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LONG-TERM OUTCOME OF BIPOLAR I AND II DISORDERS

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ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine, University of Helsinki, for public examination in the Christian Sibelius Auditorium, HUCH Psychiatry Centre, Välskärinkatu 12, on 23 November 2018, at 12 noon.

Helsinki 2018

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Dissertationes Scholae Doctoralis Ad Sanitatem Investigandam Universitatis Helsinkiensis

ISBN 978-951-51-4685-4 (pbk.)
ISBN 978-951-51- 4686-1 (PDF)
ISSN 2342-3161 (print)
ISSN 2342-317X (online)

Cover graphic: Anne Kolhinen
Unigrafia, Helsinki 2018

To my children

TIIVISTELMÄ (FINNISH ABSTRACT)

Jorvi Bipolar Study (JoBS) on kaksisuuntaisen mielialahäiriön tutkimusprojekti, joka toteutettiin yhteistyössä Terveyden ja hyvinvoinnin laitoksen Mielenterveys-yksikön (aiempi Kansanterveyslaitoksen mielenterveyden ja alkoholitutkimuksen osasto) ja Jorvin sairaalan (HYKS Psykiatria, Helsingin ja Uudenmaan sairaanhoitopiiri) kanssa. JoBS on prospektiivinen, naturalistinen, DSM-IV mukaista kaksisuuntaista mielialahäiriötä sairastavien potilaiden kohorttitutkimus, jossa seurattiin 191 potilaan tilaa 5 vuoden ajan. Kaksisuuntainen mielialahäiriö on vakava mielenterveyden häiriö, jossa masennusjaksot, maaniset ja sekamuotoiset sekä oireettomat jaksot vaihtelevat. Tyyppi I häiriössä esiintyy maniajaksoja, kun taas tyyppi II häiriössä ainoastaan lievempiä hypomaanisia jaksoja.

Mood Disorder Questionnaire (MDQ)-seulontakaavakkeella seulottiin sisäänottovaiheessa 1630 (ikä 18-59 vuotta) potilasta, joista 490 haastateltiin strukturoidulla SCID-haastattelulla. DSM-IV:n mukainen kaksisuuntaisen mielialahäiriön akuutti sairausvaihe todettiin 191 potilaalla, jotka muodostivat tutkimuskohortin. DSM-IV-luokitukseen perustuvaa lifechart-metodologiaa käyttäen potilaat haastateltiin seurannassa 6 ja 18 kuukauden sekä 5 vuoden kohdalla. Kaikissa tutkimusvaiheissa käytettiin SCID-I – ja –II-haastattelujen lisäksi useita potilaan itse täyttämiä ja tutkijan täyttämiä kaavakkeita, mm. eri oiremittareita. Tämän 5-vuotisseurantatutkimuksen tarkoituksena oli tutkia pitkäaikaisennustetta käyttäen päätemuuttujina oireettomuuden saavuttamista, taudin uusimista, ja itsemurhayrityksiä sekä näihin vaikuttavia tekijöitä. Lisäksi tutkittiin, miten dominoiva polariteetti vaikuttaa ennusteeseen ja ennustavatko sairaudenkulun jatkumoluonteiset kuvaajat ensimmäisen 18 kk:n ajalta sairaudenkulkua myöhemmin.

Tutkimuksessa todettiin, että potilaat olivat oireisia noin puolet ajasta; noin kolmasosan varsinaisissa sairausjaksoissa ja 15 % lievemmissä oiretiloissa. Tilastollisesti merkitsevää eroa masennustiloissa vietetyssä ajassa kaksisuuntaisen mielialahäiriön tyyppi I ja II välillä ei todettu. Lähes kaikki potilaat (96%) toipuivat indeksiepisodista, mutta 87%:lla tauti uusi seurannassa. Masennusoireiden vaikeusaste, C-klusterin persoonallisuushäiriö ja elämänaikaiset psykoosioireet liittyivät huonompaan ennusteeseen.

5-vuotisseurannassa 28 % potilasta yritti itsemurhaa. Elämänaikaisesti yli puolella (57%) oli ainakin yksi itsemurhayritys. Seurannassa itsemurhayritysten ilmaantuvuus eri sairaustilojen välillä erosi huomattavasti. Korkein ilmaantuvuus, yli 120-kertainen verrattuna eutymiaan, oli sekamuotoisten jaksojen aikana. Ilmaantuvuus oli korkea, lähes 60-kertainen verrattuna eutymiaan, myös masennusjaksojen aikana, jolloin itsemurhayrityksen riskiä lisäsivät masennusjakson pidempi kesto ja vaikeusaste sekä C-klusterin persoonallisuushäiriö. Itsemurhayritysten ilmaantuvuuden vaihtelu eri sairaustilojen välillä oli huomattavasti merkittävämpää

kuin potilaan piirreominaisuuksien vaikutus itsemurhayritysten riskiin. Kaksisuuntaisessa mielialahäiriössä itsemurhariskin pienentämiseksi sairaustiloihin liittyvän riskin tunnistaminen saattaa olla tärkeämpää kuin yrittää tunnistaa riskihenkilöitä piirreominaisuuksien perusteella. Itsetuhoisuuden ehkäisemiseksi on oleellista pyrkiä hoidolla vähentämään riskitiloissa vietettyä aikaa.

Jatkumoluonteiset sairaudenkulun kuvaajat ensimmäisen 18 kk:n seurannan ajalta ennustivat sairaudenkulkua aikavälillä 18kk:sta viiteen vuoteen. Aikaosuus masentuneena, masennusoireiden vaikeusaste ja aikaosuus maanisena ennustivat enemmän aikaa sairaana jälkimmäisellä seuranta-jaksolla. Aikaosuus maanisena, maanisten oireiden vaikeusaste ja masennuksesta suoraan maniaan kääntyvä sairaudenkulku ennustivat suurempaa sairaalahoidon todennäköisyyttä. Löydökset olivat tilastollisesti merkitseviä myös, kun ikä, sukupuoli ja kaksisuuntaisen mielialahäiriön tyyppi kontrolloitiin. Jatkumoluonteiset sairaudenkulun kuvaajat saattavat olla hyödyksi ennustettaessa kaksisuuntaisen mielialahäiriön pitkäaikaiskulkua.

Noin puolella potilasta (52%) voitiin todeta joko maaninen tai depressiivinen dominoiva polariteetti, kun rajana käytettiin vähintään 2/3 maanisten tai depressiivisten jaksojen elämänaikaista määrää suhteessa kaikkiin jaksoihin. Maaninen polariteetti todettiin 16%:lla, depressiivinen polariteetti 36%:lla, ja 48%:lla polariteettia ei voitu määrittää. Käytetty aikaikkuna vaikutti polariteettijakaumaan. Viisivuotisseurannassa maanisen polariteetin ryhmä oli merkitsevästi suuremman osan aikaa oireeton, vietti vähemmän aikaa depressiossa ja enemmän aikaa maanisena kuin depressiivisen tai määrittämättömän polariteetin ryhmä. Maanisen polariteetin ryhmässä itsemurhayrityksiä ja rinnakkaisia elämänaikaisia ahdistuneisuushäiriöitä oli merkitsevästi vähemmän, mutta elämänaikaisia psykoosioireita esiintyi useammin. Ensimmäisen sairausjakson polariteetti ennusti dominoivaa polariteettia. Tämän tutkimuksen perusteella dominoivalla polariteetilla on ennustevaikutusta pitkäaikaisseurannassa. Maanisen polariteetin ryhmällä näytti olevan parempi ennuste kuin kahdella muulla polariteettiryhmällä, jotka monin tavoin vaikuttivat muistuttavan toisiaan.

Tämän tutkimuksen mukaan kaksisuuntaista mielialahäiriötä sairastavat potilaat kärsivät toistuvista sairausjaksoista vaikka toipuivatkin indeksiepisodista. Psykoosioireiden ja C-klusterin persoonallisuushäiriön esiintyminen liittyi huonompaan ennusteeseen, ja näiden sekä itsetuhoisuuteen liittyvien riskitilojen tunnistaminen ja hoito on tärkeää. Dimensionaaliset sairaudenkulun kuvaajat sekä dominoiva polariteetti saattavat olla hyödyllisiä ennustettaessa sairaudenkulkua.

Avainsanat: kaksisuuntainen mielialahäiriö, ennuste, pitkäaikaisseuranta, remissio, rekurrenssi, itsemurhayritys, dominoiva polariteetti

ABSTRACT

The Jorvi Bipolar Study (JoBS) is a collaborative bipolar research project between the Unit of Mental Health of the National Institute for Health and Welfare (former Department of Mental Health and Alcohol Research of the National Public Health Institute), Helsinki and the Department of Psychiatry, Jorvi Hospital (HUCH), Espoo, Finland. JoBS is a prospective, naturalistic cohort study of 191 secondary level care psychiatric in- and outpatients who at intake had a new episode of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) bipolar disorder (BD).

Bipolar disorder is a serious mental disorder characterized by recurrent episodes of hypomania, mania, mixed states, and depression. In type I disorder (BD I), one or more lifetime manic or mixed episodes occur with major depressive episodes. In type II disorder (BD II), at least one hypomanic episode during the lifetime occurs with major depressive episodes.

At intake, 1630 patients (aged 18-59 years) were screened using the Mood Disorder Questionnaire (MDQ) for a possible new episode of DSM-IV BD and 490 patients were interviewed using a semi-structured interview (the Structured Clinical Interview for DSM-IV Disorders, researcher version with Psychotic screen, SCID-I/P). An acute phase of DSM-IV BD was verified in 191 patients, who were included in the study cohort. Lifechart -methodology based on DSM-IV was used at baseline and in follow-up interviews at 6 months, 18 months, and 5 years to gather information on the course of the illness in the form of a graphic lifechart. Observer- and self-reported scales were used both at baseline and at follow-up assessments. The aim of this study was to investigate the 5-year outcome with regard to remission, recurrence, time spent ill, and suicide attempts, to assess the influence of the predominant polarity on outcome, and to test whether clinically relevant course characteristics or course classes from the first 18 months predict the long-term outcome.

In this 5-year follow-up, BD patients spent about half of their time ill; about one-third of their time in illness episodes and another 15% with subthreshold symptoms. Contrary to earlier long-term studies, no difference was found between patients with BD I and BD II in time spent in depressive states. Almost all (96%) of the patients recovered from the index episode, but the majority (87%) had a recurrence in follow-up. Severity of depression, cluster C personality disorder, and lifetime psychotic symptoms predicted worse outcome.

During the 5-year follow-up, 28% of the patients attempted suicide. More than half (56.5%) had a least one suicide attempt (SA) during their lifetime. The variations in incidences of SAs between the illness phases were remarkably large. The incidence was highest, over 120-fold that in euthymia, during mixed states, and also very high, almost 60-fold that in euthymia, in

major depressive episodes (MDEs). During MDEs, duration and severity of depression and comorbid cluster C personality disorders predicted the risk. The variations in incidence rates exceed the potency of trait characteristics as risk factors, implying that the question of when is the risk highest, rather than who is at risk, might be more relevant for suicide prevention in BD. Reducing time spent in high-risk states is crucial for prevention.

Dimensional course characteristics established from the first 18 months of follow-up predicted outcomes over the subsequent follow-up period up to 5 years. The proportion of time depressed, the severity of depressive symptoms, and the proportion of time manic predicted more time spent ill in follow-up. The proportion of time manic, the severity of manic symptoms, and depression-to-mania switching predicted a greater likelihood of hospital admissions in follow-up. These dimensional descriptors of clinical course may be useful in predicting the long-term outcome of BD.

About half (52%) of the patients had a predominant polarity when setting the threshold in at least two-thirds of lifetime episodes to be either manic or depressive polarity. For 16% of the patients, the predominant polarity was manic (MP), for 36% depressive (DP), and for 48% a predominant polarity could not be applied (no-polarity group, NP). However, the classification of predominant polarity was influenced by the time frame used. In the 5-year follow-up, the MP group spent significantly more time euthymic, less time in MDEs, and more time in manic states than the two other groups. The MP group had significantly lower incidence of SAs in follow-up and lower prevalence of lifetime comorbid anxiety disorders, but more lifetime psychotic symptoms. An association existed between the predominant polarity and the polarity of the first illness episode. Overall, according to this study, predominant polarity has predictive validity in the long-term course of BD. The MP group seemed to have a better prognosis than the two other groups, which resembled each other in many respects.

According to this long-term follow-up study, most BD patients recovered from the index episode, but suffered from recurrent illness episodes. Occurrence of psychotic symptoms and cluster C personality disorders may indicate worse outcome, and, among high-risk states with regard to suicidality, should be recognized and intensively treated in clinical practice. Dimensional course descriptors and predominant polarity may be helpful in predicting outcome.

Keywords: bipolar disorder, outcome, long-term follow-up, remission, recurrence, suicide attempt, predominant polarity, clinical course

ACKNOWLEDGMENTS

This study was carried out at the Mental Health Unit of the National Institute for Health and Welfare (former National Public Health Institute); the Department of Psychiatry, Jorvi Hospital, Hospital District of Helsinki and Uusimaa; and the University of Helsinki. I am grateful to the former and current heads of the Unit, Professors Mauri Marttunen and Jaana Suvisaari, for providing excellent facilities. I express my gratitude to the former heads of the Psychiatric Department of Jorvi Hospital, Mikko Roine and Jukka Häivä, who provided the possibility to collect the Jorvi Bipolar Study cohort.

I warmly thank Professor Jouko Lönnqvist for introducing me to the world of science as part of my medical studies. Being strongly oriented towards clinical work, I had never considered doing further research, but that gratifying experience gradually, and unexpectedly, led me towards this thesis project.

I owe my deepest gratitude to my supervisor, Professor Erkki Isometsä for his endless support, kind encouragement, and assertive guidance during all these years. He must have sometimes shared the despair I felt when the work inched along, but he never let it show. Instead, by sharing his enormous knowledge in the field of mood disorders and suicidology, and by always finding time to answer my questions, he managed to push me forward not only during the difficult times, but throughout the whole project. It has truly been a privilege to have him as a supervisor. I am also deeply grateful to my other supervisor Docent Kirsi Suominen, who along with her broad scientific merits possesses excellent clinical skills in the field of bipolar disorder, and in spite of numerous responsibilities was always ready to help me with both scientific and practical matters.

The official reviewers of the thesis, Professor Jouko Miettunen and Professor Juha Veijola, are warmly thanked for valuable comments and kind criticism that greatly improved the final manuscript.

I am grateful to co-authors and fellow researchers Petri Arvilommi, M.D., PhD., Outi Mantere, M.D., PhD, Hanna Valtonen, M.D., PhD, and Sami Leppämäki, M.D., PhD, for their crucial contributions over the years. I warmly thank Mikko Ketokivi, PhD (coauthor of Studies I and II), and Tom Rosenström, PhD (coauthor of Study IV), for excellent statistical guidance. I am most grateful to Rudolf Uher, PhD (first author of Study III), Barbara Pavlova, PhD (coauthor of study III), Eduard Vieta, PhD, Francesc Colom, PhD, Iria Grande, PhD, and Aitana Garcia-Estela, PsyD (coauthors of Study IV) for kind collaboration. It has been a true privilege to be able to work with such professionals.

I warmly thank Tuula Rahkonen, who made enormous efforts to reach the patients when the 5-year interviews were ongoing. I thank Marjut Schreck for crucial help with data management. I warmly thank all personnel at the

National Institute for Health and Welfare and at HUCH Psychiatry Centre for their kind help with various practical matters. Special thanks to Piia Frondelius for her helping hand so many times.

I deeply thank my colleague Annakaija Helén for being such an admirable role model in what it is to be a skilled clinical psychiatrist, but even more for being a trusted friend and for the numerous interesting discussions of professional matters and beyond. I thank her also for her excellent food service and chauffeuring in Kuusankoski when I was repeatedly on-call to earn money for my research periods. Furthermore, I am grateful for her kind support during the last months of this project. I am most grateful to have had Docent Tarja Melartin as my clinical supervisor. Her wise and broad views have guided me not only in clinical work but also in the scientific field. I warmly thank Kari Aaltonen, Laura Hiltunen, Suoma Saarni, Veera Pohjolainen, Lumikukka Socada, and all other colleagues and coworkers who have contributed to my professional and scientific skills with inspiring discussions. I thank all my bosses who, by flexible working arrangements, made it possible to do research work at the same time as specializing in psychiatry and later working as a specialist when finalizing this theses.

I deeply thank my dear friends and their families for all the care and support. Thank you Nina, Satu, Pauliina, Piia, Jonna, Soili-Sisko, Hanna, Anne, Jonna, Kaisu, and all the others and your spouses as well. I am indebted to my friend Pauliina Koponen for her professional on-line help with editing tables and figures and other IT-issues during all these years. I warmly thank Pia Elfving, MD, PhD, and Tiina Teivaanmäki, MD, PhD, for their friendship and invaluable advice during the last months of this project. I owe so much to my American parents Nancy and Dale for their love and the opportunities they have provided to me and my family. I warmly thank Jenni for taking such good care of our children the many times she came to help. I am most grateful to my parents, Laura and Carlos, my sister Essi, my brother Tuomo, and Ilkka, Dan, and Suvi for help with child care and various other matters in life during these years. Words are insufficient to thank Satu, Soili-Sisko, Kari, and Piia for taking care of me and the children in Taipalsaari when I was totally occupied with writing in July 2017. I deeply thank all of my friends and relatives who have shared the joy and responsibility of my “third child”, the old school project. The house has provided me with a warm and cozy shelter to write this thesis, and the wisdom of past generations present there managed to calm my mind during most stressful times. I also thank Pauli for his support during the happy years that we shared.

Finally, I owe my deepest gratitude to my precious children, who just by being the wonderful persons that they are bring joy and happiness to my life unequalled by any professional or scientific accomplishment.

I warmly thank the Jalmari and Rauha Ahokas Foundation, the Finnish Medical Society, the Finnish Psychiatric Association, the Finnish Foundation for Psychiatric Research, the Helsinki City Department of Social Services and

Healthcare, and the Helsinki and Uusimaa Hospital District for the financial support.

My deepest appreciation is exteded to all patients who took part in this study in spite of the potentially disabling state of their serious illness.

Helsinki, October 2018

Sanna Pallaskorpi

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

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

I Pallaskorpi S, Suominen K, Ketokivi M, Mantere O, Arvilommi P, Valtonen H, Leppämäki S, Isometsä E. Five-year outcome of bipolar I and II disorders: findings of the Jorvi Bipolar Study. Bipolar Disord 2015;17:363-74.

II Pallaskorpi S, Suominen, K, Ketokivi M, Valtonen H, Arvilommi P, Mantere O, Leppämäki S, Isometsä E. Incidence and predictors of suicide attempts in bipolar I and II disorders: A five-year follow-up study. Bipolar Disord 2017;19:13-22.

III Uher R, Pallaskorpi S, Suominen K, Mantere O, Pavlova B. Clinical course predicts long-term outcomes of bipolar disorder. Psychol Medicine 2018;28:1-9.

IV Pallaskorpi S, Suominen K, Rosenström T, Mantere O, Arvilommi P, Valtonen H, Leppämäki S, Garcia-Estela A, Grande I, Colom F, Vieta E, Isometsä E. Predominant polarity in bipolar I and II disorders: A five-year follow-up study. Submitted.

ABBREVIATIONS

AD	antidepressant
ADHD	attention deficit hyperactivity disorder
BAI	Beck Anxiety Inventory
BD	bipolar disorder
BD I	bipolar disorder type I
BD II	bipolar disorder type II
BDI	Beck Depression Inventory
BDNF	brain-derived neurotrophic factor
BDRS	Bipolar Depression Rating Scale
BPD	borderline personality disorder
CDS	Collaborative Depression Study
CNS	central nervous system
DALY	disability-adjusted life-years
DMX3	depressive mixed state; a major depressive phase with three or more simultaneous hypomanic symptoms
DNA	deoxyribonucleic acid
DP	depressive predominant polarity
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DYS	dysthymic disorders
ECT	electro-convulsive therapy
HAM-D	Hamilton rating scale for depression
5-HIAA	5-hydroxy-indoleacetatic acid
HVA	homovanillic acid
HR	hazard ratio
HS	Hopelessness Scale
ICD-10	International Classification of Diseases, 10th edition
IL-4	interleukin 4
ISBD	International Society for Bipolar Disorders
JoBS	Jorvi Bipolar Study
LIFE	Longitudinal Interval Follow-up Evaluation
MADRS	Montgomery-Åsberg Rating Scale
MDD	major depressive disorder
MDI	manic-depressive insanity
MDQ	Mood Disorder Questionnaire
MEAF	Mental Health in Early Adulthood in Finland Study
MINI	Mini-International Neuropsychiatric Interview

MP	manic predominant polarity
NCS-R	US National Comorbity Study Replication
NESARC	National Epidemiological Survey on Alcohol and Related Conditions
NIMH	National Institute of Mental Health
OCD	obsessive-compulsive disorder
ODD	oppositional defiant disorder
OR	odds ratio
PD	personality disorder
PDQ-4	Personality Disorder Questionnaire, version 4
PIF	The Psychoses in Finland study
PP	predominant polarity
PSSS-R	Perceived Social Support Scale-Revised
RCT	randomized controlled trial
RDC	Research Diagnostic Criteria
SA	suicide attempt
SADS	Schedule for Affective Disorders and Schizophrenia
SCID	Structured Clinical Interview
SCID-I	Structured Clinical Interview for DSM-IV Axis I disorders
SCID-I/P	Structured Clinical Interview for DSM-IV Axis I disorders, researcher version with psychotic screen
SCID-II	Structured Clinical Interview for DSM-IV Axis II disorders
SFBN	Stanley Foundation Bipolar Treatment Outcome Network Study
sIL-2R	soluble interleukin 2 receptor
sIL-6R	soluble interleukin 6 receptor
SMR	standardized mortality ratio
SNP	single nucleotide polymorphism
SOFAS	Social and Occupational Functional Assessment Scale
SSI	Scale for Suicidal Ideation
SSRI	selective serotonin reuptake inhibitor
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
STOP-EM	Systematic Treatment Optimization Program for Early Mania
TCA	tricyclic antidepressant
TNF-α	tumor necrosis factor alpha
WMH	World Mental Health Survey
WHO	World Health Organization
YMRS	Young Mania Rating Scale

1 INTRODUCTION

Bipolar disorder (BD) is a recurrent, chronic and symptomatically diverse illness often causing life-long burden for affected individuals and their next of kin (Goodwin & Jamison 2007). During the illness-course, the depressive, (hypo)manic and mixed illness episodes recur with intervening symptomless or subsyndromal periods with large individual variation in the duration and frequency of episodes. In bipolar disorder type I (BD I), manic or mixed episodes during lifetime occur with major depressive episodes, whereas in bipolar disorder type II (BD II) hypomanic episodes occur with major depressive episodes.

Due to the high rates of suicidality, psychosocial and vocational disability, and morbidity and mortality (Grande et al., 2016), BD is a major global public health concern (Conus, Macneil & McGorry, 2014). According to the Global Burden of the Disease Study, there were 48.8 million cases of BD globally in 2013 and BD accounted for 9.9 million disability-adjusted life-years (DALYs) (Ferrari et al., 2016).

