Cf. section 3.2.3

Alcohol and/or substance use disorder
Alcohol and/or substance misuse was recorded within both, the two-year pre- and post-mirror periods. This was deemed to be present, when either an alcohol or substance use disorder was diagnosed according to DSM or ICD in their various editions, or when it was clearly documented in the medical records.

Outcome variables

Psychiatric hospital admissions
Number of psychiatric hospital admissions including type of admission (e.g compulsory or voluntary) and type of affective episode or other reason recorded at admission.

Psychiatric bed-days
Number of bed-days spent in hospital during psychiatric admissions.

Suicidal behaviour
Information regarding deliberate self-harm, regardless of intention, was retrieved from psychiatric records during the two year pre- and post-mirror periods. This meant that both suicide attempts and NSSI events were monitored (163) (henceforth referred to as suicide attempts/NSSI events). Events were abstracted from the medical records when patients came directly to psychiatric services in connection with the event or through consultation requests or emergency referrals. The following events were included: (a) attempts with a clear stated suicide intent, (b) events of NSSI (c) events where the intention was unclear and could be either a suicide attempt or a NSSI, and (d) deliberate, self-inflicted self-poisoning events where the intention was unclear and could be either a suicide attempt or a NSSI. Thus, self-poisoning was considered a NSSI when the intention was stated as an action of self-harm without suicidal intent. This deviates some from the general definition of NSSI, which comprises deliberate,

self-inflicted destruction of the body, such as cutting, burning or scratching oneself (163,164). The proposed diagnostic criteria for NSSI in the DSM-5 also states that the intentional self-inflicted damage is directed to the surface of the body (165).

Exclusion

Intoxications were excluded, when related to explicitly non-suicidal harmful substance use or addiction.

Stratification of outcomes

Outcomes were further assessed in relation to type of underlying affective disorder, BD-I/SZD vs. BD-II/ other BD, with and without a mixed specifier. In accordance with the mirror-image design, observations before and after the index event were paired for each individual. For further details cf. section 3.3.5.

3.3.4 Control for bias

Cf. section 3.3.2. Some patients (n = 21) were excluded from the final analysis, since their follow-up fell short of the required two-year period. In this group, there were more men. Excluded patients were also older than included patients. Therefore, a second analysis was conducted, also including patients with incomplete follow-up. The analysis based on this sample (n = 215) yielded the same significant results as for original sample (n = 194).

3.3.5 Statistical analysis

Descriptive statistics were used including frequencies and percentages for categorical data, means and standard deviations for continuous data, and when relevant, median, ranges and minimum and maximum values. In accordance with the mirror-image design**,** observations before and after the index event were paired for each individual. This way, patients acted as their "own controls" and results reflected within-individual changes. For continuous data (admissions, bed-days and suicide attempts/NSSI events)**,** paired t-test was used for group sizes of $\geq$40 in either group and Wilcoxon signed rank test for group sizes < 40 in either group (166). McNemar's test was used for paired categorical data (patients with admissions and patients with suicide attempts/NSSI events) and Pearson's chi-squared test for other categorical comparisons. Additionally, three multiple linear regression analyses were conducted. These explored whether the association between change in admissions and bed-days in relation to the diagnostic group, BD-I/SZD versus BD-II/other BD, was influenced by other potential confounding factors. Each model was adjusted for gender, mean age at lithium discontinuation, episode with mixed features *ever*, mean lithium concentration in the pre-mirror period, alternative mood-stabiliser treatment at lithium discontinuation, post-mirror stable mood-stabiliser treatment, speed of

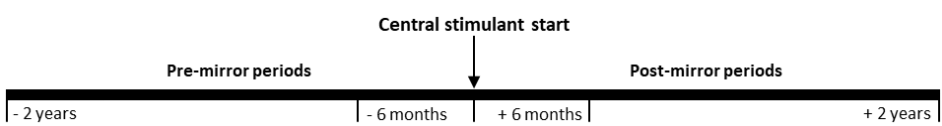
lithium withdrawal, consulted with a doctor before discontinuing, alcohol and/or substance misuse. Further, Kaplan-Meier plots were used to map the time periods from the point of lithium discontinuation until first admission. Four separate survival functions were created to account for type of bipolar disorder and speed of lithium discontinuation. Potential group differences were tested with the log rank test. Throughout, statistical significance level was set to $p < 0.05$. For the statistical analysis, we used the IBM SPSS Statistics version 25 (Armonk, NY; IBM Corp).

3.4 Specific method study III

3.4.1 Study design

Study III also had a mirror-image design in the framework of a retrospective cohort study. The index event for the mirror was the CS initiation. There were two mirror periods, (a) six months before and after CS initiation and (b) two years before and after CS initiation (*Figure 7*). Both pairs of mirror-periods were then compared regarding to changes in outcome variables. For study III, routine clinical data was retrospectively examined until 31 December 2017. Data extraction and validation were performed in 2018 and 2019. The data was analysed in 2019. Study III followed partly the method of study II in regard to the exposure variable definitions and control for bias. Thus, where appropriate the method of study II is referred to.

Figure 7: Study design



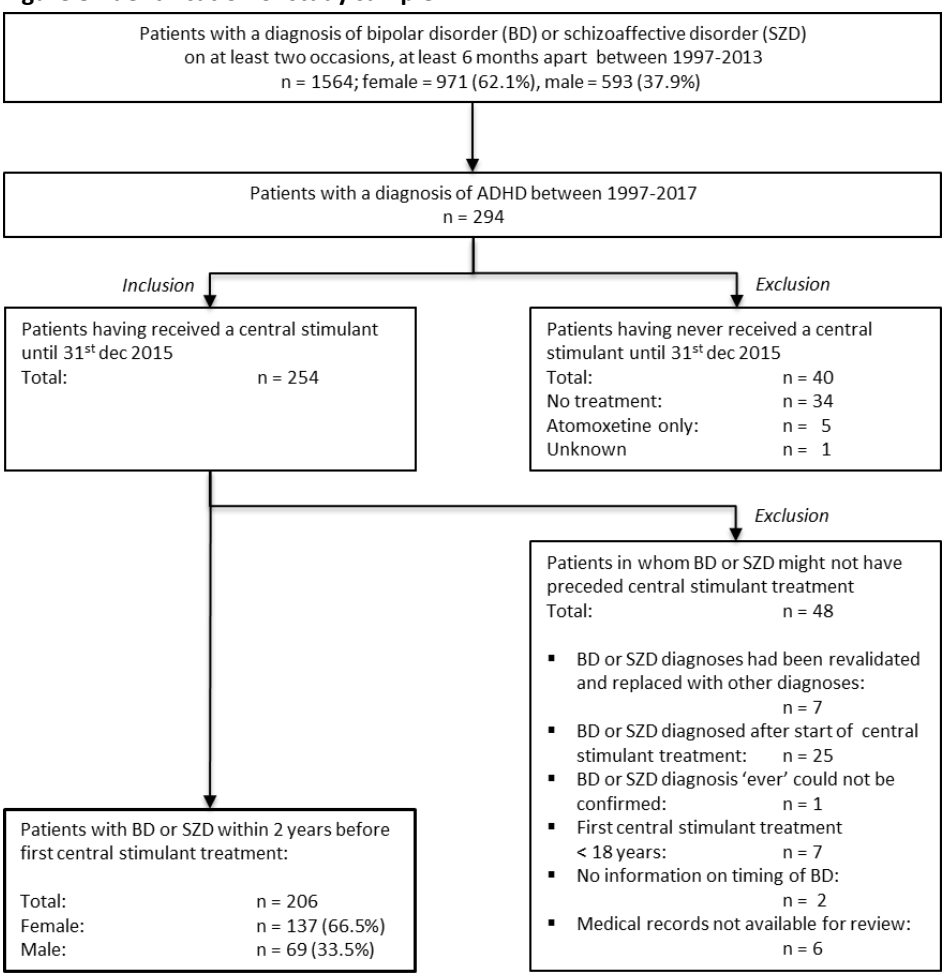
3.4.2 Participant selection and inclusion criteria

Study III concerned patients with a dual diagnosis of BD or SZD and ADHD at start of their first CS treatment. In a first step, all patients were identified who apart from their BD or SZD had also been diagnosed with ADHD (F90) at any time between 1997 and 2017 (n = 294). From this group, all patients were identified who had started CS treatment at any time until 31 December 2015 (n = 254). In the final sample, 206 patients were included who (a) had received their ADHD diagnosis *after* the diagnosis of BD or SZD, and (b) had maintained their BD or SZD diagnosis at start of CS treatment.

Exclusion

For the final analysis, 48 patients were excluded. For these, it could not be established that their BD or SZD diagnoses had proceeded first CS treatment (*Figure 8*).

Figure 8. Identification of study sample



3.4.3 Variable definitions

Exposure variables

Diagnosis
This variable is described in detail in section 3.1.8. We obtained the diagnoses including working diagnoses of BD/SZD and ADHD within two years before CS initiation.

ADHD
Throughout the review period, clinicians had recorded a diagnosis of ADHD according to ICD or DSM in their various editions. ADHD diagnoses included ADHD, ADD or unspecified hyperactivity disorder corresponding to F90.0/8/9. For the baseline, type of ADHD diagnosis was recorded at CS start. Method of diagnosing ADHD was divided into three categories, (a) diagnosis obtained after neuropsychological assessment, (b) clinical diagnosis based on psychiatric assessment complemented by psychometric rating scales and, (c) clinical diagnosis only.

Central stimulants
The following CS were included: methylphenidate extended and immediate release preparations, lisdexamfetamine, dexamfetamine and amfetamine. Dose of CS treatment was abstracted at the point of CS insertion and at the end of the two-year post-mirror period. If CS was discontinued before the end of the two-year post-mirror period, the dose at the point of discontinuation was used. Some patients subsequently restarted CS after a futile attempt to discontinue. For these, a mean CS dose was calculated. CS discontinuation was used as a proxy for "stable" CS treatment or "unstable" episodic/discontinued treatment. For each patient, the total duration of CS treatment during the two-year post-mirror period was calculated.

Dose of central stimulants
Based on extended release CS formulations available in Sweden, doses were divided into four categories, (a) low (starting), (b) intermediate, (c) high, and (d) exceeding the highest recommended dose in adults according to the Swedish national formulary (FASS (167)). Where patients also received immediate release formulations, these were added to the extended dose formulations. The Swedish dose recommendations were checked against the British National Formulary (BNF (155)) (*Table 5*). Then, the four dose categories were regrouped into two categories, (a) *low* for low or intermediate dose, and (b) *high* for high dose or a dose exceeding the highest recommended dose.

Central stimulant dose determination
Type and dose were determined at the point of and two years after CS initiation. When a CS was discontinued earlier, type and dose at the point of discontinuation was used instead. When CS was discontinued and subsequently reinstated, a mean dose was calculated accordingly.

Table 5. Central stimulant extended release formulations and dosing for adults (155,167)

Active ingredient	Methylphenidate				Lisdexamfetamine
Central stimulant brand used	Concerta®	Equasym®	Medikinet®	Ritalin®	Elvanse®
Dose categories based on Swedish national formulary					
Low (starting), mg	18	10-20	10 -20	10 -20	30
Intermediate, mg	27-36	30-40	30 -60	30-60	50
High, mg	54	50-60	70 -80	70-80	70
Highest recommended dose, mg	54	60	80	80	70
For comparison: dose recommendations derived from the Nice British National Formulary					
Highest recommended dose, mg	108	100	100	Not available	70

Mood-stabilisers
Mood-stabilisers used during the whole four-year review period were recorded. They were categorized into three groups; (a) lithium, (b) AC, and (c) SGAs and further stratified according to (a) *never* used during four-year review period, (b) used in the pre-mirror period *only*, (c) used in the post-mirror period *only* and, (d) used in *both* pre-and post-mirror periods. The effect of combinations of mood-stabilisers were not separately analysed.

Psychiatric admissions
Psychiatric admissions in the pre- and post-mirror periods were used as a proxy for severe relapses. The number of psychiatric hospital admissions in the pre- and post-mirror periods were abstracted. Type of affective episode or other reason for admission was also recorded.

Alcohol and/or substance use disorder
Cf. section 3.3.3

Outcome variables

Suicidal behaviour

Number of suicide attempts/NSSI events in the six months and two year pre- and post-mirror periods. Cf. section 3.3.3 Also, occurrence of suicide within the two years after CS initiation was recorded and confirmed by the Swedish Cause of death register (168).

3.4.4 Statistical analysis

Descriptive statistics were used including frequencies and percentages for categorical data, means and standard deviations for continuous data, and when appropriate, median, ranges and minimum and maximum values. Throughout, statistical significance level was set to $p < 0.05$. For the statistical analysis, we used the IBM SPSS version 26 (Armonk, NY; IBM Corp). In accordance with the mirror-image design**,** observations before and after the index event were paired for each individual. This way, patients acted as their "own control". Results reflected therefor within-individual changes. To account for the non-normal distribution of data, Wilcoxon signed rank test was used for comparison of paired continuous variables (suicide attempts/NSSI events and admissions). McNemar's test was used for paired categorical data (patients with suicide attemtps/NSSI events, patients with admissions and use of mood-stabilisers). Additionally, potential confounding factors that might have been associated with suicide attempts/NSSI events within the whole four-year review period were explored. For this a generalised linear mixed model (GLMM) was used. In the GLMM, the following variables were included: period (respective pre- and post-mirror period), age, gender, type of underlying affective disorder (BD-I/SZD or BD-II/other BD), CS dose (high/low), mood-stabilisers (never, used only in pre-mirror period, only in the post-mirror period or in both periods), alcohol or substance misuse (never, used only in pre-mirror period, only in the post-mirror period or in both periods), and CS discontinuation in post-mirror episode.

3.5 Ethical consideration

All medical research involving human subjects must be grounded on a careful risk-benefit assessment with the primary purpose of improving prophylactic, diagnostic or therapeutic procedures (169). Patients with psychiatric disorders "constitute a particularly vulnerable research population" (170).

The ethical trade-off

The breach of the patients' integrity by accessing their clinical data has to be weighed against the potential benefits of each study.

Medical records contain personal, sensitive and confidential information. Such comes to the reviewer's knowledge in studies based on retrospective review of medical records. Hence, informed consent and patient confidentiality are cornerstones in ethical considerations relating to medical record reviews. This study was a non-interventional retrospective study and implied no direct patient contact. Clinical information was extracted from patient records and validated. The data was coded and then analysed anonymously. Only authorized persons had access to the stored data. All study subjects had either given consent to the study or were included after approval by the ethical committee after they were deceased. Living patients could withdraw consent at any time. For deceased patients, no consent was obtained. Due to the retrospective structure of LiSIE, close relatives of deceased participants would not have been easily identified. Further, we judged it nearly impossible to decide whom to ask several years after an individual had died if there were any relatives. To ensure that patients who had not given consent were not included after they had died, the LiSIE cohort was locked after consent procedures had been completed. No further patients were entered after this point.

However, our studies have substantial benefits. The results can be used to:

(a) improve identification and treatment of serious adverse effects of treatments with mood-stabilisers in general and lithium treatment in particular

(b) avoid unnecessary discontinuation of mood-stabilisers in general and lithium treatment in particular

(c) reduce the risks of relapse, suicidal and NSSI behaviour as a consequence of mood-stabiliser discontinuation

(d) improve the safety of simultaneous treatment with CS and mood-stabilisers in patients with a dual diagnosis of BD/SZD and ADHD

(e) enable clinicians to assess risks and benefits of mood-stabiliser treatment more evidence-based and communicate more effectively and empathically with patients who face difficult treatment decisions.

Taken together, we judge the general benefits of the studies included in this thesis to outweigh the risks of breaching individuals' integrity. The findings are directly applicable to the treatment of patients with BD or SZD, even if the patients participating in the study may not benefit personally.

4 RESULTS

4.1 Summary of main findings

This thesis identifies adverse effects of lithium treatment, subgroup of bipolar disorder and CS treatment as three factors that affect the pharmacological treatment of bipolar disorder.

Study I showed that more than half of all patients discontinued their lithium treatment at some point during study period. Adverse effects were the most common causes for quitting lithium therapy, with diarrhoea, tremor, creatinine increase, polyuria/polydipsia/diabetes insipidus and weight gain being the top five adverse effects. Perceived or actual lack of effectiveness was much more often recorded as a reason for lithium discontinuation in patients with BD-II/other BD than in patients with BD-I/SZD. Men were more likely to stop lithium when feeling well. Also, men were less likely to consult with a doctor prior to lithium discontinuation.

Study II showed that both psychiatric hospital admissions and bed-days spent in hospital during admissions doubled within the two-year period after lithium discontinuation. This increased need for in-patient hospital care was exclusively attributable to patients with BD-I/SZD. Speed of lithium withdrawal did not have any significant effect on admissions. However, not having consulted with a doctor prior to lithium discontinuation or no treatment with an alternative mood-stabiliser at the time of lithium discontinuation were associated with more admissions.

Study III showed that treatment with CS reduced suicidal and NSSI behaviour in patients with a dual diagnosis of BD and ADHD. This effect was seen within six months after start of CS treatment and was preserved to the end of the two-year follow-up period.

4.2 Results of study I

4.2.1 Baseline characteristics

Lithium treatment was discontinued in 468 (54%) patients (cf. section 3.2.2). Of these, 60.5% were female. Concerning underlying affective disorder, 42.5% were diagnosed with BD-I/SZD and 57.5% with BD-II/other BD. Lithium treatment was discontinued on more than one occasion in 19% of all patients, i.e. these patients had more than one attempt at lithium treatment. Thus, there were 561 episodes of lithium discontinuation.

More than one reason for lithium discontinuation was recorded in 36% of these 561 episodes. In total, 922 individual reasons for lithium discontinuation were recorded.

4.2.2 Reasons for lithium discontinuation

Adverse effects and other reasons

Adverse effects were reported as reasons for lithium discontinuation in 62% of episodes, psychiatric reasons in 44% and physical health reasons in 12%. Discontinuation due to adverse effects was significantly more common than discontinuation due to psychiatric or physical health reasons ($p < 0.001$). Diarrhoea (13%), tremor (11%), polyuria/polydipsia/diabetes insipidus (9%), creatinine increase (9%) and weight gain (7%), were the five single most prevalent adverse effects leading to lithium discontinuation. Intentional litium intoxication was rarely a reason for stopping lithium treatment (1%). Unintentional overdoses and increasing lithium concentration, i.e. concerns about lithium toxicity, led to discontinuation in 7% of episodes. Of psychiatric reasons, non-adherence and perceived or actual lack of effectiveness were the two commonest reasons for lithium discontinuation, reported in 22% and 21% of episodes respectively. Lithium was reinstated in 26% of patients who had discontinued lithium due to a perceived or actual lack of effectiveness.

Diagnostic subgroups

Patients with BD-I/SZD discontinued their lithium treatment more often than patients with BD-II/other BD ($p < 0.01$). They also discontinued their lithium treatment more often for psychiatric reasons ($p < 0.01$). However, perceived or actual lack of effectiveness as a reason was more frequently reported in patients with BD-II/other BD than in patients with BD-I/SZD (30% vs. 10% of episodes, $p < 0.001$). Concerning adverse effects, creatinine increase was reported in 15% of patients with BD-I/SZD and in 5% of patients with BD-II/other BD ($p<0.001$).

Gender differences

Overall, lithium treatment was significantly more common among men (59%) than women (54%, $p < 0.05$). However, the absolute difference in proportions was small. There was no significant difference in proportion of women or men who discontinued their treatment. Women were more likely than men to report weight gain as a reason for stopping lithium (10% vs. 3% of episodes, $p < 0.01$). Men were more likely than women to discontinue lithium for feeling well (8% vs. 2%, $p < 0.01$). Finally, lithium was discontinued twice as often in men without consulting a doctor before ($p < 0.01$).

Agent who took the initiative to discontinue lithium

Lithium discontinuation occurred more often at initiative of the patients ($p < 0.001$). Twenty-eight percent of all discontinuation episodes were attributable to

lack of adherence on the part of the patient ($p < 0.001$). In 11% of episodes, doctors took the initiative to discontinue lithium, when patients did not adhere to lithium monitoring ($p < 0.01$). Along the same lines, lithium was discontinued at the initiative of the doctor due to fear of intoxication. This concerned intentional and unintentional lithium intoxication, as well as increasing lithium concentrations ($p < 0.01$). Emotional blunting ($p < 0.001$), diarrhoea ($p < 0.05$) and abdominal pain ($p < 0.001$) were more often given by patients as a reason to stop lithium. Finally, creatinine increase or chronic kidney disease accounted for 20% of episodes where doctors took the initiative to stop lithium ($p < 0.001$).

4.2.3 Lead-time to first lithium discontinuation

In the sub-analysis based on 371 patients who discontinued lithium treatment for the first time, the total mean duration of lithium treatment before discontinuation was 3.6 (SD 6.1) years with a median of 1.1 years (min 6 days, max 39.9 years). There was a significant difference in mean duration of lithium treatment between patients with BD-I/SZD and BD-II/other BD; 4.8 (SD 7.4) years versus 2.9 (SD 5.2) years, ($p < 0.01$). Among the top ten most common individual reasons for lithium discontinuation, nausea and diarrhoea tended to lead to earlier lithium discontinuation. Nausea led to lithium discontinuation after a mean lithium exposure of 0.5 (SD 0.5) years. Diarrhoea led to lithium discontinuation after a mean lithium exposure of 1.6 (SD 2.2) years. Concerning renal adverse effects, nephrogenic diabetes insipidus/polyuria/polydipsia were recorded in discontinuation episodes after a mean duration of lithium treatment of 4.8 (SD 5.5) years. Lithium discontinuation due to creatinine increase/lithium nephropathy occurred after a mean of 17.2 (SD 11.2) years of treatment.

4.3 Results of study II

4.3.1 Baseline characteristics

Of the 194 patients included (cf. section 3.3.2), 62% were female. Concerning underlying affective disorder, 51.5% were diagnosed with BD-I/SZD and 48.5% with BD-II/other BD.

Mixed features in a mood-disorder episode

Overall, 29% of all patients had experienced a mood-disorder episode with mixed features at some point. Concerning underlying diagnostic subgroup, 35% of patients with BD-I/SZD and 22% of patients with BD-II/other BD had been diagnosed with mixed features ever ($p = 0.052$).

Lithium treatment

The mean age at the point of lithium discontinuation was 52.5 (14.4) years. The mean duration of lithium treatment before discontinuation was nine years (SD

8.0). The mean duration on lithium treatment differed significantly between patients with BD-I/SZD and BD-II/other BD; 11.5 (SD 8.6) years and 7.2 (SD 6.6) years respectively ($p < 0.001$). The mean lithium concentration during the pre-mirror period was 0.6 (SD 0.2) mmol/L and did not differ significantly between the two diagnostic subgroups ($p = 0.845$).

Mood-stabiliser use after lithium discontinuation

Alternative mood-stabiliser treatment at the point of lithium discontinuation was recorded in 37% of patients. 34% of patients were considered to have a "stable treatment with an alternative mood-stabiliser during post-mirror period". There was no significant difference between use of alternative mood-stabilisers in patients with BD-I/SZD and BD-II/other BD; neither at the point of lithium discontinuation ($p = 0.741$), nor at 3 months ($p = 0.101$), nor at 24 months after lithium discontinuation ($p = 0.649$). There was no significant difference between the two diagnostic groups concerning "stable treatment with an alternative mood-stabiliser during post-mirror period" ($p = 0.649$). However, lithium was significantly more often restarted during the post-mirror period in patients with BD-I/SZD than in patients with BD-II/other BD ($p = 0.003$).

Patient consulted a doctor before lithium discontinuation

A doctor was consulted in 63% of patients before lithium was discontinued. There was no significant difference in proportion of patients with BD-I/SZD or BD-II/other BD who consulted a doctor before stopping lithium ($p = 0.310$).

Alcohol and/or substance misuse

In the whole sample, 8% of patients had documented alcohol and/or substance misuse during the post-mirror period. Alcohol and/or substance misuse was significantly more common in patients with BD-II/other BD (13%) than in patients with BD-I/SZD (4.0%, $p = 0.012$).

4.3.2 Hospital utilisation after lithium discontinuation – whole sample

Psychiatric hospital admissions

The number of admissions increased for 33% of all patients, decreased for 10%, and for 57% there was no change. The total number of admissions increased from 86 to 185 after lithium discontinuation. During the two-year pre- and post-mirror periods, overall pair-wise comparison showed that 37 patients were admitted for psychiatric in-patient care before, and 79 after lithium discontinuation ($p < 0.001$). The intra-individual mean number of admissions/patient increased from 0.44 in the pre-mirror period to 0.95 in the post-mirror period ($P < 0.001$).

The intra-individual mean number of admissions/patient increased for both compulsory and voluntary admissions and for all types of mood episodes recorded at admission.

Psychiatric bed-days
The number of bed-days spent in hospital during psychiatric admissions increased for 33% of all patients, decreased for 13%, and for 54% there was no change. The total number of bed days increased from 2218 to 4240 after lithium discontinuation. The intra-individual mean number of bed-days/patient increased from 11.4 in the pre-mirror period to 21.9 in the post-mirror period ($p = 0.025$).

4.3.3 Hospital utilisation after lithium discontinuation – bipolar I or schizoaffective disorder

Psychiatric hospital admissions
The number of admissions increased for 50% of patients with BD-I/SZD, decreased for 7%, and for 43%, there was no change. The total number of admissions increased from 33 to 130 after lithium discontinuation (*Table 6*). During the two-year pre-and post-mirror period, overall pair-wise comparison showed that 18 patients were admitted for psychiatric in-patient care before, and 56 after lithium discontinuation ($p < 0.001$). The intra-individual mean number of admissions/patient increased from 0.33 in the pre-mirror period to 1.30 in the post-mirror period ($p < 0.001$).