The recognition of BD is not optimal even in psychiatric care (Mantere et al., 2004, Hantouche et al., 1998, Shen et al., 2018), the mean delay between illness onset and diagnosis being approximately 5-10 years (Berk et al., 2007a, Fritz et al., 2017). The reasons for a delay in correct diagnosis are numerous. Depressive symptoms dominate in the illness course (Judd et al. 2003a), mixed symptoms in BD as well as subthreshold hypomanic symptoms in major depressive disorder (MDD) being common and often unrecognized (Phillips, Kupfer, 2013). Patients tend not to report mild hypomanias, which are the diagnostic feature of BD II, and mostly seek treatment when depressed. Full-blown manias often lead to hospitalization and to a correct diagnosis of BD, but they can develop quickly and often cause severe harm to the patient before the (involuntary) treatment takes effect. There is also an inevitable delay of diagnosis caused by the nature of the disease itself, i.e. onset of the illness with depressive episode(s) in more than half of the cases (Angst, Sellaro, 2000, Baldessarini, Tondo & Visioli, 2014, Grande et al., 2016). Some features of unipolar depression may increase the likelihood of conversion to BD (Vieta et al., 2018a), and the clinician should pay special attention to MDD patients with early-onset depression and family history of BD. The adverse consequences of inappropriate treatment deriving from misdiagnosis may influence both short- and long-term outcomes (Altamura et al., 2010, Knezevic, Nedic, 2013, Altamura et al., 2015). Frequent comorbid disorders among BD patients (Di Florio, Craddock & van den Bree, 2014, Pavlova et al., 2015) often leave the clinician struggling not only with diagnostic evaluation, but also with treatment design and prediction of long-term outcomes. Incorporating the bipolar spectrum into the variety of mood symptoms in BD challenges the clinician all the more (Angst, 2007, Ghaemi, 2013).

As the longitudinal (retrospective) evaluation of mood symptoms is essential in diagnosing and treating BD, a prospective viewpoint is needed in the long-term (Yatham et al., 2018). Evaluating such features as the risk of recurrence, risk of suicide attempts, and polarity of future episodes is relevant to the clinician, but the tools available to assist in this evaluation have remained somewhat insufficient (Colom, Vieta & Suppes, 2015). Despite increasing knowledge of the long-term outcome of BD and factors affecting outcome, there is marked inherent inter-individual variation in the long-term course of the illness, which puzzles the clinician (Grande et al., 2016). The division into BD I and BD II and the current specifiers in the DSM-5 capture some of the variation, but additional clinically functional course specifiers are needed.

Among psychiatric disorders, BD is associated with one of the highest risk of suicide (Harris, Barraclough, 1997, Gonda et al., 2012, Tondo et al., 2016). About one tenth of BD patients die by suicide and 30-50 % attempt suicide during their lifetime (Angst al., 2005a, Nordentoft, Mortensen & Pedersen, 2011, Coryell et al., 2016). Identified trait-related risk factors of suicide attempts and completed suicides are multiple and often prevalent among BD patients (Schaffer et al., 2015a), limiting their predictive value, whereas scant knowledge exists on state-related factors influencing the risk of suicidality during different illness states. For a clinician, evaluation of suicidality and prevention of a suicidal act of an individual BD patient are always a professional challenge, and research should yield clinically practical aids for prevention of suicides.

The Jorvi Bipolar Study (JoBS) is a naturalistic, prospective long-term cohort study including 191 secondary-level care BD I and BD II in- and outpatients, who at intake had a new episode of DSM-IV BD. This thesis focuses on the 5-year outcome of BD with regard to remission, recurrence, time spent ill, and suicide attempts. It also aims to investigate the influence of predominant polarity on long-term outcome of BD patients, and to examine, whether the clinical course in the first 18 months predicts the long-term outcome.

2 REVIEW OF THE LITERATURE

2.1 BIPOLAR DISORDER

2.1.1 DEFINITION OF BIPOLAR DISORDER

Bipolar disorder, previously called manic-depressive illness, is a serious mental disorder characterized by recurrent episodes of hypomania, mania, mixed states and depression. BD is divided into BD I and BD II disorders. In BD I, one or more lifetime manic or mixed episodes during lifetime occur with major depressive episodes. In BD II, at least one hypomanic episode during the lifetime occurs with major depressive episodes.

2.1.2 HISTORY OF BIPOLAR DISORDER

Mania and melancholia have been recognized as illnesses since the ancient times, Hippocrates (460-337 BC) being the first to describe them systematically as a biological disturbance of the four body humors – blood, yellow bile, black bile, and phlegm. An excess of yellow bile was seen as the cause of mania whereas melancholia, literally meaning "black bile", was attributed to an excess of black bile. Arataeus of Cappadocia, who lived in 2nd century AD, was presumably the first to propose that mania was an end state of melancholia, a view that dominated for centuries (Angst, Marneros, 2001, Goodwin & Jamison 2007) .

In the 18th century, the longitudinal association between melancholia and mania was described by several scientists in Germany, England and Italy (Angst, Marneros, 2001), but the explicit conception of manic-depressive illness as a single disease entity was proposed independently and almost simultaneously by the two French "alienists" Falret and Baillager. In 1854, Falret described "la folie circulaire", a circular disorder in which "this succession of mania and melancholia manifests itself with continuity and in a manner almost regular". In the same year, "la folie a double forme" (double insanity) was described by Baillager, who highlighted that the manic and depressive episodes were not two different attacks, but rather two states of the same attack (Goodwin & Jamison 2007).

Emil Kraepelin (1856-1929), often called "the father of modern psychiatry", separated the two major psychotic illnesses as dementia praecox and manic-depressive insanity stating that the latter was distinguished from the former by an episodic course, better prognosis and family history of manic depressive illness. Kraepelin was also first to note that psychological stress could trigger the episodes, and by including "slight colorings of mood", which "pass over without sharp boundary into the domain of personal predisposition", he laid

the foundation for the bipolar spectrum to be introduced later (Kraepelin, 1899, Goodwin & Jamison 2007). Eugen Bleuler broadened Kraepelin's views by designating several subcategories of the "affective illness" and foresaw the subsequent division based on unipolar and bipolar forms of the illness (Bleuler Eugen, 1924).

Despite the recognition of affective (in modern terms unipolar or bipolar) disorders for centuries, it was not until the 1950s that the diagnostic distinction between patients with only depressive episodes and those with both depressive and manic episodes was presented by Leonhard (Leonhard, 1957). He based his views on the observation that patients with a history of mania had a higher incidence of mania in their families than those with recurrent depressions, and this distinction was later supported by Angst (1978), Perris (1966) and Winokur et al. (1969). The American diagnostic system, the DSM, 3rd edition (DSM-III) in 1980 (American Psychiatric Association, 1980), was the first diagnostic manual to include the bipolar-unipolar distinction, which was later carried forward into the DSM-IV (American Psychiatric Association, 1994) and DSM-5 (American Psychiatric Association, 2013) and the International Classification System ICD-10 (WHO, 1993).

Milder forms of mania were described already by the ancients, but Mendel (Mendel, 1881) was the first to define hypomania as "that form of mania which typically shows itself only in the mild stages abortively", and Kahlbaum (Kahlbaum, 1882) described circular disorders closest to what we today regard as cyclothymia. The current distinction of bipolar illness as separate disorders type I and type II was first introduced by Dunner et al. (1976). They based this distinction on their studies of hospitalized depressed patients with a history of either full-blown mania requiring hospitalization (BD I) or a history of milder manic state interfering with normal role functioning, but not sever enough to require hospitalization (BD II). Subsequent studies (Coryell et al., 1985) broadened this definition to include subgroups of BD II patients without a history of hospitalization for either depressive or hypomanic state, but instead with concurrent comorbid disorders (e.g. borderline personality disorder). Finally, BD II disorder was included in the 4th edition of DSM (DSM-IV) in 1994 (American Psychiatric Association, 1994).

2.1.3 DIAGNOSIS OF BIPOLAR DISORDER

In Finland, the 10th edition of the International Classification of Diseases (ICD-10) criteria (WHO, 1993) is used in clinical practice. However, in this study, the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, 4th edition DSM-IV (American Psychiatric Association, 1994) was used when assessing the diagnoses. In these two classifications, the criteria of (hypo)manic and depressive episodes are mostly concordant from a clinical perspective, but the ICD-10 criteria do not formally recognize BD II. The Structured Clinical Interview for DSM-IV disorders (SCID) is used to increase

diagnostic validity of both Axis I and II disorders (First et al., 1997, First et al., 2002) and is, together with the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott, Spitzer, 1978), and Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), one of the most frequently used diagnostic methods in psychiatric research.

2.1.3.1 *DSM-IV criteria of episodes*

The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) was not available at the time of data collection of this study, and thus the DSM-IV criteria (American Psychiatric Association, 1994) were used (Table 1). In DSM-IV, there are five different categories of mood disorders: unipolar depression, bipolar disorders, mood disorder due to a general medical condition, substance-induced mood disorder, and mood disorder not otherwise specified.

There are four different episodes of BD in DSM-IV. The criteria regarding major depressive episode are the same for BD and MDD. The essential characteristic of *major depressive episode* is a period of two weeks representing a change from a previous functioning and during which there is depressed mood and/or markedly diminished interest or pleasure in all or almost all activities most of the day. Additionally, these main symptoms must be accompanied by at least four (or three if both of the essential characteristics are present) of the following symptoms: (i) significant weight loss or gain or decrease or increase in appetite, (ii) insomnia or hypersomnia, (iii) psychomotor agitation or retardation (observable by others), (iv) fatigue or loss of energy, (v) feelings of worthlessness or excessive or inappropriate guilt, (vi) diminished ability to think or concentrate or indecisiveness or (vii) recurrent thoughts of death, recurrent suicidal ideation, a suicide attempt or a specific plan for committing suicide. The symptoms must be present nearly every day, cause clinically significant distress or impairment in social, occupational or other areas of functioning, and must not be better accounted for by bereavement (American Psychiatric Association, 1994).

Manic episode is defined as a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least one week (or less if hospitalization is required). Additional symptoms of manic episode are (i) inflated self-esteem or grandiosity, (ii) decreased need for sleep, (iii) pressure to keep talking, (iv) flight of ideas or subjective experience of racing thoughts, (v) distractibility, (vi) increased involvement in goal-directed activities or psychomotor agitation, and (vii) excessive involvement in pleasurable activities that have a high potential for painful consequences. To fulfill the criteria for manic episode, an individual must have at least three (four if mood is only irritable) of the forementioned symptoms during a period of mood disturbance. The symptoms must not meet criteria for a mixed episode and they must be severe enough to cause marked impairment in occupational functioning or social activities or relationships with others or necessitate

hospitalization to prevent harm to self or others, or there must be psychotic features present (American Psychiatric Association, 1994).

The criteria of *hypomanic episode* are the same as those of manic episode except that a minimum duration of only four days for hypomania is required, and opposite to a manic episode, a hypomanic episode is not severe enough to cause marked impairment in occupational functioning or social activities or relationships with others or require hospitalization. Neither is there to be any psychotic features in hypomanic episodes. However, a hypomanic episode must be associated with an unequivocal change in functioning not characteristic to the person and also observable by others (American Psychiatric Association, 1994).

Mixed episode is a period of at least one week when the criteria are met for both manic episode and major depressive episode (except duration). Furthermore, the mood disturbance must be severe enough to cause marked impairment in occupational functioning or social activities or relationships with others or require hospitalization to prevent harm to self or others, or it must be characterized by the occurrence of psychotic features (American Psychiatric Association, 1994).

In any of the mood episodes mentioned above, the symptoms must not be due to the direct physiological effects of a substance or a general medical condition.

Table 1. DMS-IV diagnostic codes for bipolar disorder.

Episode	**Code**
Bipolar I Disorder, Single Manic Episode	296.0x*
Bipolar I Disorder, Most Recent Episode Manic	296.4x*
Bipolar I Disorder, Most Recent Episode Hypomanic	296.40
Bipolar I Disorder, Most Recent Episode Depressed	296.5x*
Bipolar I Disorder, Most Recent Episode Mixed	296.6x*
Bipolar I Disorder, Most Recent Episode Unspecified	296.7x*
Bipolar II Disorder	296.89

*the fifth number specifies the remission status or the severity of the ongoing mood episode: 0=unspecified, 1=mild, 2=moderate, 3=severe without psychotic features, 4=severe with psychotic features, 5=in full remission, 6=in partial remission

2.1.3.2 *DSM-IV versus DSM-5*

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) was published in 2013 (American Psychiatric Association, 2013). The significant modifications in relative to the DSM-IV (American Psychiatric Association, 1994) were the deletion of the axis system and a greater emphasis

on the dimensional nature of symptoms and the phenomenon of mental disorders.

Contrary to DSM-IV, in DSM-5, depressive disorders and bipolar disorders are separated as distinct categories and placed between the chapters on schizophrenia spectrum and other psychotic disorders and depressive disorders, underlining their position as a bridge between these two diagnostic classes in terms of symptomology, family history and heredity (American Psychiatric Association, 2013). For BD, there are seven different diagnostic categories in DSM-5: BD I, BD II, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder.

As a modification with regard to definition of episodes, in DSM-5 the main criterion A for hypomanic and manic episodes is hardened by including the change in activity and energy as well as mood. Based on their recent systematic review, Scott et al. (2017) concluded that activation may supersede mood as a salient feature of mania and depression in BD supporting the inclusion of activation as a diagnostic feature of mania and hypomania.

Furthermore, the DSM-IV diagnosis of "mixed episode" is replaced in DSM-5 with a mixed-features specifier applicable to major depressive, hypomanic, or manic episodes. In the case of manic or hypomanic episode, the mixed-feature specifier requires the presence of at least three symptoms of depression simultaneously with the episode of mania or hypomania, and analogously, in the case of depressive episode, the presence of at least three manic/hypomanic symptoms together with full criteria of major depressive episode. In addition, the mixed symptoms must be observable by others and not attributable to the psychological effects of a substance. In the case of full criteria met for both mania and depression simultaneously, the diagnosis of manic episode with mixed features should be used, due to the marked impairment and clinical severity of full mania (American Psychiatric Association, 2013).

Anxious distress has been noted as a prominent feature of both BD and MDD. Furthermore, higher levels of anxiety have been associated with higher suicide risk and greater likelihood of treatment nonresponse (American Psychiatric Association, 2013). Therefore, a specifier of anxious distress with four different levels from mild to severe has been added to DSM-5. Other specifiers included in DSM-5 are mixed features, rapid cycling, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peripartum onset, and seasonal pattern. In addition, mood episodes are coded with specifiers addressing the state of current mood symptoms (in partial remission, in full remission) and the severity of symptoms if full criteria for a mood episode are met (mild, moderate, severe) (American Psychiatric Association, 2013).

The reliability of DSM-5 psychiatric diagnoses has been tested in field trials using kappa statistics (Clarke et al., 2013, Regier et al., 2013, Clarke et al.,

2014). The interrater reliability for BD I was found to be 0.56 and for BD II 0.40, both being in good kappa range (0.40-0.59), although BD II just barely above the questionable kappa range (0.20-0.39). The diagnostic reliability of the DSM-IV and DSM-5 are likely quite similar (Chmielewski et al., 2015).

2.1.3.3 *Diagnostic challenges and conversion rate of major depressive disorder to bipolar disorder*

There is evidence of BD having a progressive nature and manifesting as milder forms prior to the classic presentation of the illness (Duffy et al., 2010, Vieta et al., 2013, Berk et al., 2014, Faedda et al., 2015, Kapczinski et al., 2017, Vieta, Berk et al., 2018). Prodromal symptoms are common but heterogeneous and vary in duration before both the initial and recurrent mood episodes (van Meter et al., 2016, Vieta et al., 2018a). Especially when BD begins in adolescence, the suspected diagnosis of BD can be particularly difficult to confirm due to potential overlapping symptoms with disorders such as attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and anxiety (van Meter et al., 2016). Furthermore, ADHD and anxiety have been proposed as precursors of BD, a presumption supported by the study of Meier et al. (2018), which found that ADHD and anxiety in earlier life increased the risk of BD 30-fold compared with those with no prior ADHD or anxiety. In the systematic review of Faedda et al (Faedda et al., 2014), early onset of panic attacks and panic disorder, separation anxiety and generalized anxiety disorders, conduct symptoms and disorder, ADHD, impulsivity, and criminal behavior were reported as clinical risk factors of BD. They also reported mood lability, subsyndromal and major depression, subsyndromal hypomanic symptoms with or without major depression, cyclothymia and BD not otherwise specified, major depression with psychotic features and other psychotic disorders as potential precursos of BD based on their systematic literature review of prospective studies (Faedda et al., 2015). Hypomanic symptoms often go undetected or misdiagnosed not only in adolescents but also in adults, and systematic screening with Mood Disorder Questionnaire (MDQ) has been proposed to improve their recognition (Hirschfeld et al., 2000, Isometsä et al., 2003, Carta, Angst, 2016). Reliable clinical scales to assess prodromal symptoms in children and adolescents are still lacking, and the tools developed need more prospective testing to evaluate their predictive validity (Bechdolf et al., 2014)

BD more often initiates with depressive than (hypo)manic episode (Angst, Sellaro, 2000, Baldessarini, Tondo & Visioli, 2014, Grande et al., 2016) which is not distinguishable from depressive episode of unipolar depression. Thus, a delay in diagnosis is partly inevitable (Fritz et al., 2017). Antidepressant treatment resistance (Sharma, Khan & Smith, 2005, Li et al., 2012, Dudek et al., 2013, Bukh, Andersen & Kessing, 2016), early onset of depression (Coryell et al., 1995, Angst et al., 2005b, Fiedorowicz et al., 2011, Dudek et al., 2013, Salvatore et al., 2013, Ostergaard et al., 2014, Tondo et al., 2014), family

history of BD (Coryell et al., 1995, Maj et al., 2007, Fiedorowicz et al., 2011, Sharma et al., 2014), and psychotic depression (Coryell et al., 1995, Goldberg, Harrow & Whiteside, 2001, Holma et al., 2008b, Fiedorowicz et al., 2011, James et al., 2015) have been proposed as common predictors of conversion from MDD to BD. Early age of onset (Ostergaard et al., 2014), functional impairment (Ostergaard et al., 2014), mixed features (Tohen et al., 2012, Salvatore et al., 2013) and previous hypomanic symptoms (Salvatore 2013) have been found to correlate with conversion to BD among patients with psychotic depression.

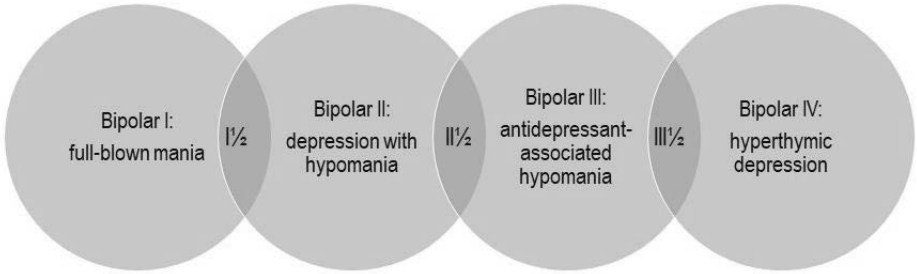
Two recent systematic reviews and meta-analyses (Kessing et al., 2017, Ratheesh et al., 2017) revealed that the conversion rate from MDD to BD decreases with time. In their meta-analysis, Kessing et al. (2017) included only studies using survival analysis and found that the conversion rate decreased from 3.9% in the first year after study entry to 3.1% in years 1-2, 1.0% in years 2-5, and 0.8% in years 5-10, the cumulative risk of conversion adding up to 12.9% in ten years. The meta-analysis of Ratheesh et al. (2017) found that during a follow-up of mean length of 12-18 years 22.5 % of adults and adolescents with MDD converted to BD, the highest risk being in the first five years.

These findings of decreasing conversion rates over time are opposite to the study of Angst et al. (2005b), which reported the conversion rate to be a linear 1.25 % per year over the 20-year follow-up, indicating lifetime conversion rate as high as 40-50 %. Angst et al. (2005b) found male gender and early onset of depression to be risk factors for a change from depression to BD I whereas female gender, later onset of depression and a positive family history of mania were risk factors for conversion to BD II. Family history of BD, earlier age of onset of depression and presence of psychotic symptoms were identified as risk factors for transition from MDD to BD in the meta-analysis of Ratheesh et al. (2017). Kessing et al. (2017) concluded that among the eight potential risk factors (gender, age at onset of MDD, number of depressive episodes, treatment resistance to antidepressants, family history of BD, the prevalence of psychotic depression, the prevalence of chronic depression and severity of depression), none was consistently confirmed to predict conversion across different studies. Methodological variation was the proposed explanation. A recent large historical prospective cohort study (follow-up 702 710 person-years) of Musliner and Ostergaard (2018) found the conversion rate (8.4%) to be slightly higher in females than in males (8.7% and 7.7.% respectively) and to decrease over time, markedly between the first and second years of follow-up. No BD diagnoses occurred after 20 years from the unipolar depression diagnosis in this study, and the strongest predictor of conversion was parental history of BD. Other notable predictors included psychotic depression and in-patient status at MDD onset and prior or concomitant non-affective psychosis (Musliner, Ostergaard, 2018).

2.1.4 BIPOLAR SPECTRUM

The basis of the concept of bipolar spectrum lies on the original Kraepelian concept of *manic-depressive insanity* (MDI), usually associated with psychotic features and later slightly rephrased as *manic-depressive illness* including also patients without psychotic symptoms. The division to *unipolar and bipolar recurrent psychosis* (Leonhard, 1957) was an interphase to concepts of *bipolar and unipolar depressive illnesses* including also non-psychotic mood presentations, which were later incorporated in DSM-III (American Psychiatric Association, 1980), DSM-IV (American Psychiatric Association, 1994), and DSM-5 (American Psychiatric Association, 2013) as *bipolar disorder and major depressive disorder*. It is noteworthy, that the concept of BD differs markedly from that of the original manic-depressive insanity and manic-depressive illness. As MDI is defined by episodicity (i.e. recurrent mood episodes irrespective of polarity), BD is defined by polarity (i.e. the presence or absence of manic symptoms), meaning that the concept of BD is much narrower than the original Kraepelian concept of MDI (Ghaemi 2013). Furthermore, the concept of MDD was broadened to include many types of depressive symptom presentation that can not be seen as part of the former recurrent depression (Ghaemi, 2013). The strict dichotomy of BD/MDD since DSM-III has been challenged by the concept of bipolar spectrum (Akiskal, 1983, Koukopoulos, Tundo, 1992, Angst, 2007) as an attempt to capture the vast variety of clinical manifestations of BD.

To date, numerous spectrum concepts with different emphasis have been developed (Ghaemi, 2013). Akiskal and Pinto (Akiskal, Pinto, 1999) stressed clinical perspectives and the depressive aspects of bipolar spectrum when introducing prototypes from full-blown mania (prototype I) to hyperthymic depression (prototype IV) (Figure 1). Akiskal's prototype I is the depression-prone illness course of BD, including constant awareness of the lifelong risk of potential full-blown manic episode(s). Prototype I½ represents patients with protracted hypomanic periods causing obvious trouble to the patient without reaching the destructive potential of full-blown manic psychosis. Prototype II stands for depressions with hypomania, what we in current diagnostic systems consider BD II. In Akiskal's classification, Prototype II½ refers to cyclothymic depressions including patients with short hypomania and major depressive episodes. The authors adduce that Bipolar II½ patients are often incorrectly diagnosed as "borderline" rather than affectively ill. The Bipolar III prototype represents antidepressant-induced hypomania and Bipolar III½ bipolarity masked by stimulant abuse. Akiskal's prototype Bipolar IV refers to hyperthymic depression including patients with lifelong hyperthymic temperament and clinical depressions occurring often later in life. The authors conclude, that extending the bipolar spectrum to what conventionally has been considered unipolar depression, substance abuse or axis II pathology, will help to shield many patients from possible side-effects of antidepressant medication.