Psychiatric bed-days
The number of bed-days spent in hospital during psychiatric admissions increased for 49% of patients with BD-I/SZD, decreased for 12%, and for 39% there was no change. The total number of bed days increased from 1018 to 3196 after lithium discontinuation (*Table 6*). The intra-individual mean number of bed-days/patient increased from 10.2 in the pre-mirror period to 32.0 in the post-mirror period ($p = 0.005$).

4.3.4 Hospital utilisation after lithium discontinuation – bipolar II or other bipolar disorder

Psychiatric hospital admissions
The number of admissions increased for 16% of patients with BD-II/other BD, decreased for 13%, and for 71% there was no change. The total number of admissions increased from 53 to 55 after lithium discontinuation (*Table 6*). Pair-wise comparisons showed neither a significant change in number of patients with admissions ($p = 0.454$) or mean number of admissions/patient ($p = 0.906$).

Psychiatric bed-days
The number of bed-days spent in hospital during psychiatric admissions increased for 16% of patients with BD-II/other BD, decreased for 14%, and for 70% there was no change. The total number of bed-days decreased from 1200 to 1044 after lithium discontinuation (*Table 6*). The intra-individual mean number of bed-days/patient did not change significantly after lithium discontinuation (p = 0.733).

Table 6. Hospital utilization within two years before and after lithium discontinuation

	BD-I/SZD n = 100		BD-II/other BD n = 94	
	Before	After	Before	After
Patients with admissions, n	18	56	19	23
Total admissions, n	33	130	53	55
Voluntary admissions,	30	90	50	54
Compulsory admissions, n	3	40	3	1
Mania/hypomania, n[a]	10	64	1	0
Depression, n	9	35	29	36
Episode with mixed features, n	2	9	0	2
Other reason, n[b]	12	22	23	17
Bed-days	1018	3196	1200	1044

BD, bipolar disorder; BD-I, bipolar disorder type I; SZD, schizoaffective disorder; BD-II, bipolar disorder type II; other BD, unspecified BD or otherwise specified BD, n, number.
a. In BD-II/other BD only hypomania.
b. Paranoid psychosis, unspecified psychosis, anxiety, insomnia, drug adjustments, substance or alcohol misuse.

4.3.5 Hospital utilisation after lithium discontinuation – comparison between diagnostic subgroups

After adjusting for multiple potential confounders (cf. section 3.3.5), after lithium discontinuation, both the intra-individual mean number of admissions overall (1.01, 95% CI; 0.50 – 1.51, p < 0.001), compulsory admissions *only* (0.38, 95% CI; 0.18 – 0.57, p < 0.001), and bed-days (23.95, 95% CI; 4.71 – 43.18, p = 0.015) were significantly higher for patients with BD-I/SZD compared to patients with BD-II/other BD.

Additionally, these models showed other factors associated with change in the mean number of admissions. Having consulted with a doctor prior to lithium discontinuation was associated with fewer admissions overall (-0.62, 95% CI; -1.18 to -0.05, p = 0.032) and with compulsory admissions *only* (-0.29, 95% CI; -0.50 to -0.08, p = 0.007). However, there was no significant association for change in the mean number of bed-days (-19.780, 95% CI; -40.96 to 1.40, p = 0.067). Treatment with an alternative mood-stabiliser at the time of lithium discontinuation was associated with significantly fewer admissions (-0.80, 95% CI; -1.43 to -0.18, p = 0.012), but not fewer compulsory admissions (-0.12, 95% CI; -0.36 to 0.11, p = 0.308) or bed-days (-18.18, 95% CI; -41.95 to 5.60, p = 0.133).

4.3.6 Speed of lithium withdrawal and time to first admission

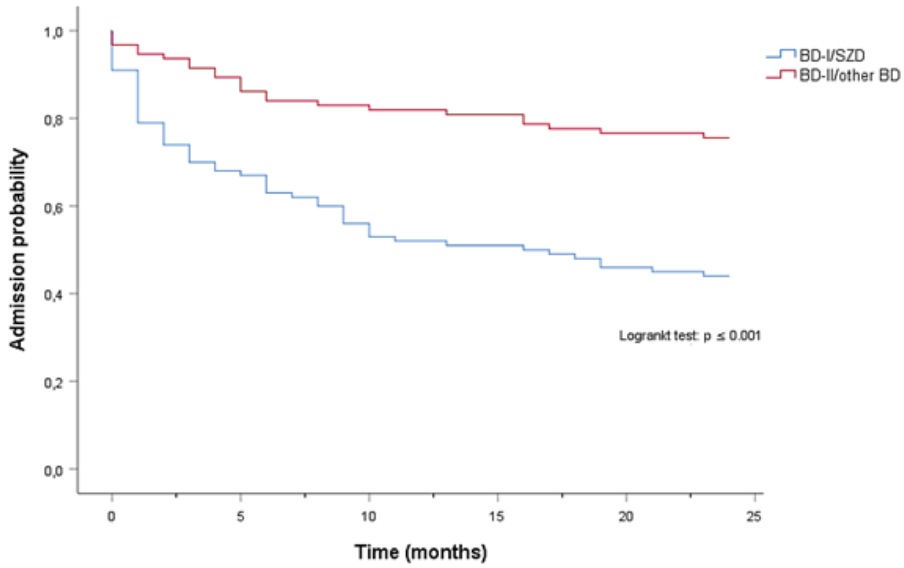
The mean 'survival' time from lithium discontinuation to subsequent admission was 14 months (95% CI; 11.7 – 15.7) for patients with BD-I/SZD and 20 months (95% CI; 18.3 – 21.5) for patients with BD-II/other. The Kaplan-Meier plots indicated a worse course for patients with BD-I/SZD ($p < 0.001$) (*Figure 9a*). No significant difference between "rapid" or "gradual" discontinuers was seen neither for the whole sample ($p = 0.079$) (*Figure 9b*), nor for the diagnostic subgroups (cf. Paper II, Figure 2c and 2d).

4.3.7 Suicidal behaviour after lithium discontinuation

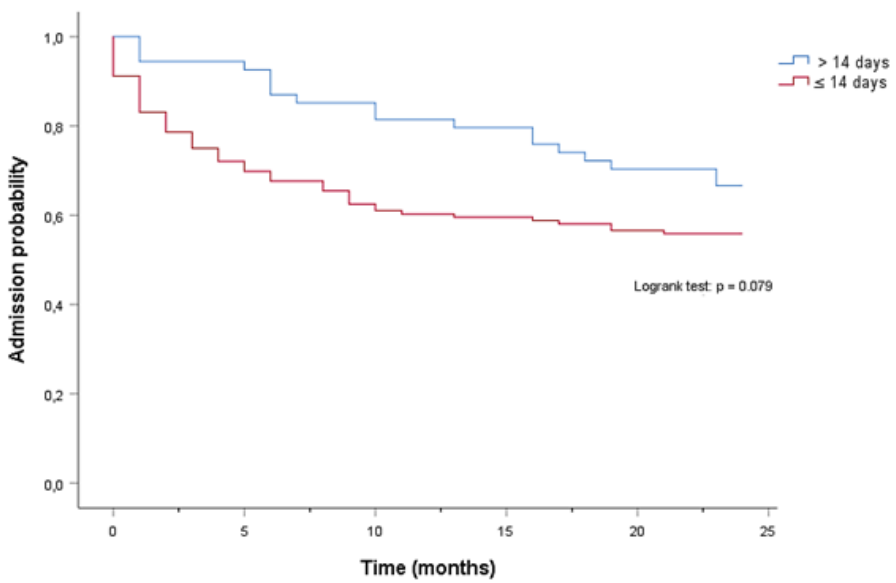
During the two-year pre- and post-mirror periods, pair-wise comparison showed that six patients had suicide attempts/NNSI events before and 12 after lithium discontinuation ($p = 0.180$). The number of suicide attempts/NSSI events increased from 8 to 18 ($p = 0.069$). The intra-individual mean number of suicide attempts/NSSI events per patient were higher in men after lithium discontinuation ($p = 0.046$). No significant intra-individual change in the mean number of suicide attempts/NSSI events was seen among women ($p = 0.249$). Regarding diagnostic subgroups, the number of suicide attempts/NSSI events after lithium discontinuation increased from zero to six in patients with BD-I/SZD with mixed features *ever*. This paired difference was statistically significant on non-parametric testing ($p = 0.034$). In other subgroups, no significant changes in suicide attempts/NSSI events or patients experiencing such events were seen.

Figure 9. 'Survival' time to first psychiatric hospital admission within 2 years after lithium discontinuation

(a) Probability of admission at time *t* or later, stratified by type of subgroup



(b) Probability of admission at time *t* or later, stratified by speed of withdrawal



4.4 Results of Study III

4.4.1 Baseline characteristics

Of the 206 patients included (cf. section 3.4.2), 66% were female. Concerning the underlying affective disorder, 91% were diagnosed with BD-II/other BD and 9% with BD-I/SZD. At CS start, 75% of patients were diagnosed with ADHD, 16% with ADD, and in 9% of patients the disorder was not specified.

Central stimulant treatment

The mean age at the beginning of CS treatment was 35 (SD 11) years. At start of CS treatment, methylphenidate was given to all but one patient. At the end of the last follow-up within the two-year post-mirror period, all but nine patients were treated with methylphenidate. At that point, 115 (56%) of patients were treated with low dose of CS and 91 (44%) with high dose of CS. CS was discontinued in 49.5% of patients at some point during post-mirror period. Some of these reinstated CS. Hence, 62% of patients were treated with CS at their last follow-up. Overall, the total mean duration of CS treatment during the two-year follow up was 17 (SD 8) months.

Mood-stabiliser treatment

Pair-wise comparison showed no significant change of overall use of mood-stabilisers between pre- and post-mirror periods ($p = 0.780$). Regarding individual substances/substance classes, fewer patients were treated with AC in the post-mirror period ($p = 0.025$). No significant differences between pre- and post-mirror periods were seen for use of lithium ($p = 0.243$) and SGAs ($p = 0.910$).

Alcohol and/or substance misuse

Alcohol and/or substance misuse was recorded in 49 (24%) of all patients within the review period. Of these, 7% had alcohol and/or substance misuse in the pre-mirror period *only*, 3% in the post-mirror period *only* and 14% in both pre- and post-mirror periods.

4.4.2 Suicidal behaviour after central stimulant start

In the six-month pre-mirror period, 14 patients had 20 episodes of suicide attempts/NSSI events before CS start. In the six-month post-mirror period, four patients had five episodes of suicide attempts/NSSI events. Pair-wise comparison showed both a significant difference in number of patients with suicide attempts/NSSI events ($p = 0.013$) and an intra-individual change in number of events ($p = 0.004$) (*Table 7*).

In the two-year pre-mirror period, 35 patients had 52 episodes of suicide attempts/NSSI events before CS start. In the two-year post-mirror period, 21 patients had 31 episodes of suicide attempts/NSSI events.

Pair-wised comparison showed both a significant difference in number of patients with suicide attempts/NSSIs (p = 0.038) and an intra-individual change in number of events (p = 0.028) (*Table 7*).

Table 7. Patients with suicide attempts or non-suicidal self-injury events before and after central stimulant initiation

Within six months (n = 204)[a]				
		After		
		Yes	No	Total
Before	Yes	2	12	14
	No	2	188	190
	Total	4	200	204
Within two years (n = 200)[b]				
		After		
		Yes	No	Total
Before	Yes	8	27	35
	No	13	152	165
	Total	21	179	200

a. Complete data available for 204 patients, p = 0.013
b. Complete data available for 200 patients, p = 0.038

After adjustment of multiple potential confounders (cf. section 3.4.4), the mean number of suicide attempts/NSSI events was still significantly lower in the two-year post-mirror period (OR 0.63, 95% CI; 0.40 – 0.98, p = 0.041).

Additionally, the model showed other factors with significant effect on the number of suicide attempts/NSSI events. There were fewer suicide attempts/NSSI events among patients with BD-I/SZD than patients with BD-II/other BD (OR 0.22, 95% CI; 0.05 – 0.96, p = 0.044). The mean number of suicide attempts/NSSI events also decreased with age (OR 0.91, 95% CI; 0.86 – 0.95, p < 0.001). In patients receiving SGAs, there was an increase in the mean number of suicide attempts/NNSI events. This increase was seen in all periods under study, i.e. in the pre-mirror period *only* (OR 3.20, 95% CI; 1.16 – 8.86, p = 0.025), in post-mirror period *only* (OR 4.37, 95% CI; 1.38 – 13.81, p = 0.012) and in *both* pre-and post-mirror period (OR 6.04, 95% CI; 2.29 – 15.88, p < 0.001), Also, there was an increase in suicide attempts/NNSI events in patients with alcohol or substance misuse in pre-mirror period only (OR 3.76, 95% CI; 1.52 – 9.53, p = 0.004) and in both pre- and post mirror periods (OR 3.52, 95% CI; 1.20 – 10.31, p = 0.022) (cf. Paper III, Table 4 for more details).