Bipolar I½ = depression with protracted hypomania
Bipolar II½ = cyclothymic depressions
Bipolar III½ = bipolarity masked – and unmasked – by stimulant abuse

Figure 1. Akiskal's prototypes of BD (Akiskal, Pinto, 1999).

Koukopoulos et al. (2007), for their part, emphasize mixed states. As these authors, and the contradistinction of the fifth digit of the criteria for MDE ("psychomotor agitation or retardation") point out, the diagnostic entity of major depressive episode in DSM-IV includes many different depressive syndromes. Furthermore, the authors state that the difference between depressive syndromes characterized by symptoms with inhibitory nature and the ones characterized by symptoms with excitatory nature was not clinically meaningful as long as electroconvulsive therapy (ECT) was the main treatment for both. However, since the overrepresentation of antidepressant drugs in the treatment repertory of depression, the distinction between these different forms of depression has become crucial with regard to treatment choice. Symptoms such as psychomotor agitation, inner agitation, racing thoughts, talkativeness, irritability, and mood lability during depressive episode might indicate the presence of mixed or agitated depression, which may respond to antidepressant drug treatment with increasing agitation, insomnia, and emergence of psychotic symptoms and suicidal impulses. Based on wide clinical observations and data, Koukopoulos et al. (2007) suggested the term "melancholia agitata" to be used for mixed (agitated) depression, as opposed to "melancholia", which they proposed to be retained in modern nosology to include all depressive syndromes characterized by melancholic features of depressed mood, psychomotor retardation, anhedonia, circadian variations, and vegetative symptoms. They state that besides specific treatment recommendations, the importance of mixed/agitated depressions lies in their prevalent occurrence among patients with mood disorders. Based on a cross-sectional cohort of unipolar and bipolar patients, they reported 33% of MDEs

in all subtypes of affective disorder to be mixed depression and 56% of these to be antidepressant-induced (Koukopoulos et al., 2007). Similar prevalences of mixed/agitated depression have been reported in other studies (Koukopoulos et al, 1992, Maj et al., 2003). Benazzi (2002), defining a mixed depressive state as a MDE with three or more hypomanic symptoms, reported a prevalence as high as 43.9 % among unipolar and bipolar II patients. Angst et al. (2011) have reported that about half of all depressive episodes involve mixed states. Finally, Kokopoulos et al. (2007) concluded that "melancholia" is particularly responsive to ECT and fairly responsive to tricyclic antidepressants (TCAs) whereas patients with "melancholia agitata" tend to deteriorate with the use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), but would better respond to ECT, antipsychotics, and mood stabilizers. Antidepressants should be used only with profound consideration for bipolar spectrum patients (Ghaemi et al., 2003).

Angst (2007) has introduced a two-dimensional bipolar spectrum model comprising 1) a continuum of severity from normal to psychotic and 2) a continuum of proportionality of mood symptoms. The latter forms a model where (recurrent) major depression and pure mania are at the ends of the spectrum, and BD II, BD I and mania with mild depression in between them. On Angst's severity spectrum mood disorders can manifest from minor symptoms to psychotic major mood disorders, whereas temperament characters and personality disorders, representing also potential endophenotypes affecting the illness course, are placed between them (Angst, 2007, Qiu et al., 2017). However, Angst points out that the precise relationship of personality disorders to the bipolar spectrum is uncertain and "an unsolved general problem of psychiatric classification" (Figure 2).

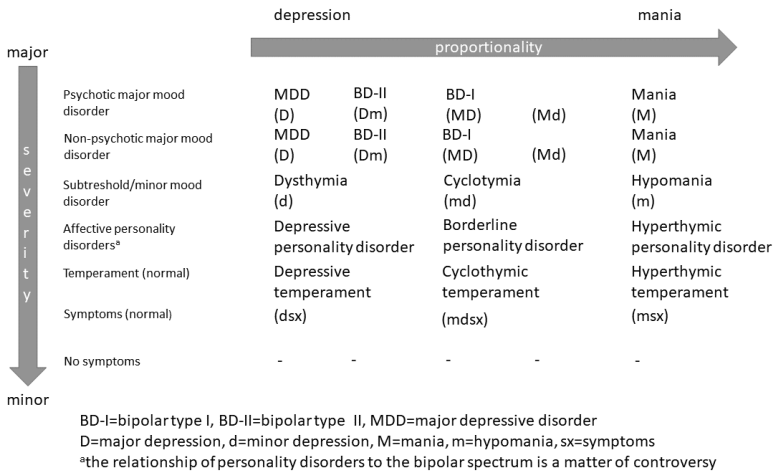


Figure 2. Two-dimensional mood/affective spectrum according to Angst (Angst 2007).

Ghaemi et al. (2002) have proposed an approach to the spectrum concept, focusing on how to distinguish it from unipolar depression. Instead of subtyping further, they proposed a diagnostic definition of "bipolar spectrum disorder" to be used in between the classic unipolar and type I bipolar extremes. "Bipolar spectrum disorder" is proposed to represent recurrent severe depression with family history of BD or antidepressant(AD)-induced mania or other features of bipolarity such as mixed or melancholic features, early age of onset, many episodes, and poor AD response or tolerance. Also the presence of hyperthymic or cyclothymic mood temperaments was suggested to be included in this bipolar spectrum concept. The authors state that when defined this way about one-third of MDD could be seen as bipolar spectrum disorder (Smith et al., 2005, Rybakowski et al., 2007, Ghaemi, 2013).

The most original approach to the bipolar spectrum concept has been proposed by Koukopoulos and Ghaemi (Koukopoulos, Ghaemi, 2009). Their primacy of mania hypothesis states that depression cannot happen without mania ("mania is the fire, depression is the ash"). By defining mania broadly as a wide range of excitatory behaviors and correspondingly narrowing the definition of depression, they base their views on evidence from clinical psychopharmacology and psychopathology, notably on favorable effects of lithium treatment for both depressive and manic states (Baastrup et al, 1967) and frequent occurrence of mixed symptoms among BD episodes (Cassidy et al., 1998). The existence and validity of pure unipolar depression, perceived as the main objection to the primacy of mania hypothesis, are disputed by the authors with the existence of hyperthymic depression (Akiskal's Prototype IV) (Akiskal, Pinto, 1999) and introduction of concepts of hypomanic equivalents (hypomanic-like symptoms linked with stressful life-events preceding depression) and anxiety-associated depression (intense anxiety preceding

depression). Continuous treatment with mood stabilizers and reducing lifestyle-related stressors are proposed clinical implications of the primacy of mania hypothesis. However, the authors acknowledge many limitations of their approach and underline their intention to raise research questions rather than to provide certified answers (Koukopoulos, Ghaemi, 2009).

2.1.5 PREVALENCE OF BIPOLAR DISORDER

The lifetime prevalence of BD I is commonly assumed to be about 1% (Merikangas et al., 2007), but epidemiological studies report varying figures (Moreira et al., 2017). BD, being relatively rare from the perspective of population studies, is difficult to detect and the prevalence rates are dependent on the diagnostic instrument used (Perälä et al., 2007). The estimations of the lifetime prevalences of BD II have been similar to BD I, but the reliability of the findings regarding BD II must be interpreted bearing in mind that the potency of epidemiological studies to detect BD II is probably even weaker than for BD I due to challenges in diagnosing hypomania.

The National Epidemiological Survey on Alcohol and Related Conditions (NESARC) in the United States reported lifetime and 12-month prevalence of BD I to be 3.3% and 2.0% respectively (Grant et al., 2005). The US National Comorbidity Study Replication (NCS-R) reported the corresponding figures to be 1.0% and 0.6% (Merikangas et al., 2007). The World Mental Health Survey (WMH), utilizing cross-sectional, face-to-face household surveys of 61392 community adults with the World Mental Health version of the World Health Organization Composite International Diagnostic Interview in 11 countries in South and North America, Europe and Asia, estimated the lifetime prevalence of BD I to be 1.0%, whereas the 12-month prevalence was reported to be 0.6% (Merikangas et al., 2011). The lifetime prevalences of BD II were 1.1% in NCS-R and 0.4% in WMH, and the 12-month prevalences 0.8% and 0.3% respectively (Merikangas et al., 2007, Merikangas et al., 2011). A recent meta-analysis of epidemiological studies of adult BD reported the following lifetime prevalences: all BD spectrum 1.02%, BD I 0.62%, BD II 0.36%, combined BD I and II 0.87 and BD NOS 0.96% (Moreira et al., 2017). The 12-month prevalences were: BD I 0.48%, BD II 0.14%, combined BD I and II 0.58% and BD NOS 0.34%.

Estimates of prevalence of BD in Finnish studies have been lower than prevalences reported internationally (Suvisaari et al., 2009). The Psychoses in Finland (PIF) study (N=8028), which used several screening methods and structural interviews to confirm the diagnosis of patients screening positive for psychotic symptoms, found lifetime prevalence of BD I to be 0.24% (Perälä et al., 2007). When register diagnoses of BD were included, the prevalence increased up to 0.42%. As part of the Mental Health in Early Adulthood in Finland (MEAF) Study, Suvisaari et al. (2009) reported lifetime prevelences of 1.87% in all BDs, 0.53% in BD I, 0.72% in BD II and 0.61% in BD NOS.

2.1.6 ETIOLOGY AND PATHOGENESIS OF BIPOLAR DISORDER

Although knowledge of the pathophysiology and pathogenesis of BD has expanded rapidly over the past few decades, the etiology of BD remains largely unknown. Historically, mood disorders were thought to result from an imbalance in the monoaminergic neurotransmitter system including the serotonergic, noradrenergic and, particularly in BD, the dopaminergic neurotransmitter system. As these systems very likely play some role, no singular dysfunction in them has been identified in the pathophysiology of BD. Instead, the etiology of BD is seen as a multifactorial longitudinal process including complex patterns of genetic, molecular, neural and environmental factors (Grande et al., 2016, Aldinger, Schulze, 2017).

2.1.6.1 *Genetics*

BD is highly heritable. This notion, familiar to all clinicians is supported by overwhelming evidence from family, twin, and to some extent, adoption studies, showing that genes strongly affect the predisposition to BD. The lifetime risk ofBD in relatives of a bipolar proband is as follows: monozygotic co-twin 40-70%, first-degree relative 5-10 %, and unrelated member of thegeneral population 0.5-1 % (Craddock, Sklar, 2013). Heritability estimates from twin studies have produced figures as high as 89 % in a British hospital register study of 67 twin pairs (McGuffin et al., 2003) and 93% in a Finnish population register study of 19 124 twin pairs (Kieseppä et al., 2004). The high monozygotic concordance and the high heritability estimates indicate that genetic factors strongly affect predisposition to BD. However, monozygotic concordance not being a full 100 % means that there are also risk factors other than genes in the etiology of BD (Craddock, Sklar, 2013). Most genetic studies have investigated the inheritance of BD as one entity, but there is some evidence for separate inheritance of mania and depression (Merikangas et al., 2014). Furthermore, there may be overlapping genetic risk across different psychiatric disorders. In a large Swedish family study partial overlap was found in familial genetic susceptibility for bipolar disorder and schizophrenia (Lichtenstein et al., 2009), and similar methodology has shown the same kind of link between BD and autism (Sullivan et al., 2012). In a recent large study of 265 218 patients using data from genome-wide association studies, common variant risk for psychiatric disorders was shown to correlate significantly, especially among BD, MDD, schizophrenia and ADHD (Brainstorm Consortium 2018). Amidst growing evidence of the genetic background of BD, a key point is that most cases of BD likely involve an interplay of several genes with a variety of environmental and stochastic factors (Craddock, Sklar, 2013).

Genetic linkage and association studies have been conducted on the heritability of BD since the 1980's. In recent years, a revolutionary new method, the genome-wide association study (GWAS) has been used to assess associations among genetic variants and BD, i.e. single-nucleotide polymorphisms in BD subjects. By using several tens of thousands of subjects,

over 40 genes with mostly small effect sizes in different studies have been identified (Ikeda et al., 2018). Single-nucleotide polymorphism (SNPs) of genes such as CAGNA1C, SYNE1, ODZ4 and TRANK1 have emerged as probable candidate genes for BD (Craddock, Sklar, 2013, Kerner, 2014, Ikeda et al., 2018). The small effect size of susceptibility SNPs, large numbers of SNPs, and their probable combination in development of BD indicate that current susceptibility of SNP is unfortunately still far from being a diagnostic tool in BD (Ikeda et al., 2018).

2.1.6.2 *Neurobiology of bipolar disorder*

The historical view of BD resulting from an imbalance in monoaminergic neurotransmitter systems (Goodwin & Jamison 2007) is supported by some later studies showing dysfunction of the dopaminergic system (Berk et al., 2007b, Cousins, Butts & Young, 2009) and imbalance of cathecolaminergic-cholinergic neurotransmitters (van Enkhuizen et al., 2015) in BD. They most probably play some role in pathophysiology of BD, but many other neurobiological factors in molecular, cellular, and neural circuitry levels operate as well (Grande et al., 2016, Phillips, Kupfer, 2013). Modulation of synaptic and neural plasticity seems substantive in regulating affective and cognitive functions (Grande et al., 2016). Neurotrophic molecules, the most known of which is the brain-derived neurotrophic factor (BDNF), mediate the differentiation and survival of neurons and neural plasticity (Grande et al., 2010). The decreased peripheral level of BDNF has been proposed as a potential biomarker of BD (Fernandes et al., 2011). Similarly, studies have shown abnormalities in peripheral inflammatory markers, including higher concentrations of soluble interleukin 2 receptor (sIL-2R), soluble interleukin 6 receptor (sIL-6R), tumor necrosis factor -alpha (TNF-α), soluble TNF receptor-1, and interleukin 4 (IL-4), among patients with BD (Munkholm et al., 2013). Immuno-inflammatory dysfunction and neuroinflammation have been suspected to represent a significant component of the underlying pathophysiology of BD (Leboyer et al., 2012) and possibly to explain the high comorbidity of cardiovascular disease and metabolic syndrome in BD subjects (Hamdani et al., 2013). A recent systematic review of biomarkers in cerebrospinal fluid of patients with BD versus healthy controls identified forty biomarkers with statistically significant differences between BD subjects and controls. Only findings of elevated homovanillic acid (HVA) and 5-hydroxy-indoleacetic acid (5-HIAA) were replicated across studies (Knorr et al., 2018). Pathophysiological pathways of BD under investigation are mitochondrial dysfunction and endoplasmic reticulum stress, oxidation, apoptosis, and epigenetic changes such as histone and DNA methylation (Grande et al., 2016).

Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in BD subjects has been well established (Taylor, MacQueen, 2006, Maletic, Raison, 2014, Muneer, 2016a). Patients with BD seem to have a hyperactive HPA axis, high levels of systemic cortisol, and nonsuppression of its circulating levels in

the dexamethasone suppression test or the dexamethasone/corticotrophin-releasing hormone (DEX/CRF) test (Watson et al., 2004). Furthermore, first-degree relatives of BD patients have been shown to have increased baseline cortisol levels and dysfunctional responses to the DEX/CRF test, indicating a possible genetic attribute of HPA axis irregularities predisposing to mood disorders (Ellenbogen et al., 2010). These disturbances are most likely attributable to deficits in cortico-limbic regulation in BD, with consequent compromised hippocampal regulatory role and an amygdala over-activity (Drevets, Price & Furey, 2008). Glucocorticoid receptors may also have diminished sensitivity in mood disorders, possibly due to an increase in inflammatory cytokines, resulting in disrupted physiological feedback regulation on the HPA axis and immune system (Pace, Hu & Miller, 2007). There is evidence that in patients with multiple mood episodes these abnormalities are more intensive, resulting in higher overall cortisol levels in addition to aberrant reactivity compared with patients who have experienced only a few episodes (Havermans et al., 2011). Elevated cortisol levels in bipolar individuals have also been associated with a history of suicidal behavior (Kamali et al., 2012).

2.1.6.3 *Brain imaging*

Neuroimaging studies of BD have generated somewhat equivocal findings and the impact of multiple confounding factors, such as age, pharmacotherapy, or mood state of the subjects at the time of scanning, is difficult to discern (Maletic, Raison, 2014, Sagar, Pattanayak, 2017). However, some consistent findings, such as the increased volume of lateral and third ventricles, have been made in several studies (Kempton et al., 2008, Hallahan et al., 2011, Frey et al., 2013). Strakowski et al. (2002) reported that lateral ventricles were significantly larger in patients with multiple episodes than in first-episode or healthy controls, this association particularly highlighted with the number of manic episodes. These findings support the putative progressive and deteriorating course of BD, indicating that recurrent illness episodes might contribute to brain tissue deterioration.

Another consistent finding is higher rates of white matter hyperintensities (WMHs), especially in the deep white matter and subcortical grey matter seen in T2-weighted magnetic resonance images of BD subjects. According to the meta-analysis of Beyer et al. (2009), individuals with BD were 2.5 times more likely to have WMHs than healthy controls, this finding being more prominent for children and adolescents with BD. However, WHMs are not specific to BD, but appear also in unipolar depression and schizophrenia, and their role in the pathophysiology of BD is unclear. A study by Kieseppä et al. (2014) showed an association with WMHs and deficits in cognitive performance in mood disorder patients.

A recent appraisal of neuroimagining studies of BD states that functional neuroimagining studies, although having several limitations, clearly show

abnormalities in neural circuitries supporting emotional processing, emotion regulation, and reward processing in BD (Phillips, Swartz, 2014). Based on their profound review of the literature, Phillips and Swartz adduced, that dysfunctions in bilateral prefrontal cortical-hippocampal-amygdala and left-sided ventral striatal-ventrolateral and orbitofrontal circuitries lead to these abnormalities, and that a potential structural basis for these functional abnormalities are gray matter decreases in prefrontal and temporal cortices, hippocampus, and amygdala and fractional anisotropy decreases in white matter tracts connecting prefrontal and subcortical regions.

2.1.6.4 *Psychosocial factors*

The rapid evolution of methods in genetic and neuroimaging fields in recent years has directed the etiological research of psychiatric disorders and BD more towards biological risk factors. However, many possible prenatal, early-life, and lifetime environmental risk factors exist (Aldinger, Schulze, 2017) and it is obvious that the biological and environmental risk factors are not distinct but interact in a complex manner (Etain et al., 2008).

Maltreatment-related childhood adversity has been proposed as one of the leading preventable risk factors for BD (Etain et al., 2008, Aas et al., 2016), not only predisposing to BD but also negatively affecting the illness course (Agnew-Blais, Danese, 2016). Similarly, negative life events in later life have been associated with the risk of developing BD as well as with manifestation and worsening of the illness episodes in those already having BD (Hosang et al., 2010, Hosang et al., 2012, Simhandl et al., 2015). The pathological pathways underlying these connections are mostly unknown, but emerging evidence suggests that childhood maltreatment alters the trajectories of brain development, thus affecting neural circuits and sensory systems involved in emotional regulation, threat detection, and reward anticipation (Teicher et al., 2016). Also inflammation, circadian system, and endocrine effects transmitted through the HPA axis have been proposed to mediate the impact of childhood trauma on risk of developing BD (Lai, Huang, 2011, Aas et al., 2016).

In their umbrella review of systematic reviews and meta-analyses on environmental risk factors of BD, Bortolato et al. (2017) evaluated 51 individual environmental risk factors for BD. They concluded that only irritable bowel syndrome emerged with convincing evidence as a risk factor for BD. In addition, childhood adversity was supported by highly suggestive evidence, asthma and obesity were by suggestive evidence, and seropositivity to toxoplasma gondii and history of head injury by weak evidence. Well-designed and statistically powerful studies are necessary to further investigate the environmental risk factors for BD.

2.1.6.5 *Kindling in bipolar disorder*

According to the kindling model proposed by Post (1992), major life stress is required to trigger initial onset and early recurrences of affective episodes in mood disorders, but successive episodes may be less tied to stressors, and episodes may eventually occur spontaneously. Kindling is regarded as the result of a process of sensitization in the central nervous system (CNS) caused by biochemical and anatomical substrates evolving over time in genetically predisposed persons (Kessing, Mortensen & Bolwig, 1998). Episode-related decreases in neuroprotective factors and increases in neurotoxic influences may cause additional cellular damage with each successive episode in such individuals (Post, 2007). While there is evidence that the risk of recurrences in BD increases with the number of previous episodes, the findings supporting the kindling model thus far have been inconsistent (Bender, Alloy, 2011), and studies have focused on BD I patients, reducing the generalizability of the findings. Stronger evidence for the kindling hypothesis is needed before incorporation of the model into treatment approaches is feasible, but nevertheless it is premature to conclude that the model is not applicable (Bender, Alloy, 2011).

2.1.6.6 *Staging in bipolar disorder*

Staging models are largely used in medicine, particularly in cardiology and oncology, to determine the prognosis and treatment of the disease by using specific biomarkers. Based on the assumptions that early-stage disease is more treatment-responsive, that treatments needed for late-stage disorder are more hazardous than earlier treatments, and that treatment could prevent progression to late stages, clinical staging is useful for any disease likely to evolve over time (Kapczinski et al., 2014). Whether BD evolves in stages is still under debate, but there is evidence that 40-50% of BD patients may present a progressive illness course (Kessing, Mortensen & Bolwig, 1998).

In psychiatry the lack of objective biomarkers has set limits on developing this concept, but interest in staging models in BD and other mental illnesses has steadily increased in recent years (Cosci, Fava, 2013, Grande et al., 2016). Since the first introduction of staging models in psychiatry (Fava, Kellner, 1993), staging models for BD with different emphasis have been presented. McGorry et al. (2006) developed a transdiagnostic model and justified the "lumping" of diseases by stating that the early-stage clinical phenotypes of many severe mental disorders overlap substantially from late childhood and early adolescence to early adulthood. Similarly, Duffy (2014) emphasized the family history, early childhood precursors and adolescent psychopathology in their model, but included only BD and divided it into classical and bipolar spectrum types of illness presenting different symptomatology and progression in adolescence.

Allostatic load and neuroprogression are phenomena described in connection to staging. The term "allostatic load" was first introduced by McEwen and Stellar (1993) to refer to the cumulative physiological wearing that is required for adaptation to stress. The adaptive mechanisms of allostasis are protective for the individual, but the cost for this is the "wear and tear" on the body and CNS resulting from over-activity or inactivity of physiological systems involved in adaptation to environmental stress (McEwen, Stellar, 1993, Vieta et al., 2013). In turn, the term "neuroprogression" is used to define the pathological reorganization of the CNS arising from multiple sources such as oxidative stress, inflammation, and mitochondrial dysfunction leading to a decrease in neurotrophins, deficient neurogenesis, and increased apoptosis, which finally endanger the normal neuronal function and structure (Muneer, 2016b, Berk et al., 2017). Recurrent affective episodes may generate the allostatic load and be connected to the pathological process of neuroprogression potentially manifesting in serum biomarkers and changes in neuroimaging (Muneer, 2016b). The most known staging models are the ones of Berk (Berk et al., 2017), Kapczinski (Kapczinski et al., 2009), Post (Post, 2010), and Cosci (Cosci, Fava, 2013).

In research of staging models, there are caveats and limitations such as large between- and within-individual variation in illness trajectories, lack of longitudinal studies and ignorance of physical and psychiatric comorbidities in the models. In spite of these limitations, the International Society for Bipolar Disorders Task Force Report (Kapczinski et al., 2014) concluded that in light of the current research knowledge, it is already proper to speak of "early" (the first or the first few episodes associated with better functioning after recovery) and "late" stages (associated with multiple episodes and impairment in many areas of functioning), but the details and optimal number of intermediary stages in the model require further consideration. The final goal is linking staging models with optimally tailored stage-specific treatments of BD. Early interventions should focus on neuroprotective strategies (Berk et al., 2010) whereas therapy during more advanced stages should be rehabilitative to control the consequences of disease progression (Muneer, 2016b). However, there is still a long way to proceed for a new era of preventive medicine in psychiatry and BD (Vieta, Salagre et al., 2018). Furthermore, also critical views have been presented on neuroprogression and staging models. Illness progression is not a rule in BD and further longitudinal prospective studies are needed to clarify the relation of neuroprogression to the findings from the fields of neuroimaging, neurocognition, and biomarkers (Passos et al., 2016).