4.4.3 Psychiatric hospital admissions after central stimulant start

Pair-wise comparison showed that significantly fewer patients were admitted for psychiatric in-patient care within six months after compared to before CS treatment start ($p = 0.029$). No significant difference in number of admissions between the mirror-periods was seen ($p = 0.071$). There were four hospital admissions due to mania before and three after CS start. Regarding the two-year pre-and post-mirror periods, there was neither a change in number of patients being admitted ($p = 0.291$), nor a change in number of admissions ($p = 0.669$). There were eight hospital admissions due to mania before and nine after CS start.

5 DISCUSSION

5.1 General discussion

The present thesis comprised three studies focusing on factors influencing the pharmacological treatment of BD in terms of treatment adherence, clinical course, and prevention of suicidal or NSSI behaviour. Adherence to treatment, which is of outmost importance to reduce the risk for relapse and suicidal behaviour in patients with BD, remains a concern. This is particularly relevant for mood-stabiliser treatment with lithium. Lithium is a first-line treatment for BD. But it is not free of adverse effects and requires extensive monitoring. Therefore, it is important to understand why lithium treatment is discontinued in patients who may benefit from long-term treatment. This constitutes a first step towards improving lithium adherence. Today, lithium is generally recommended in guidelines as a first-line treatment regardless of bipolar subtype (10,91-93) and despite the fact that most evidence of lithiums effectiveness as a mood-stabiliser is derived from studies of patients with BD-I (99-101). BD-I and BD-II seem to differ in clinical phenotypes (120). Hence, response to lithium may also differ. Patients with BD who also have other psychiatric comorbidities also require special attention. Patients with BD who have ADHD as a comorbidity are particularly difficult to treat and may have a poorer clinical prognosis (46,171). Little is known about effects of CS therapy in this patient group.

Study I explored the reasons why lithium, the gold standard among mood-stabilisers, was discontinued. The study also aimed at gaining a better understanding of factors that may affect adherence to lithium treatment. Reasons for lithium discontinuation were compared in several subgroups of patients: BD-I/SZD vs. BD-II/other BD, males vs. females or patient vs. doctor initiating lithium discontinuation.

Study II addressed the problem of lithium being recommended as treatment of BD-II mainly based on available evidence for BD-I (10,91-93). This study focused on the clinical course after lithium discontinuation in general and on the effects of discontinuation in patients with BD-I/SZD or BD-II/other BD in particular.

Study III aimed at gaining a better understanding of how patients with a dual diagnosis of BD and ADHD should be treated. Although CS treatment seems to be safe when mood-stabilisers are used concomitantly in this patient group (153), the impact of CS treatment on suicidal and NSSI behaviour has not been explored.

5.2 Prevalence of bipolar disorder and schizoaffective disorder

The prevalences of BD and SZD found in our study are largely in line with the prevalences reported by Swedish national health authorities. Small discrepancies can be explained through sampling differences. This suggests that our data is representative.

The studies in this thesis were based on 1566 individuals in Study I and 1564 patients in Study II and III. Participants were identified at first through diagnoses recorded between the years of 1997 – 2011. At the end of 2011, 1346 of 1564 patients were alive and 218 were deceased (cf. section 3.1.6, *Table 4*). Adding 24.5% of patients who declined to participate (cf. section 3.1.6, *Figure 2*) would yield 1676 patients. Based on this approximation of LiSIE-N and population data retrieved from the Statistics Sweden (Statistiska Centralbyrån, SCB) (172), the estimated prevalence of BD or SZD in the population aged 18 years or older in the region of Norrbotten by the end of 2011 can be calculated. This was approximately 0.7% for BD and 0.1% for SZD. The female:male ratio was 1.8:1 for BD and 1.3:1 for SZD.

For comparision, data was retrieved from The National Patient Register (NPR) at the Swedish National Board of Health and Welfare (Socialstyrelsen). Since 2001, this register covers visits to secondary mental health care. Information to the register is delivered once a month from each region in Sweden. Underreporting of outpatient data was high at start but has gradually improved over the years. Data loss of main diagnoses has improved sharply from about 25 to 30% in the first years to about 4% in 2016. Hence, the year of 2016 was chosen for comparision. According to data from the NPR, in 2016, the cross-sectional prevalence of BD among individuals aged 15 years or older in the region of Norrbotten was 0.4% for BD and 0.09% for SZD. The female:male ratio was 1.8:1 for BD and 1.4:1 for SZD. In Sweden, the prevalence of BD was 0.4% and of SZD 0.07%. The female:male ratio was 1.7:1 for BD and 1.5:1 for SZD (*Table 8*). The prevalence of BD or SZD in the region of Norrbotten based on the approximation of LiSIE-N and population data from the Statistics Sweden (172), was somewhat higher compared to data from the NPR (172,173) (*Table 8*). This reflects sampling differences and was therefore expected. The study sample of LiSIE-N was derived from diagnoses registered during several years, whereas the NPR data was derived from one year only. Diagnoses in LiSIE-N were derived from diagnoses registered for both out- and inpatient episodes, whereas the NPR data was derived from outpatient diagnoses only. Also, a slightly youger age group was included in the data from the NPR. The gender ratio was the same in the LiSIE-N and the NPR data.

Table 8. Prevalence of bipolar disorder and schizoaffective disorder based on the Norrbotten LiSIE cohort, data from Statistics Sweden and the National Patient Register (172,173)

	Total	Women	Men	Female/Male Ratio
Total study sample of studies II and III[a]	1564	971 (62.1)	593 (37.9)	1.6:1
Prevalence of BD and SZD in the region of Norrbotten year 2011, based on studies II and III and population data from Statistics Sweden[b]				
Patients living by the end of 2011, n[c]	1346	844 (62.7)	502 (37.3)	1.7:1
Patients living by the end of 2011 + estimated proportion who declined to participate[d]	1676	1051	625	1.7:1
Patients/100,000 inhabitants (%)	826 (0.83)	1050 (1.0)	610 (0.61)	1.7:1
BD, n (%)	1443	920 (63.8)	523 (36.2)	1.8:1
Patients/100,000 inhabitants (%)	712 (0.71)	919 (0.92)	510 (0.51)	1.8:1
SZD, n (%)	233	131	103	1.3:1
Patients/100,000 inhabitants (%)	115 (0.11)	131 (0.13)	100 (0.10)	1.3:1
Prevalence of BD and SZD in the region of Norrbotten year 2016, based on the National Patient Register[e]				
BD, n (%)	906	570 (62.9)	360 (39.7)	1.6:1
Patients/100,000 inhabitants (%)	427 (0.43)	548 (0.55)	311 (0.31)	1.8:1
SZD, n (%)	185	106 (57.3)	79 (42.7)	1.3:1
Patients/ 100,000 inhabitants (%)	87 (0.09)	102 (0.10)	73 (0.07)	1.4:1
Prevalence of BD and SZD in Sweden year 2016, based on the National Patient Register[e]				
BD, n (%)	29396	18 670	10 726	1.7:1
Patients/100,000 inhabitants, n (%)	359 (0.36)	455 (0.45)	263 (0.26)	1.7:1
SZD, n (%)	5448	3296 (60.5)	2152 (39.5)	1.5:1
Patients/100,000 inhabitants, n (%)	67 (0.07)	80 (0.08)	53 (0.05)	1.5:1

n, number; BD, bipolar disorder; SZD, schizoaffective disorder

a. Both living and deceased patients by the end of year 2011.

b. Based on inhabitants aged 18 years or older in the region of Norrbotten 2011. Population data retrived from the Statistics Sweden (Statistiska centralbyrån, SCB). Total population aged 18 years or older = 202 667; women = 100 134; men = 102 533.

c. Patients with BD or SZD diagnoses, aged 18 years or older, who were included if they had received their BD or SZD diagnosis between 1997-2011, further met inclusion critera and were alive by the end of 2011.

d. Based on an approximate 24.5% further patients with BD or SZD who declined to participate

e. Based on inhabitants aged 15 years or older. Data retrived form the National Patient Register at the Swedish National Board of Health and Welfare (Socialstyrelsen).

A skewed gender ratio has also been observed in the Swedish National Quality Register for Bipolar Disorder (BipoläR). Ever since BipoläR was established, more women have been registererd. In 2018, 63 percent of all registered patients with bipolar disorder were women (174). The ratio shows, that women in Sweden are more frequently diagnosed with BD than men. This contradicts findings from most previously published literature, pointing towards an equal lifetime BD prevalence among women and men (5,34,76). The reason for this observed diagnostic gender difference is unknown.

5.3 Comparison with other studies – main results of study I

Study I was the first to systematically identify reasons for stopping lithium treatment in a large study sample with a long follow-up. Despite the importance of lithium for BD maintenance treatment, there are only few previously published studies on this topic. These stem from the 1980s and 90s. Whereas this study included 468 patients, previous studies had sample sizes from 20 to 64 patients (128,136-138).

5.3.1 Proportion of patients discontinuing lithium

In study I, 54% of all patients treated with lithium during the study period discontinued their treatment at some point. This is well in the range of estimates reported in other studies. For psychotropic medication in general, non-adherence rates for patients with BD are around 44 to 50% (125,175). For lithium, non-adherence rates vary widely, from 6 to 61% (128-131). A variety of factors may influence adherence estimates. Such include length of the observational period, patient selection, study design and different definitions of adherence.

5.3.2 Reasons for lithium discontinuation

Adverse effects

Study I identified adverse effects (62%) as the most common cause for lithium discontinuation. This was consistent with findings from three of the four previous naturalistic studies (128,136,137). Yet, the fourth study found that patients discontinued their lithium therapy mainly due to “internal resistance to treatment”(138). In clinical trials, around 15 to 20% of patients seem to discontinue lithium because of adverse effects (107). In such studies, poor adherence and non-response to lithium treatment may be more common reasons for premature study drop-out than adverse effects (176). Due to relative short follow-up times, trial with short endpoints cannot capture adverse effects such as lithium-induced nephropathy, which tends to appear only after decades of treatment (134,177).

Strategies to manage adverse effects related to lithium treatment include (a) watchful waiting, (b) lowering of the dose, altering the time of administration, (c) changing to a different lithium formulation, (d) specifically treating adverse effects and (e) changing lithium to a different mood-stabiliser if the adverse effects become intolerable (106).

Psychiatric reasons

A substantial proportion of episodes of lithium discontinuation cited psychiatric reasons (44%), mainly non-adherence to treatment (22%, cf. section 5.3.1) and perceived or actual lack of effectiveness (21%). It has been suggested that up to 40% of patients with BD are lithium non-responders (178-180). Numerous predictors of lithium-response have been described in literature. Such include clinical, biologic and genetic factors (181).

Type of bipolar disorder

In study I, patients with BD-II or other BD were more likely to discontinue lithium due to lack of perceived effectiveness. There is no uniform view on different subtypes as clinical factors for predicting lithium response. BD-I has been suggested as a predictor for good therapeutic response (182). This also seems to correspond with psychiatrists' views (183). But according to Garnham et al., patients with BD-II may be more likely to be lithium responders (179). In a recently published systematic review of clinical predictors of lithium response, the association between subtype of BD and good lithium response was quantified in 11 studies. Ultimately, there was insufficient evidence to indicate if either BD-I or BD-II was a better predictor for a good lithium response (184).

Gender differences

In study I, women and men discontinued lithium to an equal extent. Other studies have shown worse adherence to lithium in either men (185)(184) or women (186). However, concerning causes for stopping lithium, some gender differences emerged in the results. More men stopped because they felt well. Men were also less likely to consult a doctor before discontinuing. This suggests that clinicians need to apply a more proactive approach during follow-up of men during lithium treatment. Women, however, were more likely to discontinue lithium therapy due to weight gain. It has previously been shown that women to a greater extent consider drug-induced weight-gain to be the worst of all adverse effects (187). Preventing weight gain may be easier than treating weight gain. Strategies for weight control include (a) choosing low or non-caloric drinks, (b) general diet and exercise strategies and (c) screening of other potential co-medications with weight-inducing properties (106).

Agent who took the initiative to discontinue lithium

As expected, patients initiated lithium discontinuation more often than doctors. Emotional blunting and diarrhoea were greater concerns for patients than doctors. Lithium-induced diarrhoea may subside when tablets are taken immediately after a meal (94) or by reducing serum lithium levels (106). Doctors stopped lithium because of elevated creatinine and chronic kidney disease. A risk-benefit assessment should be made individually during consultation with the respective patient. Generally, risk of suicide and relapse of manic or depressive episodes may outweigh the risk of end-stage renal disease (12,13,135,188). Finally, doctors stopped lithium after lithium intoxications had occured. Noteworthy though, lithium intoxications are relatively rare events that can be safely managed in most cases (115).

Lead-time to first lithium discontinuation

In study I, 50% of patients discontinued their first lithium treatment episode within 1.1 years. This is consistent with results from a study by McCreadie et al., where lithium was discontinued in 44% of patients within one year after starting (128). Our results indicated that some patients might have tried to cope with particularly disabling adverse effects such as diarrhoea and polyuria over relatively long time periods before stopping lithium. Lithium was stopped by doctors due to elevated creatinine or chronic kidney disease after a mean 17 years of treatment. This does not reveal the starting point of decline in renal functioning, but still points towards a decline of renal function only becoming relevant after long-term lithium treatment (134,177).

5.4 Comparison with other studies – main results of study II

Study II was the first to examine the effects of lithium discontinuation for different subtypes of BD with a mirror-image design.

5.4.1 Lithium as a maintenance treatment for different subtypes of bipolar disorder

Study II showed that lithium discontinuation led to a significant increase in admissions overall, compulsory admissions and bed days. The need for hospital care was only increased for patients with BD-I/SZD after lithium discontinuation. In patients with BD-II/other BD there was neither an increase in admissions overall nor an increase in compulsory admissions. There was no increase in affective episodes recorded at admission or in number of bed-days spent in psychiatric care either.

Previously, the therapeutic superiority of lithium as a maintenance treatment for BD has been shown in several large cohort and register studies. However, most have not distinguished between subtypes of BD (12,14,102,103,189).

A large systematic review explored the effectiveness of lithium compared to other mood-stabilisers. Of 11 studies included, only two stratified their results according to BD-I and BD-II (101). Further, an extensive systematic review and meta-analysis of randomised controlled or quasi-randomised controlled trials explored the effectiveness of various mood-stabilisers. This review suggested that lithium might be less effective for patients with BD-II. However, the evidence was judged to be too weak to draw firm conclusions (96). Another recently updated systematic review of randomised controlled trials compared effectiveness of lithium with placebo and alternative mood-stabilisers (AC or SGA). Results showed that lithium was more effective than placebo for the prevention of overall mood and manic episodes. Also, lithium was more effective than AC for the prevention of manic, but not of overall mood or depressive episodes (99,100). However, only two of 14 studies included, explicitly concerned patients with BD-II (190,191).

Taken together, the evidence of lithium treatment as maintenance treatment for patients with BD-II is sparse and mainly reflects findings from naturalistic and clinical trials of patients with BD-I. This is also acknowledged in current guidelines where evidence of the treatment of BD-II is extrapolated from the available evidence for the treatment of BD-I (10,91-93). However, several guidelines point out the importance of individualised treatment, taking the predominant polarity into account (91-93,95). The CANMAT-guideline makes an explicit recommendation for the maintenance treatment of BD-II, recommending quetiapine, lithium or lamotrigine first-line (8). The SPA-guideline points out that lithium is a first-line treatment for BD-I and that evidence for prophylactic treatment of BD-II is lacking. Based on clinical experience, the SPA-guideline suggests that lamotrigine, quetiapine, other SGAs, antidepressants, lithium, valproate and combinations of such treatments can be used as maintenance treatment of BD-II (94). Finally, the BAP-guideline suggests that lamotrigine and quetiapine may be considered as maintenance monotherapy in patients with BD-II (93).

Lithium as a maintenance treatment for bipolar disorder with mixed features

In study II, overall admissions due to episodes with mixed features increased after lithium discontinuation. Also, total number of psychiatric admissions and bed-days increased for patients with BD-I and mixed status, but not for patients with BD-II and mixed status. Evidence concerning maintenance treatment for patients with BD and episodes with mixed features remain poorly understood (91,93,192). In clinical trials, mixed features are mainly explored in the context of BD-I (193). In a systematic review of current guidelines, olanzapine seemed to have the best evidence, both as maintenance and as acute treatment of episodes with mixed features. However, authors pointed out the lack of evidence, particularly for maintenance treatment (192). Concerning lithium, there is some support for the prevention of a new episode after an index episode with mixed features (194).

Yet, in studies exploring clinical predictors of good and poor lithium response, mixed episodes and rapid cycling have been linked to poorer lithium response (180,184,195).

Lithium for the prevention of suicidal behaviour in patients with bipolar disorder

In patients with BD-II, the risk of suicide may be higher than for patients with BD-I (40). Yet, BD subtype may not always constitute a predictor of suicide attempts (69). Further, occurrence of mixed features has been associated with an increased risk of suicidal behaviour (69,196). In study II, suicide attempts/NSSI events increased significantly after lithium discontinuation only in patients with BD-I/SZD with mixed status.

Lithium has repetitively been shown to reduce suicide and suicide attempts among patients with BD (13,104,105). However, the role of lithium in the prevention of suicidal behaviour in patients with BD and mixed features is mainly unexplored. In a recent eight-year prospective Swedish register study of 50,000 patients, lithium significantly reduced suicide-related events. In the sensitivity analysis, lithium reduced suicide-related events in patients with BD-II, but not in patients with BD-I or in patients with mixed features (13).

5.4.2 Clinical outcome after lithium discontinuation in relation to the speed of lithium withdrawal

Study II did not show an association between speed of lithium withdrawal and a change in number of psychiatric admissions or bed-days. Instead, the adjusted model showed that admissions decreased significantly when patients had consulted a doctor prior to lithium discontinuation and when an alternative mood-stabiliser was used at the point of lithium discontinuation.

Comparing gradual or rapid lithium discontinuation in relation to time to first psychiatric admission, the rate until first admission was not significantly lower for gradual discontinuers. This is inconsistent with previous studies. Such have shown that gradual instead of rapid lithium discontinuation can reduce relapses, induce longer periods of stability and even reduce the suicidal risk. Also, gradual tapering has been suggested to be more advantageous for patients with BD-II than BD-I (139). Possibly, speed of lithium discontinuation becomes less relevant, when this occurs under medical supervision and when an alternative mood-stabiliser is started at that point.

5.5 Comparison with other studies – main results of study III

Study III was the first study to evaluate effects of CS treatment on suicidal and NSSI behaviour in patients with bipolar disorder and comorbid ADHD.

5.5.1 Prevalence of comorbid bipolar disorder and ADHD

In study III, the prevalence of a dual diagnosis of BD/SZD and ADHD was somewhere between 13 to 19%. Previously reported prevalence estimates of BD with comorbid ADHD vary from 4 to 48% (120,171). The estimated prevalence of study III was well in the range of overall ranges previously reported (46,197,198).

5.5.2 Suicidal behaviour in patients with bipolar disorder and ADHD treated with central stimulants

Study III showed that in patients with a dual diagnosis of bipolar disorder and ADHD, suicide attempts/NSSI events decreased significantly within both six months and two years after start of CS treatment. Despite an extensive literature review, no previously published studies on this topic were identified.

In current research, the impact of CS on suicidal behaviour has been explored in the context of ADHD *only*. Here, studies have shown either that CS treatment is risk-neutral concerning suicidal behaviour (199) or that CS reduces the risk (156,157). A large Swedish register study of 37 936 adult patients with ADHD showed a reduced within patient rate of suicide related events among CS users (156). However, most of the available evidence concern children and young adults with ADHD (147,157,158,199).

Concerning patients with BD *only*, the impact of CS on suicidal behaviour has not been explored. However, CS have been suggested as an adjunctive treatment for bipolar depression (8,200). Depressive symptoms in patients with BD have been associated with an increased risk of suicide attempts (69). Hence, one could argue that use of CS for depressive episodes may modify the risk of suicidal behaviour. However, evidence for the use of CS in bipolar depression is sparse (152). The effect of CS on suicidal behaviour in patients with bipolar depression has not been explored at all.

5.5.3 Suicidal behaviour in patients with bipolar disorder and ADHD

Comorbid ADHD in patients with BD has previously been identified as a risk factor for suicidal behaviour (145,171). Conversely, comorbid BD in patients with ADHD is also associated with increased self-injurious behaviour (201).

In study III, suicide attempts/NSSI events were more common among patients with BD-II/other BD and ADHD than among patients with BD-I/SZD and ADHD. We found no previous study comparing the risk of suicidal behaviour in

patients with BD and ADHD according to different subtypes of BD. However, the risk for suicide attempts and suicide may *per se* be higher for patients with BD-II than for patients with BD-I (40,120). In a systematic review of studies of completed suicide in patients with BD, the highest risk was observed in patients with BD-II (40).

In a large recently published Swedish cross-sectional cohort study of 8766 patients, a lifetime history of suicide attempts was more common in patients with BD-II. Yet, two previously published meta-analyses showed similar rates of suicide attempts in patients with either BD-I or BD-II (202,203).

5.5.4 Simultaneous use of central stimulants and antipsychotics

An additional finding from our study was that there were more suicide attempts/NSSI events in patients with BD and ADHD who received SGAs. The number of events were increased already before CS start and continued to increase thereafter. The reasons behind this finding is unclear. Perhaps patients who received antipsychotics were more severely ill and therefore more vulnerable to potential adverse effects of CS treatment. Also, the question arises whether CS can be safely used in combination with antipsychotics. CS enhance activity at the dopamine 2 (D2) receptor. Antipsychotics reduce D2 activity. CS may revert at least partly the D2-receptor blockade of antipsychotics. This causes "dopamine dilemma" in patients who use CS and antipsychotics concomitantly (204). Little is known of effects of such combinations (205).

5.5.5 Alcohol and substance misuse

Alcohol and substance misuse were associated with increased suicide attempts/NSSI events in patients with BD and ADHD. A high prevalence of substance use disorders among patients with BD has consistently been reported. For patients with a dual diagnosis of BD and ADHD the occurrence of substance use disorders is even higher than for patients with BD only (46,206). In patients with a dual diagnosis of BD and ADHD, the lifetime history of alcohol misuse/dependence may be as high as 61%. Forty-one percent may have drug misuse/dependence (206). In study III, within the four-year review period, 24% of patients had recorded alcohol and/or substance misuse. Already in patients with BD only, alcohol and substance misuse may increase the risk for suicide (40,49).

5.6 Discussion of method

5.6.1 General discussion

All included studies in this thesis used a retrospective cohort design based on review of medical records. Such observational studies may serve an important role in generating hypotheses and evidence for future trials (207). In general, naturalistic cohort study design allows studying multiple outcomes and multiple exposures. They are well suited for assessing the effects of rare exposures or exposures for which randomization is not possible for practical or ethical reasons (208,209). Our retrospective observational design minimized that the very act of our observation modified exposures and outcomes. Data was recorded independently of the stated outcomes of our studies (209). In prospective studies, the act of observation may run a higher risk of modifying outcome, resulting in observer bias. However, the major strength of prospective cohort designs compared to retrospective designs is the accuracy of data collection regarding exposures, confounders and endpoint (208,210).

All three studies were observational and did not constitute randomised controlled trials. It is not possible to establish causal effects since exposures were not allocated randomly according to procedures in trials. Yet, randomised controlled trials, particularly when sample sizes are small and follow-up times are short, may not be able to pick up adverse effects that occur later in treatment.

5.6.2 Strengths

The studies included in this thesis were not based on register-data but real-life detailed clinical data at symptom and treatment level. This allowed the study outcomes of high clinical relevance that may not be easily obtainable from register data (211). An extensive effort was made to define variables, collect data accordingly and hence minimize bias (207). A further strength lay in the validation of exposure variables from the case records, including diagnoses, pharmacological treatments and date of starting and stopping treatment. Access to data from the medical records permitted distinction between the various types of BD and exclusion of other diagnoses including schizophrenia.

A major strength of study I was that the long follow-up time allowed to take into account adverse effects occurring both early and late during lithium treatment. Studies II and III used mirror-image designs that allowed individuals to act as their own controls. In that way, other factors known to be associated with worse prognosis in patients with BD could be adjusted for within the design. In both studies, regression models were used to adjust for multiple confounders.

Finally, consent for participation was high and non-consenting patients did not differ from consenting patients in terms of age and sex.

5.6.3 Limitations

The major limitation built into the retrospective design in all three studies was that the quality of the data depended on the quality of the information in the medical notes. That is, all studies were based upon information that was recorded for assessments, diagnosis and planning for care and treatment but not for a structured research protocol. Hence, obtained data may contain several sources of bias. Such could include (a) selective recording based on what was deemed clinically relevant at the time, (b) poor documentation, (c) discrepancy in assessments between different clinicians, (d) variation of diagnoses and use of different DSM or ICD-editions and (e) possibly incomplete information given by patients at the time. Ultimately, it was impossible to know whether patients really had adhered to their prescribed medication.

Further, it is impossible to rule out errors during manual data collection since clinical data has scope for interpretation. Some variables were clearly listed in the electronic medical records, such as hospital admissions and length of stay during psychiatric care. In such cases, we did not consider it necessary to check the collected data for discrepancies. For variables that were subject for more interpretations, such as "reasons for lithium discontinuation", a more extensive approach was used.