2.1.6.7 *Sleep and circadian rhythms*

Sleep disturbances are core symptoms in mood disorders, to the extent that diagnostic criteria for both depression and mania include hypersomnia and/or insomnia (American Psychiatric Association, 2013). Disruption of biological

rhythms may lead to deterioration of clinical symptoms and negatively impact the course of illness in BD patients. It has been stated that disturbances of the circadian timing system play a central role in the etiology of BD. However, there is no consensus on whether the rhythm disturbances are a primary pathophysiologic process or secondary to other pathophysiologic mechanisms of the illness. Altered neurotransmitter and endocrine diurnal rhythms in BD have been proposed as probably pathophysiological mechanisms behind rhythm disturbances. Better understanding of the rhythm disturbances in BD could potentially enable new chronobiologically based interventions (Gonzalez, 2014).

2.1.7 COMORBIDITY IN BIPOLAR DISORDER

2.1.7.1 *Psychiatric comorbidity*

Psychiatric comorbidities are highly prevalent in BD, with anxiety disorders, substance abuse disorders, and personality disorders being the most prevalent comorbid disorders. Two recent meta-analyses of lifetime prevalence of anxiety disorders reported figures as high as 45% (Pavlova et al., 2015) and 43 % (Nabavi, Mitchell & Nutt, 2015). Lifetime prevalences for specific anxiety disorders in the study of Pavlova et al. (2015) were as follows: generalized anxiety disorder 20.4%, social phobia 19.9%, panic disorder 19.3%, post-traumatic stress disorder 17.3%, agoraphobia 11.7%, specific phobia 10.8%, and obsessive compulsive disorder 10.6%. The corresponding figures in the study of Nabavi et al. (2015) were concordant: panic disorder 16.8%, generalized anxiety disorder 14.4%, social anxiety disorder 13.3%, post-traumatic stress disorder 10.8%, specific phobia 10.8%, obsessive compulsive disorder 10.7%, and agoraphobia 7.8%.

In the JoBS 18-month follow-up, Mantere et al. (2010) found that depression and anxiety covaried strongly cross-sectionally and longitudinally depending on the type of the on-going mood episode, also finding that substance use disorders were associated with manic symptoms and eating disorders with depressive mood. Therefore, cross-sectional evaluation of comorbid disorders in BD patients is potentially influenced by the type the on-going mood episode. However, Pavlova et al. (2017) noted a high (34.7%) prevalence of anxiety disorders in BD during the euthymic period as well, indicating that also euthymic patients with BD should be routinely assessed for anxiety disorders to offer optimal treatment for both conditions.

DiFlorio et al. (2014) conducted a meta-analysis of lifetime prevalence of alcohol use disorders (AUDs) in BD. They found that AUDs affected more than one in three subjects with BD. Significant heterogeneity was found across studies, mostly explained by the geographical location of study populations and the gender ratio of participants. AUDs affected more than one in five women and two in five men with BD.

Discriminating between BD and borderline personality disorder (BPD) is difficult and the odds of confusing the two disorders are particularly high for severe bipolar cases (Ghaemi, Barroilhet, 2015). Fornaro et al. (2016) studied the prevalence and predictors of BD and BPD in their meta-analysis of 42 studies and found that up to 21.6% of BD patients have comorbid BDP. The rates were higher among BD II participants (37.7%) and in samples recruited in North America (26.2%). Higher percentage of males and higher mean age predicted a lower prevalence of comorbid BDP. The prevalence of BD among patients with BDP was 18.5%. The researchers concluded that future longitudinal prospective studies, and assessment of the overlapping and differential clinical moderators is needed to understand the actual boundaries of BPD and BD (Fornaro et al., 2016).

Friborg et al. (2014) reported in their meta-analysis of 122 studies that cluster B and C personality disorders (PDs) were the most prevalent personality disorders in BD, whereas cluster C dominated in MDD and dysthymic disorders (DYS). The mean proportion of personality disorders (any PD) was high in all three mood disorders (BD 0.42, MDD 0.45), but highest in DYS (0.60). The paranoid (0.11), borderline (0.16), histrionic (0.10) and obsessive-compulsive (0.18) PDs occurred more frequently in BD than MDD/DYS. Higher comorbidity rates were observed when diagnoses were based on questionnaires versus clinical interviews, DSM-III-R versus DSM-IV, when more women were included, or the duration of the disorder was longer (Friborg et al., 2014).

Post et al. (2018) studied the prevalence of axis II disorders in BD patients by using a self-rated questionnaire, the Personality Disorder Questionnaire (PDQ-4), and found the prevalence rate to be highly dependent on the state of illness (euthymia vs. depression). However, how this finding relates to having a personality disorder assessed using a structured clinical interview remains to be examined.

2.1.7.2 *Medical comorbidity*

Along with prevalent psychiatric comorbidity, the presence of a general medical comorbidity is more the rule than the exception in patients with BD. In the study of Sylvia et al. (2015), an astonishing proportion of 96.3% of BD patients were found to have at least one medical condition (including substance abuse and smoking), encompassing cardiovascular, metabolic, respiratory, and musculoskeletal systems. They also found that older age predicted the likelihood of having a cardiometabolic condition, but early age of onset of bipolar symptoms was associated with a greater chance of having other types of medical comorbidity but not with a cardiometabolic condition. Additional predictors of medical comorbidities in BD were more time spent depressed, less time spent manic/hypomanic, and longer duration of illness (Sylvia et al., 2015). Forty et al. (2014) reported the most prevalent lifetime medical conditions in the bipolar sample of 1720 patients (as well as in the

unipolar sample of 1737 patients) to be migraine headache (23.7%), asthma (19.2%), elevated lipids (19.2%), hypertension (15%), thyroid disease (12.9%), and osteoarthritis (10.8%). A high medical illness burden was associated with features of BD such as a history of comorbid anxiety disorder, rapid cycling mood, occurrence of suicide attempts, and mood episodes with typically acute onset (Forty et al., 2014).

Three patterns of associations between BD and medical conditions have been detected: (i) a reciprocal increase in the rate of comorbid conditions (such as an increase in the rate of BD in asthma or migraine and likewise an increase in asthma or migraine in BD patients), (ii) a predominantly unidirectional increase in the rate of BD in patients with certain medical disorders (such as multiple sclerosis and cerebellar diseases), and (iii) a predominantly unidirectional increased rate of medical disorders in patients with BD (cardiovascular diseases and metabolic disorders) (Sinha et al., 2018). Based on a nationwide register study, a genetic link between migraine and BD has been suggested by the finding that parental migraine predicted the development of BD in offspring regardless of parental BD (Sucksdorff et al., 2016). However, etiopathological mechanisms underlying the connection of BD with medical comorbidities are mostly unknown. While earlier studies have emphasized the adverse effects of psychopharmacological agents and unhealthy lifestyles as predisposing factors to medical comorbidities in BD, recent studies have focused also on potential pathological pathways that may underline this link (Sinha et al., 2018). The interest is in factors such as oxidative stress and immune system dysfunction that appear to be involved in multiple organ -system comorbidities with BD (Leboyer et al., 2012, Sinha et al., 2018). Given that medical comorbidity in BD increases early mortality, integrated models of care are needed to ensure proper recognition and treatment of medical comorbidities among BD patients (Crump et al., 2013).

Table 2. Long-term (>4 years) prospective clinical cohorts of BD patients.

Study cohort	**Location/sampling time**	**Bipolar type**	**Inpatient vs outpatient status**	**Size of the cohort (N)**
NIMH/CDS	Five academic centers in US, 1978-1981	Bipolar I and II	both	86-223
Chicago Follow-up Study	Michael Reese Hospital and Illinois State Psychiatric Unit, Chicago, US	Bipolar I	impatients	34 bipolar I, 89 unipolar
Naples, Italy	Center for Affective Disorders, Naples University, Italy 1978-1990	Bipolar I and II	both	194
Mc Lean Hospital Study	Mailman Research Center at McLean Hospital, Belmont, US 1983-1984	Bipolar I	inpatient	75
UCLA	Affective Disorders Clinic, University of California, Los Angeles, US 1984-1990	Bipolar I	outpatient	82
McLean-Harvard First-Episode Mania Study	Inpatients units at McLean Hospital, Belmont, US 1989-1996	Bipolar I	inpatient	166
Zurich Follow-up Study	Zurich University Psychiatric Hospital, Zurich, Switzerland 1959-1963	Bipolar I and II	inpatient	220 bipolar, 186 unipolar
Vitoria Prospective Naturalistic Study	Health catchment area of Vitoria, Spain 1994	Bipolar I	outpatient	120
Barcelona Bipolar Program	Hospital Clinic of Barcelona, Barcelona, Spain	Bipolar I and II	outpatient	120
Naturalistic Follow-up in Neuenkirchen, Austria	County Hospital, Neunkirchen, Austria 2000-2008	Bipolar I and II	inpatient	300

Table 2. Long-term (>4 years) prospective clinical cohorts of BD patients (continued).

Study cohort	Follow-up time	Diagnostic method	Key references
NIMH/CDS	up to 20 years	RDC, SADS	Judd, Akiskal 2003, Judd et al. 2003, Judd et al. 2005, Coryell et al. 2009, Winokur et al. 1994, Solomon et al. 2013, Turvey et al. 1999
Chicago Follow-up Study	10 years	RDC, SADS	Goldberg, Harrow 2004, Goldberg, Harrow & Grossman 1995
Naples, Italy	10 years	RDC, SADS	Maj et al. 1998, Maj et al. 2002
Mc Lean Hospital Study	4 years	DSM-III, DIS	Tohen, Waternaux & Tsuang 1990
UCLA	mean 4.3 years, min 2 years	DSM-III	Gitlin et al. 1995
McLean-Harvard First-Episode Mania Study	2-4 years	DSM-III-R, SCID-P diagnosis updated to DSM-IV criteria after 1994	Tohen et al. 2003, Salvatore et al. 2007
Zurich Follow-up Study	median 27 years	DSM-III (the distinction between BD I and II was based on need for hospitalization)	Angst, Preisig 1995, Angst et al. 2003, Kessing et al. 2004b
Vitoria Prospective Naturalistic Study	10 years	DSM-III-R,SCID-P diagnosis later updated to DSM-IV criteria	Gonzalez-Pinto et al. 2011
Barcelona Bipolar Program	5-10 years	DSM-IV	Colom et al. 2009, Bonnin et al. 2010
Naturalistic Follow-up in Neuenkirchen, Austria	4 years	ICD-10, Mini-International Neuropsychiatric Interview	Simhandl, Konig & Amann 2014, Simhandl et al. 2015, Amann et al. 2017

2.2 LONG-TERM COURSE AND OUTCOME OF BIPOLAR DISORDER

The long-term prospective naturalistic clinical studies (Table 2) have provided knowledge on the illness course, supporting the recurrent and often chronic nature of BD. The long-term prognosis of BD is relevant as well from the public health perspective and for individual patients and their care givers. Determining whether the duration of a follow-up is long-term is a relative matter when evaluating the outcome of BD, but five years seems to be long enough e.g. to eliminate the effect of index episode on important outcomes such as time spent ill (Mantere et al., 2010). Many studies investigating the outcome of BD do not extend the follow-up of to 5 years. The largest prospective study, the US Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), provided a 2-year follow-up (Parikh, LeBlanc & Ovanessian, 2010). It should be also noted that many long-term studies include only hospitalized patients (Tohen, Waternaux & Tsuang, 1990, Goldberg, Harrow & Grossman, 1995, Angst et al., 2003, Tohen et al., 2003, Goldberg, Harrow, 2004, Kessing et al., 2004a), exclusively patients suffering from BD I (Tohen, Waternaux & Tsuang, 1990, Winokur et al., 1994, Goldberg, Harrow & Grossman, 1995, Coryell et al., 1998, Maj et al., 1998, Solomon et al., 2003, Tohen et al., 2003, Goldberg, Harrow, 2004, Gonzalez-Pinto et al., 2011), or are drawn from tertiary-level treatment centers (Judd et al., 2002). These limitations may indicate that the milder end of the illness spectrum is underrepresented in studies. The generalization of the findings to the modern era is questioned also because many of the cohorts were sampled long before the current range of acute and maintenance psychopharmacological treatments became available. To what degree these findings are biased towards hospitalized, mania-prone type I patients or can be generalized to the current era and outpatient-focused psychiatric care is not known. This study focuses on long-term outcome (> 4 years of follow-up), but introduces some major findings from medium-term studies as well.

2.2.1 DEFINITIONS AND COURSE-SPECIFIERS OF OUTCOME

Commonly used and understood terminology is essential to making meaningful comparisons across studies (Tohen et al., 2009). Although operational definitions have been proposed to describe clinical outcomes in BD (Hirschfeld et al., 2007), the criteria used to define such terms as remission, recovery, relapse, response and recurrence have varied both in clinical trials and in observational studies (Tohen et al., 2009).

In relation to the concept of remission, it is important to note the difference between *symptomatic* and *syndromal remission*. The International Society for Bipolar Disorders (ISBD) Task Force proposes that *symptomatic remission* be evaluated with rating scales of depression and mania. The proposed threshold for symptomatic remission in depression is Hamilton

Rating Scale for Depression (HAM-D) score ≤ 5 or 7, Montgomery-Åsberg Rating Scale (MADRS) score ≤ 5 or 7, or Bipolar Depression Rating Scale (BDRS) score ≤8. Young Mania Rating Scale (YMRS) score < 8 or 5 is proposed as a threshold for symptomatic remission in mania. By contrast, *syndromal remission* is recommended to be evaluated based on DSM -criteria of MDE and (hypo)mania (Tohen et al., 2009, American Psychiatric Association, 2013). The Task Force recommendation for the definition of *recovery* is that for 8 consecutive weeks virtually no depressive or (hypomanic) symptoms occur. *Relapse* is defined as a new episode occurring *within 8 weeks* of having achieved remission from the index episode. *Recurrence* is defined as a new episode emerging *after 8 week*s of remission from the index episode. The Task Force recommends defining *subsyndromal depression* by HAM-D or MADRS scores 8-14 or BDRS scores 9-16, and *subsyndromal mania* by YMRS scores 8-14 (Tohen et al., 2009).

The most commonly used course specifier (also included in DSM-5; applicable to both BD I and BD II) is *rapid cycling*, which is defined as presence of at least four mood episodes in the previous 12 months meeting the criteria for manic, hypomanic, or major depressive episode. These episode must be demarcated by either partial or full remission or a switch to an episode of the opposite polarity (American Psychiatric Association, 2013).

A polyphasic episode, defined as a sequence of changing mood episodes without remission in between, is not included in the DSM-5 (nor was it in the DSM-IV), but might be a predictor of outcome in BD (Maj et al., 2002).

In DSM-IV (American Psychiatric Association, 1994) *chronicity* is defined as a patient being in mood episode(s) without an intervening period of eythymia for at least two years.

2.2.2 TIME SPENT ILL

Considering the chronic and often life-long symptomatic nature of BD, the proportion of time spent ill (vs. time spent symptomless) is a feasible way to evaluate the morbidity of BD in the long-term. Long-term studies have shown that patients with BD are symptomatic for about half of the time (Forte et al., 2015) and that depressive states predominate over manic states, and subsyndromal states over major syndromal episodes (Judd et al., 2002, Judd, et al., 2003b).

However, few prospective long-term studies exist on the proportions of time spent ill. Judd et al. (2002) have reported the findings of the National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS). In their seminal studies investigating the weekly symptomatic status of BD patients they found that in a prospective follow-up of 146 BD I patients, the subjects were symptomatically ill 47.3 % of weeks throughout a mean of 12.8 years of follow-up. Depressive symptoms predominated over manic/hypomanic or cycling/mixed symptoms (31.9%, 8.9% and 5.9% of weeks, respectively). Subsyndromal states (minor depressive and hypomanic

symptoms) were nearly three times more frequent than syndromal level major depressive and manic symptoms (29.9% and 11.2% of weeks, respectively). In the same study cohort, a prospective follow-up of 86 BD II patients during a mean of 13.4 years of follow-up revealed that BD II patients were symptomatic 53.9% of follow-up weeks. Depressive symptoms (50.3% of weeks) dominated over hypomanic (1.3% of weeks) and cycling/mixed (2.3% of weeks) symptoms. Subsyndromal, minor depressive, and hypomanic symptoms combined were three times more common than major depressive symptoms (41% vs. 13 % of all follow-up weeks) (Judd et al., 2003b).

Tondo et al. (2017) reported the findings of 1130 BD patients during a mean of 12 years of partly prospective follow-up. They found lower percentages of total time ill than did Judd et al. in NIMH CDS studies (Judd et al., 2002, Judd et al., 2003b), reporting that patients spent 37.2% of follow-up time in illness episodes. Different diagnostic subgroups (BD I, BD II, BD with mixed features and BD with psychotic features) differed only little, although significantly, in total proportion of time spent ill, but there were significant differences in time spent in depression versus mania among the subgroups. The proportions of time spent in depression versus mania were 17.9% vs 15.9% for BD I patients, 26.7% vs. 9.55% for BD II patients, 24.5% vs. 12.6% for BD patients with repeated mixed episodes, and 20.8% vs. 21.6% for BD patients with prominent psychotic features. The latter group had the highest proportion of total time spent ill in follow-up.

Serra et al. (2017) examined, mostly retrospectively, the early clinical predictors and correlates of long-term morbidity in a cohort of 111 BD I and 96 BD II patients for a time period of an average of 18.9 years. Total time spent ill was 33.9% for the whole cohort and greater in the BD II group (40.2%) than in the BD I group (28.4%). Time spent in depression averaged 14.3% in BD I and 26.1% in BD II, whereas time in (hypo)mania was almost the same for both bipolar subtypes (13.9% vs. 14.2%). The ratio of depressive versus manic time was 3.7-fold greater in BD II than BD I (5.74 vs. 1.96). More time spent depressed was associated with psychiatric comorbidity, agitated or psychotic first affective episode, any antecedent symptoms before first affective episode and BD II subtype. More time spent manic was predicted by fewer years of illness history and first lifetime hypomanic episode.

The main medium-term studies have given parallel results. According to the Stanley Foundation Bipolar Treatment Outcome Network Study (SFBN) of Kupka et al. (2007), daily ratings of 405 BD I and 102 BD II patients for one year revealed proportions of euthymia of 48% vs. 50%, depression 36% vs. 37 %, hypomania 12% vs. 10 %, mania 1% vs. 0 % and rapid cycling 4 % vs. 3 % for BD I and BD II respectively. Another SFBN study of Post et al. (2003) reported that in spite of comprehensive pharmacological treatment, patients were symptomatic almost half of the year (47%). Mean time spent depressed (33.2% of the year) was 3-fold higher than mean time spent manic (10.8%). Of the 258 bipolar outpatients followed, 26.4% were ill for more than three-fourths of the year, and 40.7% were intermittently ill with major affective

episodes. In the 18-month follow-up of the JoBS cohort, patients were symptomatic 42.9% of the follow-up time, and BD II patients spent a higher proportion of time ill (47.5% vs. 37.7%) and in depressive symptom states (58.0% vs. 41.7%) than BD I patients (Mantere et al., 2008).

Forte et al. (2015) analyzed data from 15 short- and long-term cohorts including 3936 BD I and/or BD II patients for a mean follow-up time of 7 years. They found the total mean time spent ill to be 44.9% for the whole sample, 43.7% for BD I patients and 43.2 % for BD II patients. Time spent depressed was over four-fold (35.4%) higher than time spent manic (8.5%) in the whole sample. Depressive morbidity accounted for more of total time ill (82.4%) in BD II patients than in BD I patients (69.6%).

2.2.3 REMISSION, RECURRENCE, CYCLE LENGTH, AND OTHER FACTORS RELATED TO LONG-TERM OUTCOME

BD is highly recurrent, and it has been stated, that the findings from modern studies are surprisingly compatible with those conducted before the introduction of modern psychopharmacological treatments (Angst et al., 2003). More than half of patients with BD have a recurrence within 2 years and over 90% experience at least one recurrence during their lifetime (Solomon et al., 1995). Findings on whether multiple past episodes are a risk factor for future episodes and predispose to shortening of the cycle length are controversial (Angst et al., 2003, Angst, Sellaro, 2000, Suppes, Dennehy & Gibbons, 2000, Simhandl, Konig & Amann, 2014).

2.2.3.1 *Findings of the National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS)*

The longest (up to 20 years) prospective follow-up study to date, the NIMH Collaborative Depression Study (CDS) has yielded exstensive research knowledge on BD during the last decades. Both types of BD have been found to be chronic in nature, and their course predominated by depressive rather than hypomanic, manic, or mixed episodes (Judd et al., 2002, Judd et al., 2003b). Nearly all (95%) patients experienced some type of affective episode during a 10-year follow-up (Judd et al., 2003c). Residual symptoms have been found to increase the risk of a relapse or recurrence in a cohort of both BD I and II patients; those recovering with residual symptoms experienced major affective episodes more than three times faster than those without residual symptoms (Judd et al., 2008). In the same study, also the number of episodes before intake predicted shorter time to recurrence. For BD I patients, polyphasic episodes predicted worse outcome (Turvey et al., 1999b). Among BD I patients, chronicity from the index episode to the end of the 10-year follow-up was rare (4%), and cycle lengths showed no decrease over the follow-up (Winokur et al., 1994). Over a 15-year follow-up, poor optimal functioning

during the 5 years preceding baseline assessment and persistence of depressive symptoms in the first 2 years of follow-up predicted poor outcome (presence of symptoms of MDE, mania or schizoaffective disorder) throughout the 15th year of follow-up. However, persistent manic symptoms during that time did not predict later manic symptoms (Coryell et al., 1998). Based on 20-year follow-up, the median duration of BD mood episodes was 13 weeks and more than 75% of the subjects recovered from their mood episode within one year of onset. Those with cycling episodes, greater cumulative morbidity, and episodes with severe onset, had a significantly decreased probability of recovery (Solomon et al., 2010), which was also found to decline with each successive episode of depression (Solomon et al., 2013). Of 345 BD I and II patients who were followed for a mean of 13.7 years, 25.8% met DSM-IV criteria for rapid cycling during at least one of the years of follow-up. The rapid cycling more often occurred early rather than late in the course of follow-up and rarely (2%) persisted for more than 3 years. Patients showing a rapid cycling pattern had an earlier onset of illness, higher risk of suicide attempts, and spent significantly more time depressed in follow-up (Coryell et al., 2003). When including both monophasic and polyphasic episodes, the ones beginning with major depression have been found to be longer than the ones beginning with mania. BD I patients with a depressive index episode had higher overall morbidity during 15 years of follow-up (Turvey et al., 1999a).

Although being seminal in the field of mood disorders, the NIMH/CDS studies have some limitations, most importantly, sampling from tertiary care treatment centers before the current era of modern treatment options.