As for all retrospectively derived narrative data, there is scope for interpretation, which may lead to misclassification. This limitation relates particularly to the outcome variables in study I when exploring reasons for lithium discontinuation and the decision of "who took the initiative to discontinue lithium"; doctor or patient. Patients were considered as intitiative takers when they had stopped lithium without consulting a doctor or when they had expressed a desire to quit treatment before stopping lithium. Doctors were considered intitiative takers when the medical records clearly identified them as such through comments about lack of effectiveness or concerns about adverse events. To minimise misclassification, all episodes of lithium discontinuation were assessed by two reviewers separately. Any discrepancies were then resolved via a third reviewer.

For study II, a major limitation concerns the diagnosis of different BD subtypes. The underlying affective disorder could vary over time. This could be due to different assessments by different clinicians, use of various DSM- and ICD-editions, and a long review period. To minimize misclassifications of diagnostic subgroups, diagnoses at four different time points were abstracted. This way, we aimed at reaching an approximation of the most likely underlying affective disorder according to the DSM-5 (15).

A major limitation of study III also relates to recording of diagnoses. BD and ADHD share overlapping symptoms. Therefore, diagnostic differentiation might be challenging (143). A further limitation related to the quantification of self-inflicted events. All events of suicide attempts/NSSI events were counted, irrespective of whether ICD-codes for intentional self-harm (X60 – X84) (212) were recorded or not. However, reliance on ICD-encodings for intentional self-harm only could have led to an understatement of self-harm events. Equally, the use of prescribed mood-stabilisers and CS and diagnoses of BD and ADHD, could be validated manually from clinical information at symptom level. Again, we consider this more accurate than relying on prescription data and diagnostic codes from national patient registers.

6 CONCLUSIONS

6.1 Conclusions and clinical implications

Study I shows that lithium discontinuation in patients with BD or SZD is common and mainly occurs because of adverse effects. It is important that patients who may benefit from lithium can continue their treatment. Therefore, clinicians should discuss and manage potential adverse effects of lithium treatment with patients before initiation and continuously during treatment. Non-adherence and lack of efficacy are also common causes for stopping lithium. Hence, it is important to assess such factors at every follow-up appointment. Patients with BD-I/SZD may require more proactive follow-up since they seem more likely to discontinue due to reasons of non-adherence. Men in particular require a proactive approach, since they may be more likely to discontinue their treatment without consulting a doctor. They seem also more likely to stop treatment when feeling well.

Study II shows that discontinuation of long-term lithium treatment in patients with BD-I/SZD comes at a cost of deteriorated mental health and a substantially increased need of in-patient psychiatric care. In patients with BD-II/other BD, judged on the impact of discontinuation alone, lithium does not seem to prevent more severe depressive episodes requiring in-patient psychiatric care. The observed higher relapse risk in patients with BD-I/SZD points towards a need to apply a higher threshold for stopping lithium for this group. The decision to continue or stop lithium depends on striking the right balance between benefits and risks. Such a decision cannot be made on statistical evidence alone but has to be individualised for each patient.

Study III shows that in patients with a dual diagnosis of BD and ADHD, addition of CS treatment may reduce the risk of suicide attempts/NSSI events. The need for hospital care did not increase after start of CS treatment. Neither was there an overall difference in the use of mood-stabilisers. Judged on this, the decrease in suicide attempts/NSSI events after CS start did not come at the expense of deterioration of illness. The findings of study III suggest that CS treatment can be safely prescribed for this patient group, as long as mood-stabilisers are given concomitantly to prevent manic relapses (153).

6.2 Implications for future research

Findings from **study I** highlight the need for further research regarding the adverse effects associated with lithium treatment and best management of such adverse effects. It has been suggested that sustained release lithium formulations may be advantageous over immediate release formulations. Such may lead to a more stable lithium serum concentration and a more gradual increase in

concentration. This way, they might reduce the risk of certain adverse effects and hence improve adherence (213). Single daily administration of prolonged lithium formulations may also improve adherence (214). Future trials comparing sustained and immediate release lithium formulations concerning effects, adverse-effects and compliance rates are warranted (213).

Lack of adherence to lithium, particularly in men and in patients with BD-I/SZD, was a common reason for stopping treatment. Subjective well-being, although desirable, seemed to increase the risk of lithium discontinuation. This emphasizes the importance of regular contact and planned follow-ups, even for patients who have been stable for years of treatment. Formal teaching and training to improve medication adherence is not covered adequately in psychiatric textbooks. Future research is warranted, since strategies to measure and improve adherence in clinical practice are mainly based on experience rather than evidence (124). Adherence to medication is of utmost importance, since non-adherence is a frequent cause of relapse in patients with BD (126). Patients may underestimate the risk of relapse when feeling well. Strategies that may improve adherence include (a) shared decision-making (SDM) (215,216), (b) motivational interviewing, (c) psychoeducation, (c) involvement of relatives (130,217) and (d) use of dedicated mood disorder clinics (130). Such strategies have only partly been explored in the context of lithium treatment.

Findings from **study II** highlight the need for future clinical trials and prospective studies concerning the effects of lithium treatment and other mood-stabilisers for the different BD types. Particularly, the lack of evidence for maintenance treatment of patients with BD-II requires further research in view of the risk of suicidal behaviour (40,120,202). Depressive subthreshold symptoms may also substantially impair social functioning (42,43). More research is also warranted regarding occurrence of mixed features and their management in patients with either BD-I or BD-II. After all, patients with bipolar mixed states are generally more severely affected compared to patients without mixed features. They have more severe symptoms, more lifetime episodes of illness, higher rates of comorbidities (25) and a higher risk of suicidal acts (196).

Findings from **study III** highlight the need of more research concerning treatment regimens of patients with a dual diagnosis of BD and ADHD in general and on suicidal behaviour in particular. This is of importance because ADHD is a prevalent comorbidity in patients with BD. In patients with such dual diagnoses, ADHD is associated with unfavorable clinical course, substance misuse and increased risk for suicide attempts (46). The finding that CS reduced suicide attempts/NSSI events in patients with BD and comorbid ADHD, must be replicated in more studies with different study designs. The majority of patients included in study III were diagnosed with BD-II/other BD. Therefore, the results are mainly applicable to this patient group.

Comparisons are warranted regarding the effects of CS according to (a) BD subtype, (b) concomitant use of different mood-stabilisers, (c) different CS preparations (immediate and prolonged formulations) and (d) CS dose-regimens.

In study III, there were more suicide attempts/NSSI events in patients with BD and ADHD who received SGAs. The numbers of events were increased already before the start of CS treatment. They increased then further. Possibly, CS and antipsychotics cancel out each other in effect. Little is known of effects of such combinations (205).

Finally, our knowledge is limited regarding CS use in patients with a dual diagnosis of BD and ADHD who also suffer from an alcohol or substance use disorder. Particular difficulties regarding pharmacological treatment have been highlighted for patients with substance use disorder and ADHD. Such include poor engagement with clinical services, poor compliance and potential risk for misuse of prescribed CS medications (218). These factors are likely to make it difficult to conduct randomized clinical trials in this patient group. For patients with BD and substance use disorder, the general recommendation is using standard approaches for treatment of the substance misuse and to treat mood symptoms concurrently (10,93). Prescribing CS to patients with substance use disorder and ADHD is controversial due to the clear risk for misuse of prescribed medications. Yet, according to one recently published International Consensus Statement, pharmacotherapy should not be avoided in patients with ADHD and substance use disorder. This statement suggests that high doses of long-acting stimulants should be preferred in patients with ADHD and stimulant use disorders. Atomoxetine should be preferred in patients with ADHD and alcohol use disorder (219).

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APPENDIX I

Diagnostic critera and classifications according to DSM-5, DSM-IV-TR and ICD-10

Diagnostic criteria of manic, hypomanic and depressive episodes according to DSM-5, DSM-IV-TR and ICD 10 (abridged) (15,16,21)

	Manic episode	Hypomanic episodes	Depressive episode
DSM-5	***Essential*** A distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy, for at least one week ***Other*** At least three symptoms, or four if mood has only been irritable, (1) Inflated self-esteem or grandiosity (2) Decreased need for sleep (3) More talkative than usual or pressure to keep talking (4) Flight of ideas of subjective experience of racing thoughts (5) Distractibility (6) Increase of goal-directed activity or psychomotor agitation (7) Excessive involvement in pleasurable activities with a high potential for painful consequences ***Functioning*** Marked impairment in functioning or need for hospitalisation or psychotic features	***Essential*** A distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy, for at least four days ***Other*** Same as for a manic episode according to DSM-5 ***Functioning*** Not severe enough to cause marked impairment or to necessitate hospitalisation, no psychotic symptoms	At least five symptoms present during a two-week period ***Essential*** (1) Depressed mood *or* (2) Loss of interest or pleasure ***Other*** (3) Significant weight loss (4) Insomnia or hypersomnia (5) Psychomotor agitation or retardation (6) Fatigue or loss of energy (7) Feelings of worthlessness or excessive or inappropriate guilt (8) Diminished ability to think or concentrate or indecisiveness (9) Recurrent thoughts of suicidal ideation, suicide attempt or specific plan to commit suicide ***Functioning*** Significant distress or impairment in functioning

DSM-IV-TR	Same as DSM-5 except for the phrase "abnormally and persistently increased energy and activity" which was added as an essential criteria in DSM-5. A manic episode that emerged during antidepressant treatment was not considered a manic episode in the DSM-IV-TR	Same as DSM-5 except for the phrase "abnormally and persistently increased energy and activity" which was added as an essential criteria in DSM-5. A hypomanic episode that emerged during antidepressant treatment was not considered a hypomanic episode in the DSM-IV-TR	Same as DSM-5
ICD 10	***Essential*** (1) Elevated mood for at least one week, may vary from carefree joviality to uncontrollable excitement (2) Increased energy resulting in overactivity ***Other*** (3) Pressure of speech (4) Decreased need of sleep (5) Loss of social inhibition (6) Attention cannot be sustained, often marked distractability (7) Inflated self-esteem (8) Grandiose and over-optimistic ideas Symptoms can increase to psychotic level including delusions, hallucinations, aggression, incomprehensibility	***Essential*** (1) Elevated mood and (2) Increased activity lesser than mania for at least several days on end. No delusions or hallucinations. ***Other*** (3) Marked feeling of well-being and both physical and mental efficiency (4) Increased sociability (5) Talkativeness (6) Overfamiliarity (7) Increased sexual energy (8) Decreased need for sleep ***Functioning*** Considerable interference with work or social activity, but not severe disruption	***Essential*** (1) Depressed mood (2) Loss of interest and enjoyment (3) Reduced energy leading to increased fatiguability and diminished activity ***Other*** (4) Reduced attention or concentration (5) Reduced self-esteem or self-confidence (6) Ideas of guilt and unworthiness (7) Bleak and pessimistic views on the future (8) Ideas or acts of self-harm and suicide (9) Disturbed sleep (10) Diminished appetite ***Functioning*** Mild: some difficulty Moderate: considerable difficulty Severe: severe difficulties or no functioning

Classification of bipolar subtypes according to DSM-5, DSM-IV-TR and ICD-10 (15,16,21)

DSM-5		**DSM-IV-TR**		**ICD 10**	
Bipolar I disorder				**Bipolar disorder**	
Code	Type	**Code**	Type	**Code**	Type
		296.40	Most recent episode hypomanic	F31. 0	Current episode hypomanic
296.41 -43	Current or most recent episode manic, mild, moderate, severe,	296.0x	Current episode manic	F31.1	Current episode manic without psychotic symptoms
		296.4x	Most recent episode manic		
296.44	Current or most recent episode manic, with psychotic features			F31.2	Current episode manic with psychotic symptoms
296.51 -53	Current or most recent episode depressed, mild moderate, severe	296.5	Most recent episode depressed	F31.3	Current episode mild or moderate depression
				F31.4	Current episode severe depression without psychotic symptoms
296.54	Current or most recent episode depressed, with psychotic features,			F31.5	Current episode severe depression with psychotic symptoms
		296.6x	Most recent episode mixed	F31.6	Current episode mixed
296- 45-46	Current or most recent episode manic or hypomanic, partial or full remission			F31.7	Currently in remission
296- 55-56	Current or most recent episode depressed, partial or full remission				
296.40	Unspecified	296.7	Most recent episode unspecified	F31.9	Unspecified
Specifiers					
With	Anxious distress Mixed features Rapid cycling Melancholic features Atypical features				

	Mood-congruent psychotic features Catatonia Peripartum onset Seasonal pattern				
Other bipolar disorder					
296.89	Bipolar II disorder	296.89	Bipolar II disorder	F31.8	Other bipolar affective disorders (including bipolar II disorders and recurrent manic episodes not otherwise specified)
296.89	Other specified bipolar and related disorder				
296.80	Unspecified bipolar and related disorder	296.80	Unspecified bipolar and related disorder		
	Substance/medication induced bipolar and related disorders				
	Bipolar and related disorder due to another medical condition				