2.2.3.2 *Other studies on recurrence, duration of episodes, cycle length and predictors of long-term outcome*

Angst et al. (2003) reported on recurrence rates of BD (and MDD) based on up to 40-years of prospective follow-up of a Swiss cohort (220 BD patients and 186 unipolar patients). They found that the cumulative risk of transition from remission to new episodes remained linear over 30-40 years after onset. The recurrence risk of BD (0.40 episodes per year) was about double that of unipolar depression (0.20 episodes per year). The risk of recurrence was slightly higher for BD II than BD I (Angst et al., 2003). Angst et al. found no association between gender and risk of recurrence, but a medium-term study of the JoBS cohort reported females to have a higher hazard of recurrence than males (Suominen et al., 2009). Kessing et al. (2004b) examined the effect of the number of episodes on the rate of recurrence in the same Swiss cohort using frailty models (taking into account the individual frailty towards recurrence). The individual rate of recurrence was found to increase with the number of episodes even when the effect was adjusted for the individual frailty toward recurrence.

In a mean of 16.7 years of retrospective and prospective follow-up of 1130 BD patients, Tondo et al. (2017) noted that the duration of depressive episodes

was significantly longer (mean 5.18 months) than the duration of manic episodes (mean 3.46 months). Furthermore, manic episodes were significantly longer in the group presenting a predominant course of mania-depression-euthymic interval pattern (MDI, 29% of the cohort) than in the group presenting a depression-mania-euthymic interval pattern (DMI, 28% of the cohort), mean durations being 3.33 months and 2.50 months respectively. The number of depressive (0.96) versus (hypo)manic episodes (0.94) per year did not differ in follow-up.

Vazquez et al. (2015) studied the recurrence rates of BD in a systematic comparison of prospective naturalistic (up to 2.5 years of follow-up) and randomized controlled trials (RCTs). They found that in naturalistic studies (3904 BD subjects, 85.8% BD I) the pooled recurrence rate was 55.2 % (26.3% per year) and in RCTs (4828 subjects, 96.0% BD I) 39.3% (21.9% per year) overall, 34.1% with mood-stabilizing treatment and 60.6% (31.3% per year) with placebo. The recurrence rate per year did not differ by study subtype, was higher among those with earlier age of onset and rapid cycling, and paradoxically declined with longer observation (Vazquez et al., 2015).

Tundo et al. (2018) reported a recurrence rate of 64.3% in a prospective 4-year follow-up of 266 BD I and II patients. This is in concordance with the long-term findings of Bromer et al. (2005) (recurrence rate of 61.2%), Fekadu et al. (2006) (recurrence rate of 65.9%), and Simhandl et al. (2014) (recurrence rate of 68%). Tundo et al. (2018) found a significant reduction when comparing the number of episodes per year before and after study entry. The length of follow-up and the number of previous (mainly depressive) episodes predicted the risk of recurrence. During the follow-up female gender, older age, and higher frequency of past mixed episodes were associated with a higher frequency of recurrences in follow-up, whereas comorbidity, bipolar type, and treatment with antidepressants were not related to the outcome (Tundo et al., 2018).

In a 10-year prospective follow-up of 97 BD I and II patients with at least one lifetime episode including mood switch and 97 BD controls with monophasic index episode, Maj et al. (2002) noted that an index episode including at least two polarity switches, especially if starting with depression, was associated with poor outcome. Switchers with more than one mood polarity switch during the index episode spent significantly more time ill in follow-up than the non-switchers or the switchers with only one polarity switch (55.8%, 20.4% and 25.8%, respectively). Among switchers, patients with BD I and BD II did not differ in time spent ill (Maj et al., 2002).

Many long-term studies have included only BD I and/or hospitalized patients (Table 2). In a 10-year prospective follow-up of hospitalized BD I and MDD patients, Goldberg et al. (2004) found poorer work and social functioning in BD than in MDD, and affective relapses to be more associated with poorer work functioning among BD than unipolar patients; less than half of BD patients had good work functioning in follow-up. Remission at the two first follow-up interviews (2 and 4.5 years) was associated with remission in

later follow-up visits (7.5 and 10 years), suggesting the importance of early sustenance of remission to prevent further episodes and the potential functional decline (Goldberg, Harrow, 2004, Goldberg, Garno & Harrow, 2005). An early study of Gitlin et al. (1995) including 82 BD I patients with a mean follow-up of 4.3 years, found 73% of patients to relapse in follow-up, and the number of previous episodes and poor job functioning to predict the risk of recurrence/relapse. A naturalistic study of 120 BD I patients (Gonzalez-Pinto et al., 2011) reported patients with mixed episodes (37% of the cohort) to have an increased risk of hospitalization in a 10-year follow-up. Mixed-episode patients with lifetime suicide attempts had a significantly shorter time to first suicide attempt in follow-up than those without (Gonzalez-Pinto et al., 2011).

Baldessarini et al. (2012a) reviewed 40 reports on cycle shortening ”in manic-depressive patients” (mainly BD I) from the beginning of the 20th century until 2011, and concluded that only one-third of the studies showed evidence of cycle -length shortening. They implemented a follow-up of 128 clinically treated DSM-IV BD I patients, originally hospitalized for their first affective or psychotic illness episode, for a mean of 5.7 years and with 6.5 episodes/person. Among this sample, the course of illness appeared mostly random or chaotic and only a minority of patients showed either cycle-acceleration or slowing (Baldessarini et al., 2012a).

The large register studies of Kessing et al. (1998b, 2004b) in Denmark have revealed a progressive course of BD showing that the rate of relapse leading to hospitalizations increases with the number of previous episodes (both in BD and MDD) (Kessing, Hansen & Andersen, 2004a) and the course of BD seems to be progressive in nature irrespective of treatment, gender, age, and type of BD (Kessing, 1998, Kessing et al., 1998b).

Colom et al. (2009) studied the efficacy of group psychoeducation in a five-year randomized clinical trial of 120 BD I and II patients, and found the psychoeducation group to have fewer recurrences, longer time to recurrence and shorter hospitalizations. The psychoeducation group also spent less time ill than the control group.

2.2.3.3 *First-episode mania studies*

Prospective studies starting near illness onset are valuable for being potentially less confounded by factors such as comorbidity and illness duration. The McLean-Harvard First-Episode Mania Study (Tohen et al., 2003) followed 166 BD I patient from their first hospitalization for a manic (75.3%) or mixed (24.7%) episode up to 48 months. Most patients (75%) were in their first lifetime affective episode, but 25% had experienced former MDEs that did not lead to hospitalization. In a 2-year follow-up, 98% of patients achieved syndromal recovery (50% achieving recovery in 5.4 weeks), 72% symptomatic recovery, and only 43% functional recovery. Factors associated with a shorter time to syndromal recovery were shorter index hospitalization,

female gender, and lower initial depression ratings. Shorter index hospitalization and older age predicted functional recovery. Within 2 years of syndromal recovery, 40% of patients experienced a new episode of mania, predicted by initial mood-congruent psychosis, lower premorbid occupational status and initial manic episode. Predictors of depressive episode, occurring in 20 % of the patients within 2 years of syndromal recovery, were higher occupational status, initial mixed episode, and any comorbid disorder. Nineteen percent of the patients switched phases without recovery.

Gignac et al. (2015a) reported 4-year prospective outcomes of Systematic Treatment Optimization Program for Early Mania (STOP-EM) for 81 BD patients with first manic or mixed episode. Within one year, all patients were remitted and 95% had recovered. The recurrence rates were high, 58% by one year and 74% by four years. Of recurrences, 60% were depressive, 28% manic and 12% hypomanic. Recurrence within the first year of follow-up was associated with a higher rate of recurrence during the whole follow-up. Older age predicted shorter time to remission, whereas substance misuse predicted delayed recovery and earlier recurrence.

In their systematic review and meta-analysis of ten prospective cohorts of first-episode mania studies (N=734), Gignac et al. (2015b) reported a syndromal recovery rate of 88% at one year, but a symptomatic recovery rate of only 62 %. The recurrence rates for 6 months, one year, and 4 years were 26%, 41% and 60%, respectively, indicating that the rate of recurrence plateaued after the first year.

2.2.4 INFLUENCE OF BIPOLAR TYPE ON OUTCOME

Albeit early studies have suggested that BD II may be less severe than BD I with regard to symptom intensity, but more severe regarding episode frequency (Vieta et al., 1997), the prospective long-term studies differentiating the outcome of BD I and II are sparse. The seminal NIMH/CDS studies have documented the more chronic course of BD II involving more minor and major depressive episodes, shorter inter-episode well intervals, and more comorbid anxiety disorders than BD I (Judd et al., 2003b, Judd et al., 2003d). In a 10-year follow-up (excluding the index episode), the total number of affective episodes did not differ between the BD types, but the mean number of major depressive episodes was over three times higher for BD II (2.5) than BD I (0.8) patients. The same pattern applied also for episodes of RDC minor/intermittent depression (mean for BD I 0.5 and for BD II 1.1). In turn, BD I patients had significantly more episodes of cycling/mixed polarity (mean 0.4) than BD II patients (mean 0.4). The mean duration of episodes during follow-up was not dependent on the type of BD, but the median duration of the intake episode after admission was twice as long for BD II (34 weeks) than for BD I (18 weeks) patients (Judd et al., 2003b). During a mean of 13 years of follow-up BD II patients spent significantly more time (mean 51.9 % of follow-up) in depressive (major, minor, and subsyndromal) states than BD I patients

(mean 30.6% of follow-up). BD I patients spent significantly more time in (hypo)manic states than BD II patients (9.8% vs. 1.4%). BD I patients spent also more time in cycling/mixed states than BD II patients (6.0% vs. 2.5%) (Judd et al., 2003d).

Serra et al. (2017) examined long-term morbidity of BD patients using retrospective and prospective information in a mean follow-up of 7.45 years, time at risk being on average 18.9 years. They found that during the time at ris, BD II subjects spent a significantly higher proportion of time in illness episodes overall (40.2%) and in depression specifically (26.1%) than BD I patients (time ill 28.4%, time in depression 14.3%). They found no difference in time spent in hypomania or mania between the subgroups of BD. The findings of Tondo et al. (2017) from a 16-year retrospective and prospective follow-up were concordant with more time spent in depressive than manic states in BD and also supportive of more depressive recurrences and more time spent in depressions among BD II than BD I patients. Those with BD I and psychotic features in at least one episode had higher manic recurrence rates and higher proportion of time spent in manic states in follow-up.

The above findings of more depressive long-term course in BD II were not confirmed in the medium-term studies of Joffe et al. (2004) and Post et al. (2003).

2.2.5 INFLUENCE OF COMORBIDITY ON LONG-TERM OUTCOME

The high rate of comorbidity in BD is well established (Grant et al., 2005, Post, Leverich et al., 2018), but has rarely been systematically investigated as a predictor for long-term outcome in prospective studies. In the long-term course of BD, comorbid disorders do not follow a course independent of mood episodes, but instead seem to covary with them (Mantere et al., 2010). Over 20 years of follow-up, in comparison with unipolar depression, BD II was found to be more often associated with the development of alcohol and benzodiazepine use/disorders, whereas manic symptoms predicted all levels of the substances investigated (alcohol abuse/dependence, benzodiazepine use, and cannabis use/abuse/dependence) (Merikangas et al., 2008). Little data exist on the effect of pre-existing comorbid substance use disorders on long-term outcome of BD. In the study of Gonzales-Pinto et al. (2010), no difference at baseline was observed in frequency of alcohol and other substance abuse between depressive and manic polarity groups, but during a 10-year follow-up the frequency of alcohol and other substance abuse decreased significantly in the manic polarity group. BD I patients with alcoholism preceding the first affective episode have been found to have fewer episodes of affective disorder in follow-up than those with secondary alcoholism (i.e. occurring after the onset of BD), indicating a less severe manifestation of BD and a possible role of substance use disorder in the emergence or course of BD in the first group (Winokur et al., 1995). In prospective follow-up of 12.8-13.4 years, Judd et al. (2002) found no

association between lifetime comorbid alcoholism or drug-use disorder and time ill for BD II, but the latter predicted more time ill in the subgroup of BD I. In the 4-year follow-up of a first episode mania study, comorbid substance misuse was found to be associated with delayed recovery and earlier recurrence (Gignac et al., 2015a). Tundo et al. (2018) found no association between recurrence and substance abuse or Axis I comorbity in prospective follow-up of 4 years.

The number and severity of concurrent anxiety symptoms during mood episodes have been found to correlate with the subsequent time spent in depressive episodes, whereas no correlation was found with pre-existing anxiety disorders (Coryell et al., 2009, Coryell et al., 2012). Serra et al. (2017) found any psychiatric comorbidity to predict more total time ill and more time depressed in long-term (prospective and retrospective) follow-up. They also found any antecedent psychiatric syndrome before first major affective episode to predict more time depressed in follow-up. In a prospective follow-up of 4 years, Amann et al. (2017) reported the presence of thyroid diseases, especially hypothyroidism, but not any psychiatric comorbidity, to be associated with an increased risk of manic relapse in BD I.

The research knowledge on prognostic value of comorbid personality disorders on long-term outcome of BD is sparse. In a medium-term study with a mean follow-up of 41 months (Bieling et al., 2003), patients with more personality disorder symptoms were less likely to reach or remain in euthymia, cluster A personality disorder being the strongest predictor of poor outcome. By using a self-rated questionnaire (Personality Disorder Questionnaire PDQ-4), Post et al. (2018) evaluated the association between personality disorder psychopathology and retrospective poor prognosis factors of BD. They found that in BD outpatients high scores on PDQ-4 were related to history of child abuse, early age of onset, anxiety disorder comorbidity, rapid cycling, and 20 or more previous episodes. However, it is not known whether the personality pathology causes the more severe course of illness, or conversely, whether the adverse illness characteristics contribute to the personality disorder burden. Altogether, the patterns of covariation between mood episodes and comorbid mental disorders are intricate, and their role in the long-term course of BD has only partly been elucidated.

2.2.6 THE INFLUENCE OF PSYCHOTIC SYMPTOMS ON LONG-TERM OUTCOME

More than half of BD patients experience psychotic mood episodes during their lifetime (Dunayevich, Keck, 2000). Furthermore, a retrospective study by Altamura et al. (Altamura et al., 2015) found that more than half of bipolar patients with psychotic symptoms are misdiagnosed at first contact with psychiatric services, and duration of untreated illness is a predictor of outcome in BD patients with psychotic symptoms. However, prospective studies on the effect of psychotic symptoms on long-term outcome are sparse. In CDS, Judd

et al. (2002, 2003b) found no association between psychotic features at intake and time ill in follow-up for either BD I or BD II patients. Serra et al. (2017) reported agitated or psychotic depressive first episode to predict more time depressed in retrospective and prospective follow-up of 18.9 years. The common clinical assumption that the presence of psychosis in BD represents a more severe type of illness has been supported by some (Bora, Yucel & Pantelis, 2010), but not all (Keck et al., 2003), cross-sectional studies. The largest largest single study to date (Burton et al., 2018) found no demographic or neuropsychological differences between BD patients with and without history of psychosis. Instead, the latter group experienced greater chronicity of affective symptoms and more often had a rapid cycling course of illness. Former studies comparing neuropsychological functioning between psychotic and affective-only BD have yielded conflicting results (Bora, Yucel & Pantelis, 2010, Demmo et al., 2016).

2.2.7 COGNITIVE AND FUNCTIONAL IMPAIRMENT AND DISABILITY WITH REGARD TO LONG-TERM OUTCOME

While syndromal and symptomatic remission is a self-evident target in treatment of BD, full functional recovery including work and social life is often not achieved even when patients are in symptomatic remission (Grande et al., 2013). Cognitive impairments in memory, processing speed, attention, and executive function during periods of remission are related to socio-occupational outcome and poor quality of life (Miskowiak et al., 2018). Meta-analytic evidence has suggested that memory and executive function are even more strongly related to occupational outcome than residual mood symptoms (Tse et al., 2014). Marked cognitive heterogeneity in remitted BD patients has been oberved: 12-40% of patients show global cognitive impairments across several domains, 29-40% present with selective deficits in attention and psychomotor speed, and 32-48% have relatively intact cognitive functions (Miskowiak et al., 2018). In clinical practice, identifying patients with persistent cognitive impairment to implement strategies for remediating these deficits is essential to improve the management of BD. The recent report of the International Society for Bipolar Disorders (ISBD) task force has made clinical recommendations on how to assess and address cognition in BD patients (Miskowiak et al., 2018).

The number of longitudinal studies on the course and outcome of cognitive dysfunctions in BD is limited as well. There is evidence that multiple episodes, and in particular manic episodes, carry more cognitive impairment and may be associated with brain tissue deterioration detectable in neuroimaging studies, but the evidence from prospective long-term studies is still mostly lacking (Vieta et al., 2013).

Despite the public health relevance, prospective long-term studies have rarely addressed proportions and predictors of functional recovery in

representative study samples. In the McLean-Harvard First-Episode Mania Study, only 43% of the patients achieved functional recovery despite the fact that almost all (98%) recovered at the syndromal level (Tohen et al., 2003). Subthreshold depressive symptoms and neurocognitive impairments in verbal memory and executive functions were found to predict poor long-term functional outcome in the 4-year follow-up study of Bonnin et al. (2010). In a cross-sectional study of Murru et al. (2017), modifiable factors associated with functional impairment were manic predominant polarity, residual depressive symptoms, and illness severity, while a non-modifiable factor was illness duration. Judd et al. (2005) found psychosocial disability to fluctuate during the illness course, to be strongly associated with depressive illness burden and subsyndromal hypomanic symptoms to enhance functioning in BD II.

The literature on long-term occupational disability and disability pension has mostly relied on cross-sectional studies while prospective studies have been sparse (Grande et al., 2013). As part of the JoBS study, Arvilommi et al. (2015) examined the predictors of work disability in a prospective 18-month follow-up of BD patients. The proportion of patients with disability pension increased from 21% at baseline to 41% at the end of the follow-up. Older age, male gender, depressive index episode, higher number of psychiatric hospitalizations, generalized anxiety disorder, avoidant personality disorder, and depressive burden predicted being granted a new disability pension during the follow-up.

2.3 SUICIDAL BEHAVIOR IN BIPOLAR DISORDER

Suicidal behavior ranges from suicidal ideation to suicide attempts to completed suicide. *Suicidal ideation* is defined as thoughts and wishes of suicide in individuals without actual suicide attempts (Beck, 1986) and may be predictive of suicide (Brown et al., 2005). *Suicide attempt* is defined as a self-injurious behavior with non-fatal outcome accompanied by evidence that the individual had an intent to die (Jacobs, Brewer, 2006). *Suicide* is defined as self-inflicted death with evidence that the individual intended to die (Jacobs, Brewer, 2006). This study emaines only suicide attempts.

2.3.1 EPIDEMIOLOGY OF SUICIDAL BEHAVIOR IN BIPOLAR DISORDER

2.3.1.1 *Epidemiology of suicide in bipolar disorder*

Up to 90% of suicide victims meet the criteria for a psychiatric disorder (Lönnqvist, 2009), with BD likely associated with the highest risk (McIntyre et al., 2008). BD has been reported to have a suicide risk of 15 times the expected (Harris, Barraclough, 1997), and according to psychological autopsy

studies, over 40% of suicides victims have suffered from affective disorders (Arsenault-Lapierre, Kim & Turecki, 2004). A recent systematic review, reported the pooled suicide rate in BD to be 164 per 100 000 person-years, 1.7 times higher for men than women, and estimated that people with BD account up to 14 % of all suicides deaths (Schaffer, Isometsa, Tondo, Moreno et al., 2015). Earlier estimates indicate that up to 15-19 % of BD patients die by suicide (Guze, Robins, 1970, Goodwin & Jamison 2007), but later estimates have been remarkably lower probably due to methodological advancements (Isometsä, 2014). In later studies, lifetime suicide rates of 4-8% in affective disorders have been reported (Inskip, Harris & Barraclough, 1998, Bostwick, Pankratz, 2000). In a retrospective analysis, Dutta et al. (2007) noted that 8.3% of BD I subjects died by suicide during an observation period of 35 years. Osby et al. (2001) found standardized mortality ratios (SMRs) for suicide of 15.0 for males and 22.4 for females in their retrospective 20-year observation of 15 386 BD patients. Systematic reviews of prospective, retrospective and psychological autopsy studies have reported the suicide risk for BD patients to be 20-30 times greater than that for general population, (Pompili et al., 2013, Plans et al., 2019) and higher for BD II than BD I (Plans et al., 2019).

To date, the most accurate estimates of lifetime suicide risk are from seminal Danish register study of Nordentoft et al. (2011). Based on first hospital contact and follow-up of up to 36 years, it yielded absolute lifetime risk of suicide of 7.77% for men and 4.78% for women with BD. Among psychiatric disorders, men with BD and women with schizophrenia (4.91%) had the highest risk. The risk of suicide for men with BD was over 10-fold and for women with BD over 18-fold higher than in the general population. Men with BD and first hospital admission due to deliberate self-harm had the highest risk (17.08%) of all. Admission due to deliberate self-harm increased the cumulative incidence of suicide for women up to 9.3 %. The lifetime risk of suicide was in between the aforementioned figures for both men and women with BD and comorbid substance abuse, 10.01% and 5.20% respectively.

Angst et al. (2005) studied the suicide risk of hospitalized MDD and BD patients in the longest to date, 40-44 years, follow-up and reported 11.1% of the whole cohort to have died by suicide during the follow-up. BD patients were divided into three subgroups of (i) BD I with hospitalizations for both mania and depression, (ii) BD II with hospitalizations for only depression, and (iii) BD with hospitalizations for only mania. The standardized mortality ratios (SMRs) for suicides in these three groups were 13.6, 10.6 and 4.7 respectively, being highest in the unipolar group (26.4). However, it is noteworthy that these findings are from the era well before current treatment options, as the cohort was sampled in 1959-1963 and followed until 1985.

Psychological autopsy is a valuable tool in research of completed suicide. This retrospective method involves collection of all available information on the suicide victim by interviews of family members and/or friends as well as attending health care personnel. Moreover, information is collected broadly from all health care and psychiatric records and forensic examination. As a

result of this extensive data collection, the psychological autopsy method aims to build a picture on the multifactorial etiology of the suicide of the deceased individual (Isometsä, 2001). More than 20 major psychological autopsy studies have revealed that the presence of a mental disorder is a necessary, albeit not a sufficient condition for a completed suicide. According to the psychological autopsy studies, the most common mental disorders among completed suicides are mood disorders and substance use disorders, comorbidity often being the rule. The prevalence of BD preceding suicide has been 0-23% whereas the prevalence of depressive disorders has been 30-90% (Isometsä, 2001). However, many of the studies are from the era before the current diagnostic systems and may underestimate the prevalence of BD. Furthermore, an early Hungarian psychological autopsy study (Rihmer et al., 1990) stated that half of the people with depression who died by suicide, and 25% of all suicide victims, had an undiagnosed BD II. Although most psychological autopsy studies have likely underestimated the prevalence of BD II, the prevalence reported in the Hungarian study markedly exceeds the prevalences of all BDs found in other psychological autopsy studies (Cavanagh et al., 2003, Arsenault-Lapierre, Kim & Turecki, 2004, Isometsä, 2001).

2.3.1.2 *Epidemiology of suicide attempts in bipolar disorder*

According to clinical studies, about one-third of BD patients have attempted suicide during their lifetime (Novick, Swartz & Frank, 2010, Tondo et al., 2016). However, in studies focusing on suicidal behavior as an outcome of BD and including also suicide attempts (SAs) that have not led to contact with health care, lifetime prevalence of SAs may exceed 50% (Valtonen et al., 2005, Valtonen et al., 2006). The meta-analysis of Novick et al. (2010) and review of Tondo et al. (2016) found no difference in the risk of SAs between BD I and BD II. The lethality of SAs of BD patients has been found to be higher than that of the general population (Tondo, Baldessarini, 2000).