Diagnostic criteria and classification of schizoaffective disorder according to DSM-5, DSM-IV and ICD 10 (abridged) (15,16,21)

	Code	Definition
DSM-5	295.70	An uninterrupted period of illness during which, at some time, there is a major mood episode (major depressive or manic) concurrent with criterion A for schizophrenia. Delusions or hallucinations for two or more weeks in the absence of a major mood episode (major depressive or manic) during the lifetime duration of the illness. Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of illness. Bipolar type Depressive type
DSM-IV	295.70	An uninterrupted period of illness during which, at some time, there is either a major depressive episode, a manic episode or a mixed episode concurrent with symptoms that meet criterion A for schizophrenia. During the same period of illness, there have been delusions or hallucinations for at least two weeks in the absence of prominent mood symptoms. Symptoms that meet criteria for a mood episode are present for a substantial proportion of the total duration of the active and residual periods of illness. Bipolar type Depressive type
ICD 10	F25.0-2,8,9	Both definite schizophrenic and definite affective symptoms are prominent simultaneously within a few days of each other, within the same episode of illness. Manic type Depressive type Mixed type Other Unspecified

Diagnostic criteria of ADHD according to DSM-5, DSM-IV-TR and ICD 10 (abridged) (15,16,21)

	Code	Definition
DSM-5	314.0	A persistent pattern of inattention and/or hyperactivity/impulsivity that interferes with functioning or development, as characterised by inattention *or* hyperactivity or impulsivity. Inattentive or hyperactive-impulsive symptoms • have persisted for at least six months. • were present prior the age of *12 years*. • are present in at least two settings.
DSM-IV-TR	314.0	As DSM-5. Inattentive **or** hyperactive-impulsive symptoms • have persisted for at least six months. • were present prior the age of *seven years*. • are present in at least two settings.
ICD 10	F90	Impaired attention *and* overactivity Symptoms • should be of long duration • should be of early onset (before age *6 years*) • are present in at least two settings

Classification of ADHD according to DSM-5, DSM-IV-TR and ICD 10 (abridged) (15,16,21)

DSM-5		**DSM-IV-TR**		**ICD 10**	
Code	Type	**Code**	Type	**Code**	Type
314.01	Attention-Deficit/Hyperactivity Disorder Combined type	314.01	Attention-Deficit/Hyperactivity Disorder Combined type	F90.0	Disturbance of activity and attention
314.00	Attention-Deficit/Hyperactivity Disorder Predominantly inattentive type	314.00	Attention-Deficit/Hyperactivity Disorder Predominantly inattentive type	F98.8	Other specified behavioural and emotional disorders with onset, usually occurring in childhood and adolescence
314.01	Attention-Deficit/Hyperactivity Disorder Predominantly hyperactive-impulsive type	314.01	Attention-Deficit/Hyperactivity Disorder Predominantly hyperactive-impulsive type	F90.0	Disturbance of activity and attention
314.01	Attention-Deficit/Hyperactivity Disorder Other			F90.8	Other hyperkinetic disorders
314.9	Attention-Deficit/Hyperactivity Disorder Unspecified	314.9	Attention-Deficit/Hyperactivity Disorder Unspecified	F90.9	Hyperkinetic disorder, unspecified

APPENDIX II

STROBE Statement (159)

Checklist for Study I (refers to Paper I)

Strobe requirement	#	Our review
Title and abstract	1	
(a) Indicate the study's design with a commonly used term in the title and abstract		*(a)* Given. Clinical course and hospital utilisation after lithium discontinuation in patients with bipolar I or II disorder: *a mirror-image study based on the LiSIE retrospective cohort.*
(b) Provide in the abstract an informative and balanced summary of what was done and what was found		*(b)* Structured abstract provided.
Introduction		
Background/rationale: Explain the scientific background and rationale for the investigations being reported	2	Background outlined in introduction.
Objectives: State specific objectives, including any pre-specified hypotheses	3	Aims clearly stated in text: Here, we compare the impact of lithium discontinuation on clinical course and hospital utilisation in patients with BD-I or schizoaffective disorder (SZD) and patients with BD-II or other bipolar disorder (other BD).
Methods		
Study design: Present key elements of the study design early in the paper	4	Described or the LISIE study as a whole and for this mirror-image as part of a retrospective cohort study. Key elements of the study included in the manuscript: study design, participants, chart review, variable definitions and outcomes, control for bias, statistical analysis.
Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	Described for the LISIE study as a whole and for this mirror-image study.
Participants: *(a)* Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (*b*) For matched studies, give matching criteria and the number of controls per case	6	*(a)* Described for the LISIE study as a whole and for this mirror-image study. (b) Described: The pre-and post-mirror-image periods were both set to two years to achieve a perfect mirror. Every patient served as her/his own control.
Variables: Clearly define all outcomes, exposures, predictors, potential	7	Definition for outcomes, exposures and variables clearly defined in text. Criteria for diagnoses given in text.

confounders, and effect modifiers. Give diagnostic criteria, if applicable		
Data sources /measurement: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8	Source: Medical records, both manual and electronically extracted Definition for each variable given in text.
Bias: Describe any efforts to address potential sources of bias	9	Described: "Of all patients approached, 75% consented to inclusion into the LiSIE study. In accordance with the ethical approval granted, we controlled for selection bias in the whole LiSIE study, comparing age, sex, maximum recorded serum lithium and creatinine levels as key parameters, available in anonymized form. We did not find any significant difference between participating and non-participating patients. To minimize observer and recording bias, all data was abstracted by two separate reviewers".
Study Size: Explain how the study size was arrived at	10	Described in text and flow chart.
Quantitative variables: Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11	Described, cf. Statistical methods
Statistical methods: *a)* Describe all statistical methods, including those used to control for confounding *(b)* Describe any methods used to examine subgroups and interactions (*c)* Explain how missing data were addressed *(d)* If applicable, explain how matching of cases and controls was addressed *(e)* Describe any sensitivity analyses	12	*(a)* We conducted a descriptive analysis, establishing the frequency of all variables in our database. Means, standard deviations were calculated for continuous data. Frequencies and percentages were calculated for categorical data. We then stratified further according to type of bipolar disorder. For group comparisons of continuous variables, we used paired t-test when group sizes were sufficiently large (≥ 40 in either group), since this test is fairly robust against violations of the normal distribution assumption.[15] For smaller group sizes, we used Wilcoxon signed rank test. For categorical variables, we used McNemar's and Pearson's chi square tests. We conducted a multiple linear regression analysis in order to adjust for possible confounders in the analysis of the association between the change in hospital utilisation on one hand and diagnostic group, BD-I/SZD versus BD-II/other BD, on the other. We created three models with following outcomes (1) change in total number of admissions, (2) change in number of *compulsory* admissions only, and (3) change in number of bed-days. The selection of potential confounders was based on factors identified in the published literature: [9,13,16,17] age, mixed status, lithium concentration, mood stabiliser treatment at lithium discontinuation, post mirror stable mood stabiliser treatment, fast or gradual withdrawal, consulted with a doctor before discontinuing, alcohol

		and/or substance use disorder. Effects were reported as estimated marginal means (EMMs), which give the mean increase in unit of outcome, number of admissions or bed-days, according to factors under study. Kaplan-Meier plots were used to map the time periods from stopping lithium to first admission after lithium discontinuation. To account for type of BD and speed of lithium discontinuation, we created 4 separate survival functions, comparing (1) BD-I/SZD versus BD-II/other BD, (2) rapid versus gradual lithium discontinuation for the whole group, (3) rapid versus gradual lithium discontinuation for patients with BD-I/SZD only and (4) rapid versus gradual lithium discontinuation for patients with BD-II/other BD only. We tested potential differences between groups using the log rank test. Throughout, statistical significance level was set to $p < 0.05$. The statistical analysis was conducted with IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA). *(b)* see (a) *(c)* For the purpose of this study, we only considered the first episode of discontinuation preceded by two years of continuous lithium treatment. To achieve a perfect mirror, we excluded all patients whose review periods fell short of two years post-lithium discontinuation. Cf. also methods to control for bias. *(d)* N/A *(e)* N/A
Results		
Participants: *(a)* Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed *(b)* Give reasons for non-participation at each stage *(c)* Consider use of a flow diagram	13	*(a)* *(b)* 16 patients had died within our follow-up period. Fifteen deaths were due to natural courses. One death was due to suicide. Two patients moved out of region and for three were medical records not available. *(c)* Flow diagram included in the manuscript as figure 1.
Descriptive data: *(a)* Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders *(b)* Indicate number of participants with missing data for each variable of interest	14	*(a)* Baseline characteristics described in table 1 of the manuscript. Of 1565 eligible patients, 872 (56%) had been treated with lithium during the study period. 467 (54%) patients discontinued lithium on at least one occasion with the intention to stop for good. 194 patients met the inclusion criteria (figure 1); their baseline characteristics are described in table 1 (table 1). The mean lithium concentration over the two years before lithium discontinuation was 0.61 (SD 0.19) mMol/L. *(b)* none for included patients 21 patients did not achieve the follow-up period of two years after lithium discontinuation required for our mirror-image, including 16 patients who had died. 15 of these deaths were due to natural courses. One death was due to suicide within the first year after lithium had been stopped (Figure 1). Thus, 194 patients were included in the final sample.

Outcome data: Report numbers in each exposure category, or summary measures of exposure	15	Outcome data presented in tables 2, 3 and in text.
Main results *(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *(b)* Report category boundaries when continuous variables were categorized *(c)* If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16	*(a)* Within-group differences reported. We conducted a multiple linear regression analysis in order to adjust for possible confounders in the analysis of the association between the change in hospital utilisation and diagnostic group, BD-I/SZD versus BD-II/other BD. We created three models with following outcomes (1) change in total number of admissions, (2) change in number of *compulsory* admissions only, and (3) change in number of bed-days. We tested for factors identified in the published literature: [9,13,16,17] age, mixed status, lithium concentration, mood stabiliser treatment at lithium discontinuation, post mirror stable mood stabiliser treatment, rapid or gradual withdrawal, consulted with a doctor before discontinuing, alcohol and/or substance use disorder. Effects were reported as estimated marginal means (EMMs), which give the mean increase in unit of outcome, number of admissions or bed-days, according to factors under study. Statistical significance level was set to $p < 0.05$. The statistical analysis was conducted with IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA). *(b)* Continuous outcome variables were number of admissions and bed days. Categorical outcome variables included events of self-harm or suicide attempt where a patient had sought psychiatric, medical or surgical care in connection to the event. Type of admission was stratified into voluntary and compulsory as well as affective type of admission *(c) Cf. (a)*
Other analysis: Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	17	Subgroup analysis according to BD-I/SZD and BD II/other BD. Subgroup analysis for gradual and rapid lithium discontinuation for analysis of time from lithium discontinuation to fist admission after lithium discontinuation.
Discussion		
Key results: Summarize key results with reference to study objectives	18	Done
Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19	Limitation discussed in regard to its observational design and not a randomized controlled trial, lack of true control group, data quality, and potential enrichment by lithium responders.
Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20	Done

Generalisability: Discuss the generalizability (external validity) of the study results	21	Results discussed in relation to register studies, randomized trials and meta-analyses.
Funding: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22	Norrbotten County equity and equality fund, Norrbotten, Sweden Research and Development Fund (FOU) including Academic Environment Fund, Norrbotten County, Norrbotten, Sweden. Conflict to interest statement for all authors included in manuscript.