In cross-sectional studies, the prevalence of SAs has been found to be higher among BD than MDD patients (Tondo et al., 1999, Sokero et al., 2003, Valtonen et al., 2005). Prospective studies have found either similar incidences of SAs for BD and MDD (Oquendo et al., 2004, Fiedorowicz et al., 2009) or higher incidences for BD than for MDD (Tondo, Lepri & Baldessarini, 2007, Holma et al., 2014). In the study of Holma et al., (2014) the higher cumulative incidence of SAs among BD patients was mainly due to patients with BD spending more time in high-risk states, not to differences in incidence of SAs during illness phases, or to BD diagnosis itself.

2.3.2 ETIOLOGY AND RISK FACTORS OF SUICIDAL BEHAVIOR IN BIPOLAR DISORDER

The etiology of suicidal behavior is multifactorial and the range of putative risk factors is potentially unlimited. The stress-diathesis model (Mann et al., 1999) has been proposed as an attempt to explain the balance between trait- and state-related predisposing and protective factors for suicidality. According to the model, aggressive and impulsive traits as well as a tendency for pessimism may predispose an individual to suicidal behavior, and stressors, such as worsening of psychiatric condition, may lead to a suicidal act in predisposed individuals. This model is widely accepted as a conceptual framework when assessing suicidality in mood disorders, but as a limitation it fails to consider the temporal variation of time spent in high-risk states (Isometsä, 2014). There is evidence that suicide risk varies markedly over time, being extremely high after discharge from psychiatric hospital (Osby et al., 2001, Qin, Nordentoft, 2005). Medium-term studies of the JoBS cohort have revealed, that for BD patients the risk of SAs varies notably also depending on the type of illness phase, the risk being highest in mixed and depressive states (Valtonen et al., 2008). The relatively low potency of risk factors of SA found in studies that have investigated trait or cross-sectional clinical characteristics may be far exceeded by potency of marked temporal variation in incidence rates between high-risk states and euthymia (Valtonen et al., 2008, Holma et al., 2014). The specifcity of risk factors may also vary by type of illness phase (Valtonen et al., 2007). However, although temporal variations and time spent in risk states may be the main determinants of cumulative risk for suicidal behavior, only a few long-term studies on mood disorders have investigated the occurrence of SAs in relation to the illness episodes, i.e. precisely timed SAs with different illness states (Isometsä, 2014).

2.3.2.1 *Risk factors of suicide in bipolar disorder*

Knowledge of risk factors of completed suicide in BD is relatively sparse. Suicide, the most extreme unwanted outcome, is a rare event from the research point of view. A large register-based Danish study (Nordentoft, Mortensen & Pedersen, 2011) found male sex, history of suicide attempts and comorbid substance use disorder to be associated with higher risk of suicide in BD patients. The large register-based cohort study by Simon et al. (Simon et al., 2007), found male sex and comorbid anxiety disorder as risk factors for suicide in BD. The systematic review of Hawton et al. (2005) including 13 studies reported male gender, previous suicide attempts and hopelessness as risk factors for suicide in BD. A recent meta-analysis including 12 studies (Schaffer et al., 2015b), identified male gender and first-degree family history of suicide as risk factors for suicide in BD. When pooling 141 studies that examined how 20 specific factors influenced the likelihood of suicide, male sex, older age, current depressive or mixed state, manic states with psychotic features, hopelessness, psychomotor agitation, anxiety disorder, first degree family

history of mood disorder or suicide, prior suicide attempts, and psychosocial precipitants within a week prior to death were found to increase the likelihood of suicide (Schaffer et al., 2015a). A recent large Swedish cohort study of 12 850 BD patients found male sex, living alone, previous suicide attempts, comorbid psychiatric disorder, recent affective episodes, criminal conviction, psychiatric inpatient care, and involuntary commitment as risk factors for suicide (Hansson et al., 2018).

The psychological autopsy literature focusing specifically on BD is sparse. As part of the National Suicide Prevention Project in Finland, Isometsä et al. (1994) reported on suicides of 31 BD I patients, who were investigated by the psychological autopsy method. Most of the suicides occurred during a major depressive episode (79%), but some during a mixed state (11%) or immediately after remission of psychotic mania (11%). Men were found to have a higher rate of comorbid alcoholism, a lower mean age, and a shorter treatment history than women.

2.3.2.2 *Risk factors of suicide attempts in bipolar disorder*

Risk factors for SAs in BD have been extensively investigated (Hawton et al., 2005, Novick, Swartz & Frank, 2010), but due to the preponderance of cross-sectional and retrospective studies, there is limited information on whether the numerous recognized risk factors are relevant irrespective of different illness states of BD, or mostly relevant during a particular illness phase (Schaffer et al., 2015a, 2015b). A meta-analysis of Hawton et al. (2005), relying mostly on retrospective and cross-sectional studies, found family history of suicide, early onset of BD, extent of depressive symptoms, increasing severity of affective episodes, rapid cycling, presence of mixed affective states, comorbid Axis I disorders, and abuse of alcohol or drugs as risk factors for non-fatal suicidal behavior. Prospective studies have found former SAs, suicidal ideation, family history of suicidal behavior, depressive index phase, percentage of days depressed during the preceding year, subjective rating of depression severity, comorbid alcohol dependence or abuse, anxiety disorder, smoking, hopelessness, hostility, aggression and (or) impulsivity, and young age as risk factors for SAs (Isometsä, 2014). A recent comprehensive meta-analysis of risk factors of SAs in BD (Schaffer et al., 2015b), including both epidemiological and clinical and retrospective and prospective designs, reported female gender, younger age at illness onset, depressive polarity of first illness episode, depressive polarity of current or most recent episode, comorbid anxiety disorder, comorbid substance or alcohol use disorder, comorbid cluster B personality disorder, and first-degree family history of suicide to be associated with SAs. These risk factors are prevalent among high-risk populations of BD patients, their potency commonly being in the range of two- to three-fold risk, and thus, their predictive value is somewhat limited (Schaffer et al., 2015b). Paradoxically, while the cumulative risk of SAs is

dependent on the duration of follow-up, the annual incidence of SAs appears to decrease with time (Tondo et al., 2016).

2.4 PREDOMINANT POLARITY IN BIPOLAR DISORDER

During the long-term course of BD, there are marked differences in the relative predominance of types of episodes between patients. These differences may have an influence on both pharmacological and non-pharmacological treatment decisions, as different treatment options differ in efficacy in treating and preventing mania and depression (Popovic et al., 2012, Popovic et al., 2013). The presence of mood spectrum within BD has long been acknowledged (Angst, 1978), but the diagnostic focus has been on applying the lifetime worst manic symptoms as the basis for subdivision of BD into types I and II. Furthermore, treating physicians have intuitively been aware of the fact that many BD patients have a tendency towards one pole or the other (depression vs. hypomania/mania). Not until recently, however, has a clinically applicable classification of predominant polarity, based on differences in dominant types of illness episodes during illness history, been introduced (Colom et al., 2006).

2.4.1 DEFINITION OF PREDOMINANT POLARITY

The best known definition of predominant polarity (PP) has been proposed by Colom et al. (Colom et al., 2006). It sets the threshold for a patient having either manic (MP) or depressive predominant polarity (DP) at two-thirds of lifetime episodes being either (hypo)manic or depressive. Mixed episodes are not included in the definition, but in many studies, mixed episodes are included in the total sum of the episodes. This definition of predominant polarity was included in the ISBD Nomenclature Taskforce recommendations for the DSM-5, but not in the current version of DSM-5 (American Psychiatric Association, 2013).

Another, broader and simpler, definition of PP is one with a threshold of more than half of the lifetime episodes being manic or depressive polarity fulfilling the criteria for MP or DP, respectively. Colom et al. (2015) have later called this proposal the Harvard Index (Colom, Vieta & Suppes, 2015) in referenece to a large multicenter study sample using this definition (Baldessarini et al., 2012b). This definition also fails to consider mixed episodes, but the Harvard group has experimented by adding the mixed episodes to the DP category, which increased the risk of suicidal behavior remarkably (Baldessarin et al., 2012b).

The definition of Colom et al. (2006) may be more time-stable than the Harvard definition, but is potentially too restrictive, as up to 50-60% of patients remain without an assigned PP when this definition is used (Carvalho et al., 2014). The group of patients not assigned any predominant polarity

when using these definitions (no polarity, NP) has been only recently acknowledged in the literature (Belizario, Silva & Lafer, 2018, Vidal-Rubio et al., 2018).

2.4.2 PREVALENCE OF PREDOMINANT POLARITY

In previous mostly retrospective studies, predominantly manic (MP) or depressive polarity (DP) has been present in 42.4-71.8% of BD patients (Carvalho et al., 2014). The varying prevalences across studies can in part be explained by different definitions used, as studies have applied either the less strict definition of simply having more lifetime episodes of manic or depressive polarity or the more strict definition of Colom et al. (2006). Only a few studies have used both definition (Baldessarin et al., 2012b, Azorin et al., 2015) Baldessarini et al. (2012b) noted that, the broader criterion allowed nearly 30 % more cases (81.0% vs 52.7%) to be characterized as having a PP, and in study of Azorin et al. (2015), the proportions were 82.0% and 48.9%, respectively. However, broadening the definition had little impact on the predictors of polarity (Baldessarini et al., 2012b).

2.4.3 CLINICAL CORRELATES WITH REGARD TO PREDOMINANT POLARITY

To date, numerous studies have examined various clinical correlates with regard to predominant polarity. Manic onset of illness (Forty et al., 2009, Mazzarini et al., 2009, Baldessarini et al., 2012b, Janiri et al., 2017), younger age of illness onset (Gonzalez-Pinto et al., 2010, Popovic et al., 2014), higher number of hospitalizations (Vieta et al., 2009, Gonzalez-Pinto et al., 2010, Popovic et al., 2014), type I bipolar disorder (Colom et al., 2006), first illness episode with psychotic features (Baldessarini et al., 2012b), psychotic features (Azorin, Adida & Belzeaux, 2015), male sex (Popovic et al., 2014), rapid cycling (Vieta et al., 2009, Azorin, Adida & Belzeaux, 2015), lifetime history of substance abuse preceding first episode (Colom et al., 2006, Popovic et al., 2014), drug abuse (Baldessarini et al., 2012b), stressors at onset and family history of affective illness (Azorin, Adida & Belzeaux, 2015) have been associated with MP. Depressive first episode (Colom et al., 2006, Daban et al., 2006, Rosa et al., 2008, Forty et al., 2009, Mazzarini et al., 2009, Popovic et al., 2014, Azorin, Adida & Belzeaux, 2015, Janiri et al., 2017), type II BD (Colom et al., 2006, Rosa et al., 2008, Popovic et al., 2014), female gender (Nivoli et al., 2011, Baldessarini et al., 2012b), mixed onset of illness (Baldessarini et al., 2012b), higher number of mixed episodes (Colom et al., 2006, Baldessarini et al., 2012b), longer delay to proper diagnosis (Rosa et al., 2008, Baldessarini et al., 2012b), comorbid anxiety (Azorin, Adida & Belzeaux, 2015) and seasonal pattern (Goikolea et al., 2007) have been associated with DP. When interpreting the results, it should be noted, that findings of these

studies have not been fully consistent (Carvalho et al., 2014), and the associations have rarely been tested in prospective settings. A systematic review of 16 articles found MP to be associated with a manic onset of illness and drug consumption prior to onset, wheras DP was associated with depressive onset, more relapses, prolonged acute episodes, greater suicide risk, later diagnosis of BD, anxiety disorders, mixed symptoms and melancholic symptoms (Garcia-Jimenez et al., 2017).

History or higher number of suicide attempts has repeatedly been linked to DP (Colom et al., 2006, Gonzalez-Pinto et al., 2010, Baldessarini et al., 2012b, Garcia-Jimenez et al., 2017), and combining mixed -states with the depressive category almost doubled the association with SAs (Baldessarini, Undurraga et al., 2012). In contrast, Azorin et al. (2015) reported the MP group to have more SAs and proposed higher levels of cyclothymic and hyperthymic temperaments in MP as an explanation. Baldessarini et al. (2012) found DSM-IV Axis-II comorbidity and Azorin et al. (2015) the occurrence of anxiety disorders to be more frequent in the depressive polarity group, but other studies have not found association between comorbid DSM-IV Axis I and II mental disorders and PP (Koyuncu et al., 2010, Popovic et al., 2014). However, in light of the finding that the current illness phase strongly affects, the generally high, prevalence of psychiatric comorbidity, these differences are plausible (Mantere et al., 2010, Pavlova et al., 2015).

2.4.4 INFLUENCE OF PREDOMINANT POLARITY ON OUTCOME

To our knowledge, no previous studies including both BD I and BD II patients exist on the predictive validity of PP in terms of time spent ill. There are only a few prospective long-term studies on the incidence of suicide attempts or the stability of the polarity classification.In a 7-year prospective cohort study, Belizario et al. (2018) found the MP group to have worse prognosis in terms of number of hospitalizations, suicide attempts and episodes with psychotic symptoms. They found 67% of patients to maintain their polarity classification in follow-up. Garcia-Lopez et al. (2009) followed a cohort of 296 BD patients for 1-4 years and assessed affective symptomatology every 3 months with rating scales of depression and mania (Hamilton depression scale, HAM-D and Young mania rating scale, YMRS). They found no association between PP and the presence of subsyndromal or affective episodes during follow-up. Goikolea et al. (2007) examined seasonal pattern of 325 BD patients with regard to PP in a 10-year prospective follow-up and found that a seasonal pattern was associated with BD type II and a DP. However, in multivariate logistic regression only the association with BD II persisted. Gonzales-Pinto et al. (2010) followed 169 BD I patients up to 10 years and observerd that the DP group had more episodes, more suicide attempts, and more hospitalizations in follow-up. They also found that in the MP group, there was a significant decrease in alcohol and drug abuse over the follow-up period.

3 AIMS OF THE STUDY

The aim of this prospective 5-year follow-up study was to investigate the long-term outcome and its predictors in a representative secondary-level in- and outpatient cohort of BD I and II patients, who at intake had an ongoing mood episode.

Specific aims were as follows:

1. To investigate the long-term outcome of BD with regard to time ill, time to first recurrence, time to remission, and their predictors (Study I).

2. To investigate the incidence of suicide attempts during different phases of BD and to identify potential risk factors modifying the risk during major depressive episodes, when the majority of suicide attempts were expected to occur (Study II).

3. To investigate whether the course characteristics and/or classes defined on the basis of an 18-month follow-up predict total time ill and hospital admissions over a subsequent follow-up period from 18 months to 5 years (Study III).

4. To investigate whether the predominant polarity predicts the incidence of suicide attempts or the time spent ill in the prospective 5-year follow-up, and whether the different polarity groups predict the occurrence of comorbid mental disorders or other clinical variables (Study IV).

4 METHODS

4.1 STUDY DESIGN

The Jorvi Bipolar Study (JoBS) is a collaborative research project between the Department of Psychiatry, Jorvi Hospital, Espoo, Finland, and Department of Mental Health and Substance Abuse Services, National Institute of Health and Welfare, Helsinki, Finland. The Jorvi Hospital Psychiatric Clinic provides secondary-care psychiatric services to the citizens of Espoo, Kauniainen, and Kirkkonummi (261 116 inhabitants in 2002). The Ethics Committee of HUS (Helsinki and Uusimaa Healthcare District) approved the study protocol.

JoBS is the only large-scale long-term cohort study on BD conducted in Finland and has yielded several earlier research reports based on baseline and 18-month data (Mantere et al., 2004, Valtonen et al., 2005, Mantere et al., 2006, Valtonen et al., 2006, Valtonen et al., 2007, Mantere et al., 2008, Valtonen et al., 2008, Suominen et al., 2009, Mantere et al., 2010, Jylhä et al., 2010, Uher et al., 2013, Holma et al., 2014, Arvilommi et al., 2015).

4.2 SCREENING

All in- and outpatients aged 18-59 years in the catchment area of Jorvi Hospital with a possible new DSM-IV BD episode during the study period (from January 1, 2002 to February 28, 2003) were screened using the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000). Screening was carried out by the attending mental health professionals for all patients seeking treatment, being referred or currently receiving care and showing symptoms of deteriorating clinical state. In spite of a negative MDQ screen, patients suspected to have BD due to clinical diagnosis or relevant symptoms (N=28) were included in the screening. The response to item 3 in MDQ ("problems due to episodes") was ignored on the basis of a pilot study (E. Isometsa et al., 2003). ICD-10 clinical diagnosis of schizophrenia was an exclusion criterion for screening. Clinical suspicion of BD or a positive MDQ-screen resulted in fully informing the patient about the study protocol and requesting a written consent. Of the 1630 patients screened, 546 were either MDQ-positive or clinically suspected to be bipolar. Of these 546 patients, 49 refused to be interviewed and 7 could not be contacted, leaving 490 patients to be interviewed.

4.3 BASELINE EVALUATION

4.3.1 DIAGNOSTIC EVALUATION

In the second phase of sampling, those with positive MDQ or clinically suspected BD (N=490) were interviewed face-to-face by a psychiatrist using the Structured Clinical Interview for DSM-IV Disorders, research version with psychotic screen (SCID-I/P) (First et al., 2002). All available information, including psychiatric and medical records, interviews with family members, and observations of attending personnel, was used in the interviews. BD with a current mood episode was diagnosed in 201 patients, 10 of whom refused to participate, leaving 191 patients in the study cohort. Inter-rater reliability was evaluated by videotaping interviews, which were then blindly evaluated by another researcher. For 20 videotaped diagnostic interviews selected randomly, an absolute agreement was found (kappa for BD=1.0, for BD I=1.0 and for BD II=1.0). Diagnoses on Axis II were assessed by using the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) (First et al., 1997).

4.3.2 OBSERVER AND SELF-REPORT SCALES

Observer tools for baseline measurements included the Young Mania Rating Scale (YMRS) (Young et al., 1978), the 17-item Hamilton Depression Scale (HAM-D) (Hamilton, 1960), the Scale for Suicidal Ideation (SSI) (Beck, Kovacs & Weissman, 1979) and the DSM-IV Social and Occupational Functional Assessment Scale (SOFAS) (Goldman, Skodol & Lave, 1992). The self-report tools included the 21-item Beck Depression Inventory (BDI) (Beck et al., 1961), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), the Beck Hopelessness Scale (HS) (Beck et al., 1974), the Perceived Social Support Scale-Revised (PSSS-R) (Blumenthal et al., 1987), and the short Eysenck's Personality Inventory (EPI) (Al-Issa, 1964).

4.3.3 OTHER CHARACTERISTICS

A retrospective lifechart was used to collect information on former illness and treatment history and demographic characteristics. The age at illness onset was specified to be the time of onset of the first mood episode fulfilling the DSM-IV criteria. Monophasic episode included only one phase whereas polyphasic episode was defined as an episode consisting of more than one phase. The distinct phases were manic, hypomanic, depressive, mixed and depressive mixed phase. The depressive mixed state was defined according to Benazzi and Akiskal (2001) as three or more simultaneous intra-episode hypomanic symptoms occurring at least 50 % of the time during a MDE. The minimum duration of hypomania was defined at 2 days instead of 4 days to

include the BD NOS (not otherwise specified) patients with hypomanias of 2-3 days. The soft bipolar spectrum was excluded.

4.4 FOLLOW-UP AT 6 MONTHS,18 MONTHS AND 5 YEARS

The patients were interviewed at 6 months, 18 months and 5 years. We used a lifechart method similar, but not identical, to the Longitudinal Interval Follow-up Evaluation (LIFE) methodology developed by Keller et al. (1987) originally for use in the National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS). Using the lifechart, we retrospectively identified the duration and timing of major depressive, hypomanic, manic, mixed, depressive mixed, cyclothymic, and substance-induced phases of BD as well as the subsyndromal states of hypomanic and depressive symptoms in follow-up. Unlike in LIFE, the strict DSM-IV criteria were used (with two exceptions mentioned below), when defining the follow-up periods. The DSM-IV criteria that we used for euthymia (no symptoms) were more stringent than those used in the CDS (no symptoms or 1 to 2 symptoms to a mild degree). Thus, the proportions of time spent in different illness states in the studies using LIFE and in our study are not directly comparable. As with LIFE, change points in the psychopathological states were inquired using probes related to important life events to improve the accuracy of the assessment. At all follow-up points, semistructured interviews (SCID-I and SCID-II) were conducted and the same scales and tools as in baseline were used to collect information on rating -scales, comorbid disorders, psychosocial factors, and suicidality. The interviews typically lasted 2-3 hours per patient. The flow -chart of Jorvi Bipolar Study 5-year follow-up is provided in Figure 3.

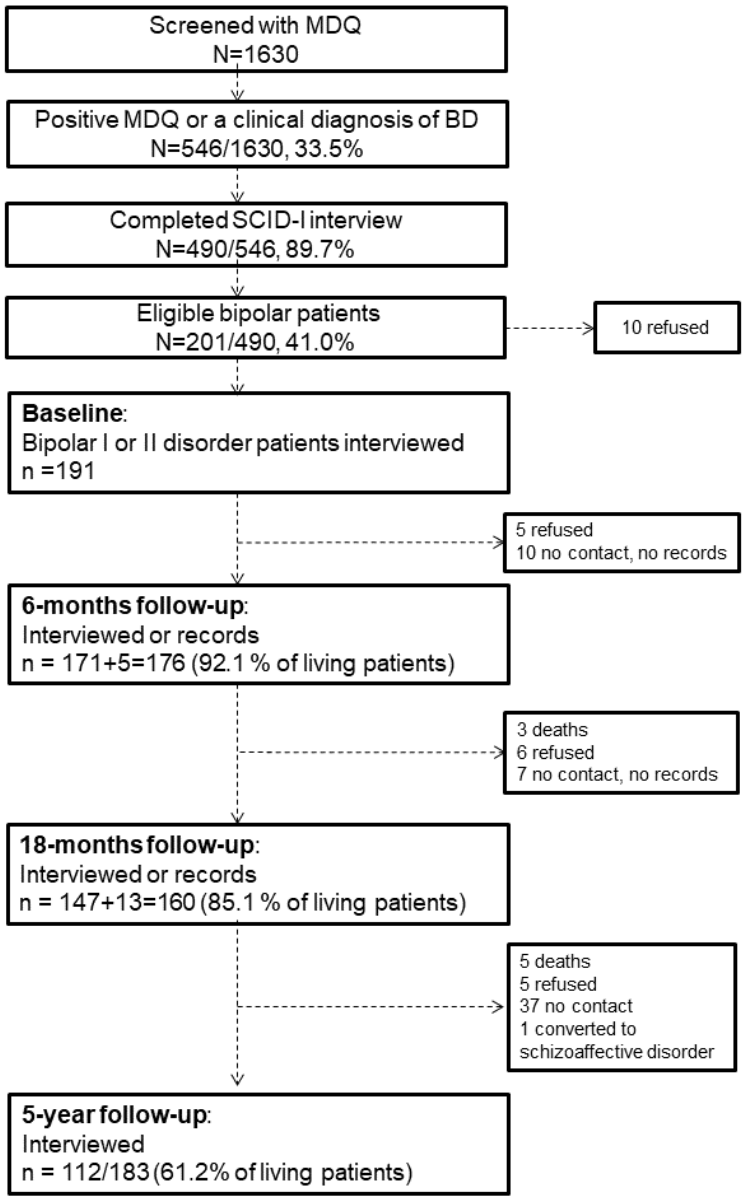


Figure 3. Flowchart of the Jorvi Bipolar Study 5-year follow-up. MDQ=Mood Disorder Questionnaire; SCID-I=Structured Clinical Interview for DSM-IV Axis I Disorders

4.5 LIFECHART

4.5.1 DEFINITIONS FOR TIME PERIODS OF LIFECHART

At the 6-month and 18-month interviews, the follow-up time was divided into ten different time periods: mania, hypomania, hypomanic symptoms, euthymia, mixed state, depressive mixed state, cyclothymia, depressive symptoms, major depressive episode, and substance-induced mood phase. A longer time from the previous interview at the 5-year point than at the 6-month and 18-month interviews potentially caused a greater probability of recall bias at the 5-year interview. Thus, at 5 years we included a category of time period termed "not known" for situations in which the interviewer could not classify a certain period of the follow-up time reliably. This category of "not known" covered 3% of the whole follow-up time of the interviewed patients (N=112) at 5 years.