Checklist for Study II (refers to Paper II)

STROBE requirement	**#**	**Our review**
Title and abstract	1	
(a) Indicate the study's design with a commonly used term in the title and abstract		*(a)* Given. Clinical course and hospital utilization after lithium discontinuation in patients with bipolar I or II disorder: *a mirror-image study based on the LiSIE retrospective cohort.*
(b) Provide in the abstract an informative and balanced summary of what was done and what was found		*(b)* Structured abstract provided.
Introduction		
Background/rationale: Explain the scientific background and rationale for the investigations being reported	2	Background outlined in introduction.
Objectives: State specific objectives, including any pre-specified hypotheses	3	Aims clearly stated in text. To compare the impact of lithium discontinuation on hospital utilization in patients with BD-I or schizoaffective disorder (SZD) and patients with BD-II or other bipolar disorder (other BD).
Methods		
Study design: Present key elements of the study design early in the paper	4	Study design: Mirror-image as part of a retrospective cohort study. Key elements of the study included in the manuscript: study design, participants, chart review, variable definitions and outcomes, control for bias, statistical analysis.
Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	Setting described in manuscript: For this study, we retrospectively examined routine clinical data recorded until 31 December 2015 and performed the data extraction and validation in 2016 and 2017. The data was then analysed in 2018. Patients were potentially eligible for inclusion into this study, when we found a lithium prescription discontinued in the electronic prescription database. We defined as "exposed", patients who had received a diagnosis of bipolar disorder or SZD on at least two occasions at least six months apart any time between 1997 and 2013, and for whom at least two positive lithium serum levels were available. We included all

		patients, who (1) had discontinued lithium at any time between 1997 and 2013 for more than seven days with the intention to stop for good as indicated by the medical records, (2) had continuously received lithium for at least two years before stopping lithium, and (3) were available for follow-up for two years after stopping lithium. The index event for our mirror image study was the date of lithium discontinuation. For the included sample, we systematically extracted routine clinical data from the case records.
Participants: *(a)* Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (*b*) For matched studies, give matching criteria and the number of controls per case	6	*(a)* We defined as "exposed", patients who had received a diagnosis of BD or SZD on at least two occasions at least six months apart any time between 1997 and 2013, and for whom at least two positive lithium serum levels were available. Patients were potentially eligible if a lithium prescription had been discontinued in the electronic prescription database. We included all episodes for which the medical records then indicated that lithium was discontinued with the intention to stop for good. We included all eligible patients who had been on lithium treatment continuously for at least two years before discontinuation and who also had two years follow-up available for review. Subtypes of diagnoses were established as an approximation of individual diagnoses set at four different time points, (1) time of lithium start, (2) before lithium discontinuation, (3) at the end of the post-mirror period, and (4) last diagnosis before 31 December 2015. (b) N/A.
Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7	Definition for outcomes, exposures and variables clearly defined in text. The pre-and post-mirror-image periods, were both set to two years to achieve a perfect mirror. This way every patient served as their one control. Criteria for diagnoses given in text.
Data sources /measurement: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8	Source: Medical records. Definition for each variable given in text.
Bias: Describe any efforts to address potential sources of bias	9	Of all patients approached, 75% consented to inclusion into the LiSIE study. In accordance with the ethical approval granted, we controlled for selection bias in the whole LiSIE study, comparing age, sex, maximum recorded lithium and creatinine level as key parameters, available in anonymized form. We did not find any significant difference between participating and non-participating patients. To minimize observer and recording bias, all data was abstracted by two separate reviewers.
Study Size:	10	Described in text and flow chart.

Explain how the study size was arrived at		The total cohort comprised of 1565 patients. Of these, 872 (56%) had received lithium at some point during the study period. 467 (54%) patients discontinued lithium at least on one occasion. For the analysis of this study, we identified 194 patients who had been on lithium treatment continuously for at least two years before lithium discontinuation and who also had two years follow-up available for review.
Quantitative variables: Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11	Descriptive analysis of continuous variables (mean/SD and min/max/range) and categorical variables (frequencies and percentages). We stratified by type of bipolar disorder and having had a mixed episode ever or not. Groupings were chosen according to clinical relevance.
Statistical methods: *a)* Describe all statistical methods, including those used to control for confounding *(b)* Describe any methods used to examine subgroups and interactions (*c)* Explain how missing data were addressed *(d)* If applicable, explain how matching of cases and controls was addressed *(e)* Describe any sensitivity analyses	12	*(a)* Descriptive analysis, establishing the frequency of all variables in our database. Means, standard deviations, range and min/max values were calculated for continuous data. Frequencies and percentages were calculated for categorical data. Stratification according to type of bipolar disorder. We analysed differences with both non-parametric and parametric tests. Our sample size was mostly sufficiently large to yield t-tests robust to non-normality. Concerning within-group differences, we used paired t-test or Wilcoxon signed rank test for continuous variables and McNemar's chi square for categorical variables. Concerning between-group differences, we used independent t-test for continuous data and Pearson's chi square test for categorical variables. Statistical significance level $p < 0.05$. *(b)* N/A *(c)* 21/215 patients had missing data in the post-mirror period. They were excluded to achieve a perfect mirror of the periods before and after lithium discontinuation. Cf. also methods to control for bias. *(d)* N/A *(e)* N/A
Results		
Participants: *(a)* Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed *(b)* Give reasons for non-participation at each stage *(c)* Consider use of a flow diagram	13	*(a)* Of 1565 eligible patients, 872 had received lithium at some point during the study period. 467 (54%) patients discontinued lithium at least on one occasion with intention to stop for good. Of these, 223 (48%) had received lithium continuously for more than two years. After validation of diagnosis, 215 were eligible for inclusion. Twenty-one patients did not achieve the follow-up period of two years after lithium discontinuation required for our mirror. 194 patients were included in the final sample. *(b)* 16 patients had died within our follow-up period. Fifteen deaths were due to natural courses. One death was due to suicide. *(c)* Flow diagram included in the manuscript as figure 1.
Descriptive data: *(a)* Give characteristics of study participants (e.g. demographic,	14	*(a)* Baseline characteristics described in table 1 of the manuscript. *(b)* N/A for included patients

clinical, social) and information on exposures and potential confounders *(b)* Indicate number of participants with missing data for each variable of interest		
Outcome data: Report numbers in each exposure category, or summary measures of exposure	15	Outcome data presented in tables 2,3 and in text.
Main results *(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *(b)* Report category boundaries when continuous variables were categorized *(c)* If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16	*(a)* Between and within group differences reported. Significance level set to 95% precision for group comparisons. *(b)* N/A, outcome variables were number of admissions, bed days and costs. *(c) Cf. (a).*
Other analysis: Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	17	Mixed status ever reported in subgroup analysis.
Discussion		
Key results: Summarize key results with reference to study objectives	18	Done
Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19	Limitation discussed in regard to its observational design, lack of true control group, data quality, and potential enrichment by lithium responders.
Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20	Done
Generalisability: Discuss the generalizability (external validity) of the study results	21	Results discussed in relation to register studies, randomized trials and meta-analyses.
Funding: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22	Norrbotten County equity and equality fund, Norrbotten, Sweden Research and Development Fund (FOU) including Academic Environment Fund, Norrbotten County, Norrbotten, Sweden. Conflict to interest statement for all authors included in manuscript.

Checklist for Study III (refers to Paper III)

STROBE requirement	#	Our review
Title and abstract	1	
(a) Indicate the study's design with a commonly used term in the title and abstract		*(a)* Given. *Suicidal and other deliberate self-injurious behaviour in patients with bipolar disorder and comorbid attention deficit hyperactivity disorder after initiation of central stimulant treatment – a mirror-image study based on the LiSIE retrospective cohort*
(b) Provide in the abstract an informative and balanced summary of what was done and what was found		*(b)* Structured abstract provided.
Introduction		
Background/rationale: Explain the scientific background and rationale for the investigations being reported	2	Background outlined in introduction.
Objectives: State specific objectives, including any pre-specified hypotheses	3	Aims clearly stated in text: *The aim of this study was to evaluate the impact of CS treatment on events of suicidal and other deliberate self-injurious behaviour events (henceforth referred to as suicidal/self-injury events) in patients with a pre-existing diagnosis of BD or schizoaffective disorder (SZD). Specifically, we tested the hypothesis that CS treatment significantly decreased the number of self-injury events.*
Methods		
Study design: Present key elements of the study design early in the paper	4	Described for the LiSIE study as a whole and for this mirror-image study as part of a retrospective cohort study. Key elements of the study included in the manuscript: study design, participants, chart review, variable definitions and outcomes, control for bias, statistical analysis.
Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	Described for the LiSIE study as a whole and for this mirror-image study.
Participants: *(a)* Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (*b*) For matched studies, give matching criteria and the number of controls per case	6	*(a)* Described for the LiSIE study as a whole and for this mirror-image study. (b) Described: We used a mirror-image design to compare the frequency of suicidal/self-injury events within six months and two years before (pre-mirror periods) and after CS initiation (post-mirror periods).
Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7	Definition for outcomes, exposures and variables clearly defined in text. Criteria for diagnoses given in text.

Data sources /measurement: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8	Source: Medical records, both manual and electronically extracted Definition for each variable given in text.
Bias: Describe any efforts to address potential sources of bias	9	Described: *Seventy-five percent of all approached patients consented to inclusion into the LiSIE study. In accordance with the ethical approval granted, we controlled for selection bias in the whole LiSIE study, comparing age, sex, maximum recorded serum lithium and creatinine levels as key parameters, available in anonymized form. There were no significant differences between participating and non-participating patients.*
Study Size: Explain how the study size was arrived at	10	Described in text and flow chart (figure 2).
Quantitative variables: Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11	Described, cf. Statistical methods
Statistical methods: *a)* Describe all statistical methods, including those used to control for confounding *(b)* Describe any methods used to examine subgroups and interactions (*c)* Explain how missing data were addressed *(d)* If applicable, explain how matching of cases and controls was addressed *(e)* Describe any sensitivity analyses	12	*(a) The clinical data was abstracted into a database and anonymised before analysis. In a first step, we analysed the data descriptively, establishing the frequency of all variables in our database. Means and standard deviations were calculated for continuous data and frequencies and percentages for categorical data. We then compared suicidal/self-injury events in the pre- and post-mirror periods. Here we compared (a) number of patients who had experienced such events and (b) number of events per patient. As the data was not normally distributed, we used non-parametric tests for pairwise (before/after) comparisons. For these pairwise comparisons, we used McNemar's exact test for the number of patients with suicidal/self-injury events and Wilcoxon signed rank test for the numbers of events. Additionally, we explored potential confounding factors that might have been associated with suicidal/self-injury events within the two-year pre- and post-mirror periods taken together (whole four-year review period) with a generalized linear mixed model (GLMM). We considered the following factors, period (respective pre-and post-mirror period), age, sex, type of underlying affective disorder, CS dose (high/low), mood stabilisers (never, used only in pre-mirror period, only in the post-mirror period or in both periods), alcohol or substance misuse (never, used only in pre-mirror period, only in the post-mirror period or in both periods), and CS discontinued in post-mirror episode. With this set-up it was possible to analyse (a) our outcome, i.e. counts of events, and (b)*

		repeated observations for each individual, i.e. the number of events before and after the first administration of CS. The GLMM was set-up using a negative binomial distribution and a log link, and individual patients were modelled as a random effect. This is explained in further detail in the SPSS syntax given in appendix (Appendix 1). Throughout, statistical significance level was set to p ≤0.05. For the statistical analysis, we used the IBM SPSS version 26 (IBM, Armonk, NY, USA). *(b)* see (a) *(c) For some patients, data was missing in either pre- or post-mirror period. However, complete data was available for > 97% so missing data is unlikely to have distorted the results.* Cf. also methods to control for bias. *(d)* N/A *(e)* N/A
Results		
Participants: *(a)* Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed *(b)* Give reasons for non-participation at each stage *(c)* Consider use of a flow diagram	13	*(a)* Described in text and flow chart. *(b) For some patients, data was missing in either pre- or post-mirror period. However, complete data was available for > 97% so missing data is unlikely to have distorted the results.* *(c)* Flow diagram included in the manuscript as figure 2.
Descriptive data: *(a)* Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders *(b)* Indicate number of participants with missing data for each variable of interest	14	*(a)* Described in text and table 2. *(b)* Described in text and flow chart (figure 2).
Outcome data: Report numbers in each exposure category, or summary measures of exposure	15	Outcome data presented in text and tables 3 and 4
Main results *(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *(b)* Report category boundaries when continuous variables were categorized *(c)* If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16	*(a) Cf statistics: Additionally, we explored potential confounding factors that might have been associated with suicidal/self-injury events within the two-year pre- and post-mirror periods taken together (whole four-year review period) with a generalized linear mixed model (GLMM). We considered the following factors, period (respective pre-and post-mirror period), age, sex, type of underlying affective disorder, CS dose (high/low), mood stabilisers (never, used only in pre-mirror period, only in the post-mirror period or in both periods), alcohol or substance misuse (never, used only in pre-mirror period, only in the post-mirror period or in both periods), and CS discontinued in post-mirror episode. With this set-up it was possible to analyse (a) our outcome, i.e. counts of*

		events, and (b) repeated observations for each individual, i.e. the number of events before and after the first administration of CS. The GLMM was set-up using a negative binomial distribution and a log link, and individual patients were modelled as a random effect. This is explained in further detail in the SPSS syntax given in appendix (Appendix 1). Throughout, statistical significance level was set to p ≤0.05. For the statistical analysis, we used the IBM SPSS version 26 (IBM, Armonk, NY, USA). *(b)* Applicable to CS dose: described in table 1 and text. *To account for discrepancies between the highest recommended doses in Sweden and the UK, we amalgamated these four categories into two groups, (a) low for low or intermediate dose, and (b) high for high dose or a dose exceeding the highest recommended dose.* *(c) Cf. (a).*
Other analysis: Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	17	N/A.
Discussion		
Key results: Summarize key results with reference to study objectives	18	Done
Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19	Limitation discussed in regard to its observational design and not a randomized controlled trial, lack of true control group, data quality, identification of suicidal/self-injury events
Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20	Done
Generalisability: Discuss the generalizability (external validity) of the study results	21	Results discussed in relation to register studies, randomized trials and meta-analyses.
Funding: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22	Norrbotten County equity and equality fund, Norrbotten, Sweden Research and Development Fund (FOU) including Academic Environment Fund, Norrbotten County, Norrbotten, Sweden. Conflict to interest statement for all authors included in manuscript.