Definitions of DSM-IV for the phases (manic, hypomanic, MDE, mixed, depressive mixed) of BD were used with two exceptions: (i) the minimum duration of hypomania was defined as 2 days instead of 4 days and (II) the depressive mixed state was defined according to DMX3 definition (i.e. three or more simultaneous intra-episode hypomanic symptoms present for at least 50 % of time during a major depressive episode) of Benazzi and Akiskal (2001). *States of subsyndromal symptoms* (depressive or hypomanic symptoms, either prodromal or subsyndromal) were rated when the patient was not euthymic, but did not fulfill the criteria for any illness phase. *Depressive symptoms* was considered as presence of 1-4 depressive criteria symptoms for at least 2 weeks and *hypomanic symptoms* as presence of 1-3 hypomanic criteria symptoms for at least one week. *Substance-induced mood episode* was defined if a phase was induced by a psychoactive substance. An episode according to DSM-IV could be defined as *monophasic* or *polyphasic*. *A phase* thus refers to a monophasic episode or a single phase of a polyphasic episode. *An episode* refers to a monophasic or polyphasic episode. For hypomanic symptoms a duration of more than one week was required and for depressive symptoms and cyclothymia a duration of more than 2 weeks was required. To allow rating of a state of euthymic mood, a minimum duration of 2 weeks was required.

4.5.2 INTEGRATION OF INFORMATION INTO A LIFECHART

After data collection, in which all available information from the interviews and psychiatric records was used, the data were integrated into the form of a graphic lifechart based on DSM-IV criteria (American Psychiatric Association, 1994) with the above-noted exceptions. In the statistical data, the information on time periods and suicide attempts was recorded as precise dates allowing

the performance of time-related analysis such as incidence of suicide attempts, time to remission, and time to recurrence.

4.6 DEFINITION OF REMISSION AND RECURRENCE (STUDY I)

The two main outcome measures in the 5-year follow-up analyses were (i) time to full remission and (ii) time to first recurrence. Their definitions were strictly based on DSM-IV criteria. *Full remission* was considered as at least 2 consecutive months of euthymia. When the syndromal criteria for depression, hypomania, mania, mixed episode, or depressive mixed episode were no longer met but some residual symptoms remained, a period of partial remission was considered to start. If a euthymic period lasted less than 2 months, it was also considered as partial remission. *Time to full remission* was the time from baseline to the onset of a state of full remission lasting at least two consecutive months. *Time to recurrence* was the time from onset of remission lasting at least 2 consecutive months to onset of a new episode. Predictors for time to full remission and time to first recurrence were analyzed in the subgroup of patients with a depressive index phase, because the index phase strongly affects the outcome and MDE was the most prevalent type of index episode.

4.7 DEFINITION AND TIMING OF SUICIDE ATTEMPTS (STUDY II)

At all follow-up points, the dates of SAs were documented precisely using the lifechart method in order to accurately time those with the different phases of the illness, and thus, to be able to investigate time-related outcomes such as incidences of SAs. All available information, including psychiatric and medical records, was used to ensure the best possible accuracy of the assessment. A suicide attempt was defined as self-injurious behavior with the intention to die (Jacobs, Brewer, 2006). Self-harm with no suicidal intention was excluded.

4.8 STUDY DESIGN, COURSE CHARACTERISTICS, AND OUTCOME MEASURES IN STUDY III

We have previously reported on course characteristics and proposed a typology of clinical course on the basis of an 18-month follow-up (Uher et al., 2013). The purpose of the present study was to see whether the course characteristics from the 18-month follow-up predict the long-term outcomes during a follow-up period from 18 -months to 5 years. Only patients who participated at both the 18-month and 5-year follow ups (N=111) were

included. The clinical course was described with nine dimensional course characteristics: (i) proportion of time depressed (time spent in MDEs and depressive symptoms divided by the total follow-up time), (ii) severity of depression (average severity of depressive symptoms at times when depressive symptoms or episode were present), (iii) stability of depressive symptoms (correlation of depressive symptoms between time-points 8 weeks apart), (iv) proportion of time manic (time spent in hypomanic symptoms or (hypo)manic episodes divided by the total follow-up time), (v) severity of (hypo)manic symptoms (average severity of hypomanic symptoms when hypomanic symptoms or episodes were present), (vi) stability of manic symptoms (correlation of manic symptoms between time-points 8 week apart), (vii) mixed affective symptoms (correlation of depressive and manic symptoms at the same time-point), (viii) transitions from depression to mania (correlation of depressive symptoms with manic symptoms 8 weeks later), and (ix) transitions from mania to depression (correlation of manic symptoms with depressive symptoms 8-weeks later). These nine characteristics were used to group patients into nine course types (four common and five uncommon), which at 18 months were as follows: (i) episodic bipolar type (47%), (ii) depressive type (32%), (iii) extended hypomanias (10%), (iv) mixed episodes (5%), (v) mania-to-depression switching (2%), (vi) depression-to-mania switching with extended (hypo)manic episodes (2%), (vii) depression-to-mania switching with brief (hypo)manic episodes (2%), (viii) chronic mixed symptoms (1%), and (ix) long depressive and manic episodes with no intervening euthymia (1%). The outcome measures in the present study were *time ill* (proportion of time spent in any mood symptoms, including syndromal and subsyndromal states) and *hospital admissions* during the follow-up period from 18 months to 5 years.

4.9 DEFINITION OF PREDOMINANT POLARITY (STUDY IV)

When defining the polarity, we used the definition of Colom et al. (2006), requiring two-thirds of the past episodes to be either (hypo)manic or depressive in order to fulfill the criteria of that polarity. Time of the baseline interview was used as a cut-off point when counting the episodes and the index episode was included. In the analysis, we used the categorization where mixed phases were combined with manic and hypomanic phases, and depressive mixed phases combined with major depressive episodes (MDEs). This is in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (American Psychiatric Association, 2013), which replaces the former term “mixed episode” with a mixed-features specifier that can be applied to episodes of hypomania, mania or major depression. Nevertheless, we conducted sensitivity analysis also with the category excluding the mixed phases (including, however, the mixed phases in the total sum of the phases).

4.10 STUDY DROP-OUTS

4.10.1 DROP-OUTS AT THE 6-MONTH AND 18-MONTH FOLLOW-UPS

Of the original sample of 191 subjects, at the 6-month follow-up 15 (7.9%) were missing, 5 (2.6%) refused to participate, and 171 (89.5%) were interviewed. For five of the missing patients, reliable information was available in patient records. Thus, at 6 months, lifechart information was available for 176/191 patients (92.1%). At 18 months, of the original cohort of 191 patients, 11 refused to be interviewed, 3 were known to have died, 142 were interviewed face-to-face, and 5 were interviewed by phone. For 13 of the missing patients, information in patient records was sufficient to graph a lifechart with a minimum duration of one year. Thus, at 18 months, lifechart information was available for 160/188 living patients (85.1%).

4.10.2 DROP-OUTS AT THE 5-YEAR FOLLOW-UP

At the 5-year follow-up, 113 patients of the original sample of 191 patients were interviewed. Between the 18-month and 5-year interview, one patient had converted to a schizoaffective disorder, leaving 112 interviewed BD patients at 5 years. For the switcher, the follow-up time regarding the different states of illness episodes was taken into account until the diagnosis changed. At the 5-year follow-up, eight patients were known to have died and 16 refused to be interviewed. For those who were not reached (N=54), some information could be gathered from patient records in 41 cases, 2 of which were known to have converted to schizoaffective disorder. Due to the unreliability and disunity of the information gained from patient records after the 18-month follow-up, that information was not included in the final analyses. The number of cases included in distinct 5-year analyses differed depending on whether the outcome measure was available already in the 18-month follow-up data (i.e. if the missing patient had reached remission or had a recurrence by the 18-month follow-up) or whether the analysis was restricted only to lifechart data required to reach the 5-year follow-up point (e.g. the proportions of time spent ill in follow-up).

4.10.2.1 *Missing data on recurrence and remission (Study I)*

When adding to the 18-month data the follow-up data collected at the 5-year interviews, information on having a remission was available in 156 cases and information on having a recurrence in 151 cases. Patients missing information on remission were more often women (79.3% vs. 48.1%, $x2 = 9.573$, df=1, p=0.002) and, at baseline more often had a lifetime diagnosis of social phobia (41.4% vs. 22.1%, $x2=4.831$, df=1, p=0.028), rapid cycling course (55.2% vs. 28.6%, $x2=7.836$, df=1, p=0.005) and higher BD I scores (28 vs. 22, df=178,

p=0.026). Patients for whom the information on recurrence was missing had more often a polyphasic index episode (66.7% vs. 48.3%, x2=3.908, df=1, p=0.048) and rapid cycling course of illness at baseline (52.8% vs. 27.9%, x2=8.127, df=1, p=0.004).

4.10.2.2 *Missing data on suicide attempts (Study II)*

When adding to the 6- and 18-month data the follow-up data collected at the 5-year interviews, prospective data on suicide attempts (SAs) were available for 177/191 patients (92.7%, median follow-up time 62.2 months). Altogether, there were 90 SAs during the follow-up eligible for the 5-year analysis. The missing patients (N=14) were those who did not take part in any follow-up interviews. There was one patient who missed both previous follow-up interviews (i.e. was not included in the 6- and 18-month analyses on suicide attempts), but participated in the 5-year interview, thus the total number of patients was 177 at the 5-year analysis compared with 176 in the 18-month analysis. Attrition of previously suicidal patients was somewhat higher than attrition of non-suicidal patients between the 6- and 18-month follow-ups (Valtonen et al., 2006). Nevertheless, those who missed the 5-year interview (N=79) did not differ from those who participated (N=112) in terms of SAs before the index episode (i.e. episode upon entering the study) [43% (34/79) vs. 46% 51/112; p = 0.732)] or SAs during the index episode [27% (21/79) vs. 16% (18/112); p = 0.076]. By the 5-year follow-up, 2 of 177 patients were known to have converted to schizoaffective disorder, remaining in the cohort until censored at the change of diagnosis or dropping out.

4.10.2.3 *Missing data on course characteristics (Study III)*

Patients who did not complete both 6- and/or 18-months and 5-year follow-ups (N=111) were more often female (64% 51/80 vs. 45% 50/111, p=0.011) and younger (t=-3.11, p=0.002) than patients who did, but there was no difference in BD type (50% 40/80 vs. 53% 59/111, p= 0.667), the occurrence of psychotic symptoms lifetime (14% 11/80 vs. 18 % 20/111, p= 0.430) or the occurrence of lifetime comorbid anxiety disorders (54% 43/80 vs. 53% 59/111, p=0.935), substance use disorders (50% 40/80 vs. 51% 57/111, p=0.854), and personality disorders (48% 38/80 vs. 40% 44/111, p=0.279).

4.10.2.4 *Missing data on polarity (Study IV)*

When defining predominant polarity, patients with more than 100 lifetime mood episodes were excluded as outliers. Thus, 188 patients (98.4%) of the original cohort of 191 were included when defining the PP and analyzing the cross-sectional baseline data. The prospective follow-up data for mood episodes and SAs was available for 175 patients (91.6%) justifying the inclusion

in the analysis of time ill and the incidence of suicide attempts in follow-up. The patients not included in the analysis (N=16) did not differ from those who were included (N=175) in terms of gender (male 31.3% vs. 48.6%, p=0.184), BD type (type I 62.5% vs. 45.7 %, p=0.198), having lifetime psychotic symptoms (37.5% vs. 50.3%, p=0.327), having former suicide attempts (50.0% vs 48.6%, p=0.913), having some anxiety disorder (43.8 % vs. 46.9%, p=0.812) or substance use disorder lifetime at baseline (43.8% vs. 49.7%, p=0.648), being inpatients at baseline (43.8 % vs. 33.1%, p=0.391) or having depressive first episode (37.5% vs. 52.5%, p=0.248). When excluding the outliers (more than 100 lifetime mood episodes at baseline), the subjects not included in the follow-up did not differ in terms of number of former episodes (t=0.59, p=0.556).

4.11 STATISTICAL METHODS

Univariate analysis was conducted using Student's t-test, Mann-Whitney *U*-test, or Pearson's χ^2 test. The Poisson log linear model was used in calculation of the confidence interval (CI) for the SAs in different phases in Study II. In the case of no SAs during a phase, a net calculator was used to estimate CI. Logistic regression model or Cox regression model (both univariate and adjusted) was used to investigate the various predictors of outcomes in all four studies. Odds ratios (ORs) were reported for logistic regression models and hazard ratios (HRs) for Cox regression models. In Study I, the final analyses were multivariate Cox proportional hazard models including variables from all important domains. In Study II, logistic regression analysis was conducted in two ways, using self-reported and observer-rated data (when available), as there is evidence that "subjective" self-reports of depression may be more strongly associated with suicidal ideation than "objective" observer-rated symptoms (Keilp et al., 2012). Kruskall-Wallis test was used to compare the time periods of different illness states in Study I and to examine the differences in time spent ill between the polarity groups in Study IV. In Study IV, Poisson regression was used when comparing the number of phases, the incidence of suicide attempts and the number of hospitalizations between the three polarity groups. To clarify the differences between all three groups, the analyses were conducted in two ways, first using the no polarity group and then the depressive polarity group as a reference category. Multinomial logistic regression was used when comparing the differences in clinical variables and occurrence of comorbid disorders between the polarity groups. In the analysis, we used the categorization where mixed phases were combined with manic and hypomanic phases, and depressive mixed phases with major depressive episodes (Definition 5, Table 8), but we also conducted sensitivity analyses excluding the mixed phases (Definition 2, Table 8).

In Study I, patient-level differences in time spent in different illness states between BD I and II patients were examined by estimating regression models

for the seven different states (hypomania, hypomanic symptoms, euthymia, mixed depressive state, cyclothymia, depressive symptoms and depression). The models were analysis of covariance (ANCOVA), the factor being the BD category (I or II) and the covariates set as control variables (age, sex and patient's state at intake). Because the dependent variable was either zero or a positive value, the models were specified as Tobit regression models, the dependent variable being a floor restricted (at zero) continuous variable (Tobin, 1958).

In Study II, we intended to predict the occurrence of an SA in a given MDE. There were 65 SAs in 519 MDEs. The factors modeled in the MDE-level analysis were MDE duration and the ordinal sequence number of the MDE. In the patient-level analysis, we modeled various factors that might be predictive of SAs. As the dependent variable was binary, the model was a two-level random-intercept logistic regression, where the unit of analysis was the MDEs and the variable to be predicted was whether or not an SA was observed in a given MDE. Two different models (subjective and objective approaches, as described above), were tested in this analysis as well.

In Study III, time spent ill, which was a proportion variable ranging from 0 to 1, was tested in Tobit regression models. Since few patients had more than two hospital admissions, the number of admissions was merged into a three-level ordinal variable (0=no admission; 1=one admission, 2=two or more admissions). Ordered logistic regression was used to test the effect of predictors on the probability of hospital admissions. For each hypothesis, eleven predictors (nine dimensional course characteristics and two latent classes) were tested. A detailed description of the course characteristics, course classes, and typology is available in a previous publication (Uher et al., 2013). Since we expected multiple course characteristics to be predictive of outcome, and statistical power is limited by the moderate sample size, we also reported which predictors remained significant after applying Bonferroni's correction for the number of predictors (corrected p value threshold=0.05/11 =0.0045). Results with BD type (I or II) as a predictor are reported as well. To quantify the predictive power of models with different types and numbers of predictors, McFadden's pseudo R-square (Long 2014) was used to approximate the explained proportion of variance in outcome.

As statistic tools, IBM SPSS statistic version 22 and 24, Mplus 7.1 and 7.2, the robust maximum likelihood (MRL) estimator, and STATA 15 were used. In Study IV, polychoric correlation analysis with R package "polycor" (version 0.7-9) was used to examine the stability of the polarity types. As our data was recorded in ordinal variables with only a few scale steps, methods assuming a polarity continuum (an interval scale) would provide biased results. Therefore, we computed polychoric correlation coefficient that estimates correlation between continuous variables from their ordinal proxies (Olsson, 1979). This is essentially an unbiased ordinary correlation of the unobserved continuum, estimated from the observed ordinal scores.

5 RESULTS

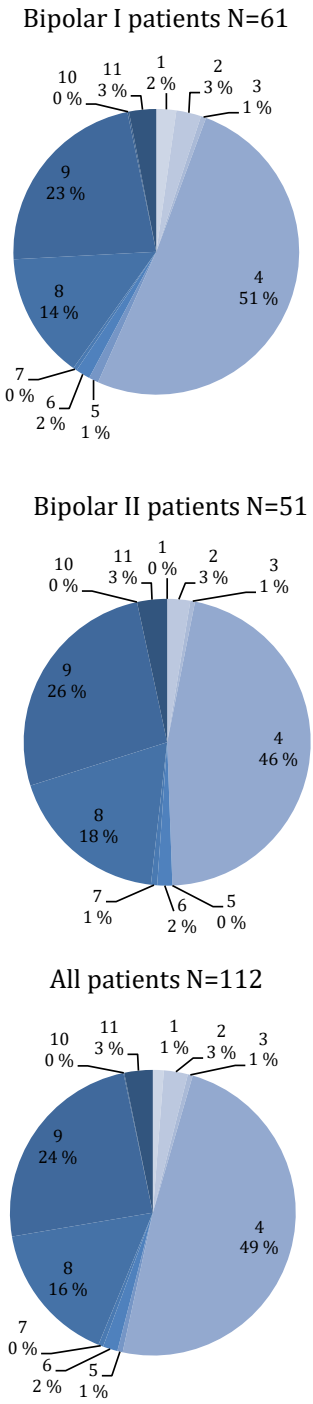
5.1 FIVE-YEAR OUTCOME OF BIPOLAR I AND II DISORDERS: FINDINGS OF THE JORVI BIPOLAR STUDY (STUDY I)

5.1.1 RESULTS OF CROSS-SECTIONAL ANALYSIS

The sociodemographic and clinical characteristics of the patients in the 5-year follow-up are shown in Table 3. At 5 years, 59.8% of the patients (67/112) were euthymic. For those not euthymic, the current episode was hypomania or hypomanic symptoms in 1.8% (2/112), mixed depressive episode in 1.8% (2/112), cyclothymia in 2.2% (3/112), depressive symptoms in 17.9% (20/112), and major depressive episode in 16.1% (18/112). For euthymic patients, the median score in the YMRS was 0.0 and in the HAM-D 3.0, and 49.2% of them were working or studying at the time of the 5-year interview. Currently, 77.6% (87/112) were using some pharmacotherapy, but 16.0% (18/112) were not receiving any treatment. Overall, 61.6% of the patients (69/112) were in psychiatric care, and of these 44.6% (50/112) were receiving some psychosocial treatment. Psychotherapeutic support was received by 41.1% (46/112) and weekly psychotherapy by 2.7% (3/112). Almost one-third (27.7%, 31/112) had been hospitalized at least once after the 18-month follow-up. Of the original sample (N=191), three patients (1.6%) had converted to schizoaffective disorder (information from patient records for two patients) and 5.8% (11/191) from BD II to BD I during the 5-year follow-up.

Table 3. Baseline sosiodemographic and clinical characteristics of 151 patients included in the 5-year follow-up of the Jorvi Bipolar Study.

Variable	BD I N(%)	BD II N(%)	Total N(%)	Sig. χ^2	Sig. p
Gender, male	42(60.9)	36(43.9)	78(51.7)	4.3	0.038
Marital status, married	29(42.0)	35(42.7)	64(42.4)		NS
Work status, employed	33(47.8)	37(45.1)	70(46.4)		NS
Depressive index phase	36(52.2)	48(58.5)	86(57.0)		NS
Rapid cycling	17(24.6)	27(32.9)	44(29.1)		NS
Psychotic symptoms lifetime	45(65.2)	30(36.6)	75(50.0)	12.3	<0.001
Suicide attempts lifetime	32(46.4)	38(46.3)	70(46.4)		NS
Any anxiety disorder lifetime	30(43.5)	51(62.2)	81(53.6)	5.3	0.022
Any substance abuse lifetime	41(59.4)	35(42.7)	76(50.3)	4.2	0.040
Cluster A personality disorder	9(13.0)	8(9.8)	17(11.3)		NS
Cluster B personality disorder	19(27.5)	19(23.2)	38(25.2)		NS
Cluster C personality disorder	15(21.7)	21(25.6)	36(23.8)		NS
Inpatient at baseline	36(52.2)	17(20.7)	53(35.1)	16.3	<0.001
	Mean(SD)	**Mean(SD)**	**Mean(SD)**		
Age at entry	40.1(11.9)	36.5(12.3)	38.1(12.2)		NS



1- mania

2- hypomania

3- hypomanic symptoms

4- euthymia

5- mixed state

6- mixed depressive state

7- cyclothymia

8- depressive symptoms

9- depression

10- a mood episode caused by substance use

11- a period of unknown mood

Figure 4. Time spent in different illness states in the 5-year follow-up of the Jorvi Bipolar Study.

5.1.2 PROPORTIONS OF TIME SPENT ILL

The time spent in different illness states for the whole cohort during the 5-year follow-up is seen in Figure 4. BD I patients spent more time euthymic (51% vs. 46%) and less time in subsyndromal state of depressive symptoms (14% vs. 18%) and in MDEs (23% vs. 26%) than BD II patients. However, the patient-level analysis did not reveal significant differences between these two groups after controlling for age and gender. The result remained also when the index phase was controlled for as a confounding factor. During the latter follow-up period from 18 months to 5 years, the proportion of time spent in MDE was smaller than during the first 18 months of the follow-up, 33.5% and 20.6%, respectively. The corresponding proportions of time spent in mixed states were 1.9 % and 4.1%.

5.1.3 TIME TO FULL REMISSION

In the 5-year follow-up, 96% of the patients (150/156) reached full remission of at least 2 months. Only two participants (2/156, 1.3%) did not reach either partial or full remission during the follow-up period. The median time to full remission (from baseline) was 6.6 months. The duration of index phase, time to full remission, and time to first recurrence by type of index phase are seen in Table 4. The index phase ended in transition to euthymic period or a subsyndromal depressive state (of at least two weeks) in 67% of the patients. In about 20 % of the patients, the depressive phase was followed by a transition to a manic or hypomanic phase, and in 12 % to a mixed or depressive mixed phase. Thus, the total time to full remission included time in other phases as well in the cases where the index episode was polyphasic after baseline.

In the subgroup of patients with a depressive index phase, numerous factors predicted longer time to full remission in the univariate Cox regression model. These factors were higher score in the BDI (HR 0.938, $p<0.001$), in the 17-item HAM-D (HR 0.940, $p=0.001$), in the BAI (HR 0.969, $p=0.008$), and in the SSI (HR 0.966, p=0,033). Furthermore, a comorbid lifetime diagnosis of obsessive-compulsive disorder (HR 0.158, $p=0.012$), comorbid lifetime diagnosis of alcohol dependence (HR 0.553, $p=0.042$), comorbid lifetime diagnosis of any anxiety disorder (HR 0.592, $p=0.033$), and comorbid lifetime cluster C personality disorder (HR 0.515, $p=0.040$) predicted longer time to full remission. However, in the multivariate Cox proportional hazard analyses, only severity of depression (higher score in 17-item HAM-D) and cluster C personality disorder were significant predictors for longer time to full remission (Table 5). For those with a HAM-D score of more than 25 it took nearly 5 times longer to achieve full remission than for those with a HAM-D score of 25 or less (median time to full remission 30.3 and 6.5 months, respectively). For patients with cluster C personality disorder it took nearly 3 times longer to achieve full remission than for patients without cluster C personality disorder (median time to full remission 22.8 months and 7.4 months, respectively).

Table 4. Duration of index phase, time to full remission and time to recurrence (months) by type of the index phase in the 5-year follow-up of the Jorvi Bipolar Study.

	Median
Duration of the index phase from baseline (N=143)	1.2
By the type of the index phase[b,c]	
-MDE (N=82)	2.6
–hypomania(N=11)	0.7
-mania (N=16)	1.0
-mixed state (N=12)	0.8
-depressive mixed state (N=22)	0.6
Time to full remission from baseline[a,d] (N=133)	6.6
By the type of index phase[c,e]	
-MDE (N=71)	7.5
-hypomania (N=14)	8.0
-mania (N=18)	1.8
-mixed state (N=12)	5.3
-depressive mixed state (N=18)	8.7
Time to recurrence from the beginning of remission[a] (N=130)	5.0
By the type of index phase[c,f]	
-MDE (N=70)	5.2
-hypomania (N=15)	3.3
-mania (N=16)	14.3
-mixed state (N=7)	3.4
-depressive mixed state (N=22)	4.3

[a] including all index phases
[b] p<0.0011, df=4
[c] Kruskal-Wallis Test
[d] full or partial remission lasting at least 2 months
[e] p=0.003, df=4
[f] p=0.012, df=4

MDE=major depressive episode

Table 5. Baseline predictors of time to full remission in the 5-year follow-up of the Jorvi Bipolar Study. Only patients with depressive index episode included in the analysis.

	Time to Full Remission[a]		
Predictor	**Sig.**	**HR**	**95 % Cl**
Age (years)	0.558	0.991	0.963 – 1.021
Gender (male)	0.377	1.328	0.708 – 2.490
Bipolar I vs. II	0.873	0.952	0.524 – 1.730
17-item HAM-D[b]	0.022	0.951	0.911 – 0.993
Alcohol dependence	0.219	0.655	0.333 – 1.287
Cluster A personality disorder	0.776	1.146	0.448 – 2.929
Cluster B personality disorder	0.956	1.019	0.526 – 1.972
Cluster C personality disorder	0.040	0.452	0.211 – 0.966
Any anxiety disorder	0.084	0.619	0.360 – 1.066
Young Mania Rating Scale	0.411	0.927	0.773 – 1.111
Number of previous phases	0.405	1.003	0.996 – 1.011
Psychotic symptoms lifetime	0.988	0.995	0.543 – 1.826
Polyphasic index episode	0.798	1.076	0.615 -1.880
PSSS-R[c]	0.127	0.979	0.952 – 1.006
Professional education	0.588	0.854	0.483 – 1.510

[a] Multivariate Cox propotional hazard models
[b] Hamilton Depression Scale
[c]the Perceived Social Support Scale-Revised at baseline
All diagnosis lifetime

5.1.4 TIME TO FIRST RECURRENCE

By the 5-year interview, 87% of the participants (130/150) had experienced a recurrence. The median number of recurrences during the 5-year follow-up was 2.0. Nearly half of the patients (47.7 %, 62/130) had three or more recurrences during this period.

The median time to first recurrence was 10.4 months when calculated from baseline and 5.0 months when calculated from the beginning of first full or partial remission lasting at least 2 months. Time to recurrence by type of index phase is presented in Table 4.

In univariate Cox regression analyses including participants with a depressive index phase, female gender (HR 0.530, p=0.016), higher score in the Scale for Suicidal Ideation (HR 1.027, p=0.051), and lifetime psychotic symptoms (HR 2.292, p=0.004) predicted shorter time to recurrence. In the multivariate Cox proportional hazard analysis, only lifetime psychotic symptoms remained a significant predictor after adjusting for the other factors (Table 6). The median time to recurrence was 4.0 months for those with lifetime psychotic symptoms and 5.7 months for those without psychotic symptoms.

Table 6. Baseline predictors of time to first recurrence in the 5-year follow up of the Jorvi Bipolar Study. Only patients with depressive index episode were included in the analysis.

	Time to First Recurrence[a]		
Predictor	**Sig**	**HR**	**95 % Cl**
Age (years)	0.428	1.011	0.984 – 1.038
Gender (male)	0.147	0.610	0.313 – 1.190
Bipolar I vs II	0.557	0.823	0.428 – 1.580
17-item HAM-D[b]	0.568	1.013	0.968 – 1.061
Alcohol dependence	0.934	1.029	0.524 – 2.022
Cluster A personality disorder	0.648	1.233	0.502 – 3.030
Cluster B personality disorder	0.877	1.058	0.521 – 2.145
Cluster C personality disorder	0.513	0.761	0.337 – 1.723
Some anxiety disorder	0.384	1.318	0.708 – 2.455
Young Mania Rating Scale	0.511	0.946	0.803 – 1.115
Number of previous phases	0.373	1.004	0.996 – 1.012
Psychotic symptoms lifetime	0.016	2.162	1.156 – 4.044
Polyphasic index episode	0.660	1.131	0.655 – 1.952
PSSS-R[c]	0.704	0.995	0.970 – 1.021
Professional education	0.988	0.996	0.556 – 1.783

[a] Multivariate Cox proportional hazard models
[b] Hamilton Depression Scale
[c] Perceived Social Support Scale-Revised at baseline
All diagnoses lifetime

5.2 INCIDENCE AND PREDICTORS OF SUICIDE ATTEMPTS IN BIPOLAR I AND II DISORDERS: A 5-YEAR FOLLOW-UP STUDY (STUDY II)

5.2.1 INCIDENCE OF SUICIDE ATTEMPTS

During the 5-year follow-up 90 SAs per 718 patient-years by 50/177 patients (28%) occurred. Of the suicide attempts, 72% (65/90) took place during MDE, 9% (8/90) during depressive symptoms, 9% (8/90) during depressive mixed episodes, 8% (7/90) during mixed state, and 2% (2/90) during euthymia. During manic or hypomanic states there were no suicide attempts. Most of those attempting suicide (56%) had one attempt, 30% had two attempts, and 14% had three or more attempts. The overall incidence rate per 1000 patient-years was 125 (95% CI 102-154). The highest incidence rate was 765 per 1000 patient-years during mixed phases (mixed and depressive mixed together) and the rate was also very high, 65 per 1000 patients-years in MDE (Table 7). The incidence rate of SA's decreased towards the end of the follow-up: the incidence was 192 per 1000 patient-years during the first 18 months of the follow-up, decreasing to 84 per 1000 during the follow-up period from 18 months to 5 years. Based on all retrospective and prospective information

available, more than half of the cohort patients (56.5%, 100/177) had at least one SA during their lifetime.

Table 7. Incidence of suicide attempts during different phases in the 5-year follow-up of the Jorvi Bipolar Study (n=177).[a]

Phase	Events	Time (years)	Incidence per 1000 person-years	95% Cl
Mania	0	9.14	0	0-4
Hypomania	0	20.65	0	0-4
Euthymia	2	342.90	6	1-23
Depressive symptoms	8	113.77	70	35-141
Major depressive episode	65	183.79	354	277-451
Mixed states[b]	15	19.61	765	461-1269

[a]The phases and subsyndromal states with no suicide attempts and duration of less than 0.6 % of the whole follow-up time are not included in the table.
[b]Mixed states include both mixed and depressive mixed phases

5.2.2 PREDICTORS FOR SUICIDE ATTEMPTS

Those subjects attempting suicide during the prospective 5-year follow-up differed in their baseline characteristics from those not attempting suicide in several ways; they were younger (mean age for attempters 34.2 years and for non-attempters 39.4 years, t=2.6, p=0.011), more often had rapid cycling form of the illness at baseline (44% vs 24.4%, χ^2=6.6, p=0.010), more often had previous suicide attempts (80% vs 39.4%, χ^2=23.7, p<0.001) and more often had lifetime comorbid anxiety (68% vs. 48%, χ2=5.7, p=0.016), or lifetime cluster A personality disorder (20% vs. 7.1%, χ^2=6.2, p=0.012) lifetime.

The baseline variables predicting occurrence of SAs during follow-up in univariate logistic regression models (adjusted for age, gender, bipolar subtype and duration of follow-up) were younger age (OR 0.964, p=0.017), former SAs (OR 9.984, p<0.001), rapid cycling form of the illness at baseline (OR 2.355, p=0.023), higher scores in BDI (OR 1.076, P<0.001), HAM-D (OR 1.106, p<0.001), BAI (OR 1.041, p=0.006), HS (OR 1.192, p=0.006), and SSI (OR 1.138, p<0.001), lower score in SOFAS (OR 0.958, p=0.009), comorbid anxiety disorder (OR 2.080, p=0.046), comorbid cluster A personality disorder (OR 3.833, p=0.011), and neuroticism at baseline (OR 1.225, p<0.001). In the multivariate logistic regression analysis with observer-rated (objective) predictors, younger age (OR 0.941, p=0.013) and higher score in HAM-D at baseline (OR 1.105, p=0.002) increased the risk of SA. In the multivariate logistic regression analysis with self-reported (subjective) predictors, a higher score in HS (OR 1.141, p=0.013) and neuroticism at baseline (OR 1.172, p=0.022) predicted SAs in follow-up.

5.2.3 PREDICTORS FOR SUICIDE ATTEMPTS DURING MAJOR DEPRESSIVE EPISODES

Because most SAs took place during MDEs (N=65/90), the two-level random-intercept logistic regression models of predictors were carried out for that subgroup only. The results of the "subjective" and "objective" logistic regression models are seen in Table 8. In both models, MDE duration (within-level variable) emerged as a significant predictor. In the subjective model, there were no significant patient-level predictors of SA during MDEs. In the objective model, cluster C personality disorder and higher score on the Hamilton Depression Scale (the highest score in follow-up selected for analysis) were significant predictors for SA.

Table 8. Two-level random-intercept logistic regression models of predictors of suicide attempts during major depressive episodes in the 5-year follow-up of the Jorvi Bipolar Study.

Observe-rated predictor variables ("objective variables")	**Estimate (β)**	**S.E.**	**Est./S.E.**	**p**
MDE-level (within-level)				
Duration of MDE	0.003	0.001	4.351	<0.001
Sequence number of MDE	0.139	0.081	1.722	0.085
Patient-level (between-level)				
Age	-0.039	0.024	-1.597	0.110
Gender	0.017	0.363	0.048	0.962
Married or cohabiting[a]	0.721	0.372	1.937	0.053
Bipolar type	-0.085	0.355	-0.241	0.810
Psychotic symptoms lifetime[a]	-0.366	0.383	-0.954	0.340
Duration of illness	-0.003	0.029	-0.088	0.930
PSSS-R score[a]	0.003	0.014	0.230	0.818
Any anxiety disorder[b]	-0.689	0.428	-1.610	0.107
Any substance abuse[b]	0.267	0.355	0.752	0.452
Cluster A personality disorder[a]	-0.394	0.507	-0.778	0.437
Cluster B personality disorder[a]	0.481	0.407	1.181	0.237
Cluster C personality disorder[a]	0.935	0.455	2.052	0.040
HAM-D score[c,f]	0.072	0.031	2.296	0.022
Self-reported predictor variables ("subjective variables")	**Estimate (β)**	**S.E.**	**Est./S.E.**	**p**
MDE-level (within-level)				
Duration of MDE	0.002	0.001	3.871	<0.001
Sequence number of MDE	0.129	0.077	1.681	0.093
Patient-level (between-level)				
Age	-0.031	0.026	-1.199	0.231
Gender	0.061	0.445	0.136	0.892
Married or cohabiting[a]	0.354	0.346	1.024	0.306
Bipolar type	-0.433	0.383	-1.130	0.258
Psychotic symptoms lifetime[a]	-0.453	0.426	-1.064	0.287
Duration of illness	-0.009	0.027	-0.335	0.738
Any substance abuse[b]	0.412	0.383	1.076	0.282
BAI score[c]	-0.014	0.022	-0.629	0.530
HS score[c]	0.088	0.063	1.408	0.159
BDI score[c,d]	0.004	0.030	0.138	0.890
PSSS-R score[a]	0.008	0.016	0.494	0.622
Extraversion[a]	0.024	0.046	0.530	0.596
Neuroticism[e]	0.079	0.052	1.523	0.128

[a]baseline
[b]baseline, lifetime
[c]maximum score in follow-up
[d]items 2 and 9 omitted
[e]score during the lowest HAM-D score
[f]item 3 omitted

PSSS-R=the Perceived Social Support Scale-Revised
HAM-D=Hamilton Depression Scale
BAI=Beck Anxiety Inventory
HS=Beck Hopelessness Scale
BDI= Beck Depression Inventory

5.3 CLINICAL COURSE PREDICTS LONG-TERM OUTCOMES IN BIPOLAR DISORDER (STUDY III)

5.3.1 CLINICAL COURSE AND COMPLETION OF THE 5-YEAR FOLLOW-UP

In a previous study based on the 18-month follow-up, the course typology was established for 176 patients (Uher et al 2013), 111 of whom completed the 5-year follow-up. No course characteristics or membership of the major four course classes were associated with completing the 5-year follow-up (all $p>0.05$).

5.3.2 CLINICAL COURSE AND TOTAL TIME WITH MOOD SYMPTOMS

Between the 18-months and 5-year follow-ups (follow-up period 2), patients spent on average 47.2% of their time with mood symptoms, and there was no significant difference between BD I (45.8%) and BD II (48.7%) patients. Of the nine dimensional course characteristics from the first 18 months of follow-up (follow-up period 1), proportion of time depressed ($\beta=0.21$, 95% CI 0.14-0.27, $p<0.001$), severity of depressive symptoms ($\beta=0.09$, 95% CI 0.01-0.16, $p=0.023$), proportion of time manic ($\beta=0.08$, 95% CI 0.00-0.15, $p=0.047$) and transitions from depression to mania [$\beta=-0.09$, 95% CI -0.17- (-0.01), $p=0.026$] predicted time ill during follow-up period 2 in univariate analysis. These results remained significant after adjusting for age, gender, and BD type (Table 9). After correction for multiple testing, the proportion of time depressed during period 1 remained significant in predicting time ill during period 2. The proportions of variance in time ill explained by each of the four abovementioned course characteristics are seen in Table 9. No course classes or BD subtype predicted time ill during follow-up period 2. A multiple Tobit regression model with age, gender, and the four course characteristics identified as significant in univariate analysis explained 33 % of variance in time ill during the follow-up period 2. The predicted values correlated with observed values ($r=0.56$, $p<0.001$).

Table 9. Prediction of hospital admissions and time ill in the second follow-up period (from 18 months to 5 years) in the Jorvi Bipolar Study 5-year follow-up. Analysis adjusted for age, gender and BD type. Ordered logistic regression for hospital admissions and Tobit regression model for time ill.

	Hospital admissions					Time ill				
Predictor	Effect	95% CI		p	Pseudo R^2	Effect	95% CI		p	Pseudo R^2
	OR	lower	upper		(%)	beta	lower	upper		(%)
Course characteristics										
Proportion of time depressed	1.17	0.76	1.81	0.470	3.25	0.21	0.14	0.28	<0.001	26.77
Severity of depressive symptoms	0.92	0.61	1.39	0.681	2.98	0.09	0.01	0.16	0.025	4.17
Persistence of depressive symptoms	0.55	0.33	0.92	0.023	7.42	0.05	-0.02	0.13	0.180	1.74
Proportion of time manic	1.69	1.12	2.57	0.013	7.68	0.08	0.00	0.16	0.043	3.54
Severity of manic symptoms	1.77	1.10	2.83	0.018	7.40	0.02	-0.07	0.10	0.694	0.48
Persistence of manic symptoms	0.94	0.61	1.45	0.771	2.92	0.04	-0.04	0.12	0.306	1.17
Mixed symptoms	1.33	0.87	2.03	0.186	4.35	-0.06	-0.14	0.02	0.123	2.19
Transitions from depression to mania	2.39	1.08	5.30	0.032	9.02	-0.09	-0.17	-0.01	0.024	4.38
Transitions from mania to depression	1.43	0.89	2.27	0.137	4.65	-0.07	-0.15	0.00	0.067	2.94
Course classes										
Episodic bipolar course type	2.18	0.90	5.30	0.085	5.32	-0.11	-0.26	0.05	0.167	1.81
Depressive course type	0.57	0.21	1.52	0.259	4.02	0.06	-0.10	0.23	0.457	0.78
Bipolar disorder subtype										
Bipolar II vs I	0.42	0.17	1.02	0.056	3.01	0.01	-0.15	0.16	0.925	0.37

5.3.3 CLINICAL COURSE AND HOSPITAL ADMISSIONS

During follow-up period 2, altogether 31 (28%) of the 111 patients were admitted to a psychiatric hospital and 16 of them (14%) more than once. The admission rate was higher for BD I patients (21/59, 36%) than for BD II patients (10/52, 19%), and 11/59 (19%) BD I and 5/52 (10%) BD II patients had multiple admissions. However, the difference in the rate of admissions was not significant between BD I and II patients ($c^2[2]=3.69$, p=0.158). Of the nine dimensional course characteristics, proportion of time manic (OR=1.75, 95 % CI 1.17-2.63, p=0.007), severity of manic symptoms (OR=1.90, 95% CI 1.23-2.94, p=0.004) and transitions from depression to mania (OR=2.39, 95% CI 1.11-5.12, p=0.026) predicted higher rates of hospital admissions in univariate analysis. Persistence of depressive symptoms (OR=0.54, 95% CI 0.32-0.89, p=0.015) predicted a lower rate of hospital admissions. These results remained significant after adjusting for age, gender, and BD type (Table 9). After correction for multiple testing, severity of manic symptoms remained significant in predicting hospital admissions. No course classes or the BD subtype predicted the rate of hospital admissions, but a non-significant trend for less admissions among BD II patients was found (OR=0.42, 95% CI 0.18-1.00, p=0.051). The proportions of variance in rate of admission explained by abovementioned course characteristics are seen in Table 9. A full prediction model with the proportion of time manic, manic symptoms severity, depression-to-mania switching, age, gender, and type of BD type explained 18% of the variance in hospital admissions.

5.4 PREDOMINANT POLARITY IN BIPOLAR I AND II DISORDERS: A FIVE-YEAR FOLLOW-UP STUDY (STUDY IV)

About half of all patients in the cohort, 98 of 188 patients (52%), had a predominant polarity. The PP was manic in 30 (16%), depressive in 68 (36%), and in 90 (48%) patients no predominant polarity could be assigned. The impact of the different definitions on the proportions of PP is presented in Table 10. The baseline sociodemographic and clinical characteristics differed between the three groups with regard to BD type, type of index phase, type of first illness phase, occurrence of lifetime psychotic symptoms, anxiety disorders and substance abuse disorders, and outpatient versus inpatient status at intake (Table 11), but not with regard to gender, age, occurrence of lifetime SAs, rapid cycling, or personality disorders.

During the 5-year follow-up 44.4% of the MP group, 40.5% of the NP group, and 34.8% of the DP group was hospitalized at least once. No difference emerged in the number of hospitalizations during follow-up between the MP, NP, and DP groups (means 1.7, 1.2, and 0.7, respectively, median 0.00 for all groups) in Poisson regression analyses after adjustment for age, gender, and

BD type. However, there was a tendency for patients in the MP group to have more hospital admissions than patients in the DP group (B=0.441, p=0.056), and patients in the NP group were most often inpatients at intake (Table 11). At intake, inpatients in the MP group were hospitalized exclusively for manic (88.9%) or mixed state (11.1%), in the DP group more often for MDE (71.4%) than for manic (14.2%) or mixed state (14.3%), and in the NP group more often for MDE (65.0%) than for manic (25.0%) or mixed state (10.0%).

Table 10. Proportions of dominant polarity depending on different definitions among the 188 patients in the Jorvi Bipolar Study[a]. All definitions use the threshold of ≥ 66.7 % (2/3) of episodes required to be either (hypo)manic or depressive in order to fulfill the criteria of the corresponding polarity.

	All N=188 N (%)	Bipolar I N=88 N (%)	Bipolar II N=100 N (%)
Definition 1:			
WITHOUT MIXED PHASES			
(mixed phases not included in the total sum of phases)			
Manic polarity	28 (15%)	15 (17%)	13 (13%)
Depressive polarity	74 (39%)	27 (31%)	47 (47%)
No polarity dominance	86 (46%)	46 (52%)	40 (40%)
Definition 2:			
WITHOUT MIXED PHASES			
(mixed phases included in the total sum of phases)			
Manic polarity	21 (11%)	13 (15%)	8 (8%)
Depressive polarity	44 (23%)	13 (15%)	31 (31%)
No polarity dominance	123 (65%)	62 (70%)	61 (61%)
Definition 3:			
ALL MIXED PHASES SUMMED WITH DEPRESSIVE PHASES			
Manic polarity	21 (11%)	13 (15%)	8 (8%)
Depressive polarity	90 (48%)	35 (40%)	55 (55%)
No polarity dominance	77 (41%)	40 (45%)	37 (37%)
Definition 4:			
ALL MIXED PHASES SUMMED WITH MANIC PHASES			
Manic polarity	41 (22%)	22 (25%)	19 (19%)
Depressive polarity	44 (23%)	13 (15%)	31 (31%)
No polarity dominance	103 (55%)	53 (60%)	50 (50%)
Definition 5:			
MIXED PHASES (Bipolar I[b]) SUMMED WITH MANIC PHASES AND DEPRESSIVE MIXED PHASES (Bipolar II) SUMMED WITH DEPRESSIVE PHASES			
Manic polarity	30 (16%)	22 (25%)	8 (8%)
Depressive polarity	68 (36%)	13 (15%)	55 (55%)
No polarity dominance	90 (48%)	53 (60%)	37 (37%)

[a] patients with more than 100 phases (N=3) excluded from the analysis
[b] mixed and depressive mixed not specified for BD I patients

Table 11. Significant sociodemographic and clinical characteristics of 188 bipolar patients with manic and depressive predominant polarity and without polarity dominance in the Jorvi Bipolar Study.

Variable	MP[a] (N=30) N (%)	NP[b] (N=90) N (%)	DP[c] (N=68) N (%)	Sig. χ^2	p
BD type				34.694	<0.001
I	22 (73.3)	53 (58.9)	13 (19.1)		
II	8 (26.7)	37 (41.1)	55 (80.9)		
Depressive index phase	9 (30.0)	54 (60.0)	42 (61.8)	9.723	0.008
First phase of illness				35.451	<0.001
Mania/hypomania	17 (56.7)	15 (16.9)	9 (13.4)		
MDE[d]	4 (13.3)	48 (53.9)	44 (65.7)		
Mixed phase	2 (6.7)	1 (1.1)	1 (1.5)		
Polyphasic episode	7 (23.3)	25 (28.1)	13 (19.4)		
Psychotic symptoms, lifetime	21 (70.0)	48 (53.3)	27 (39.7)	8.001	0.018
Any anxiety disorder, lifetime	10 (33.3)	45 (50.0)	44 (64.7)	8.708	0.013
Any substance abuse, lifetime	12 (40.0)	55 (61.1)	29 (42.6)	7.033	0.030
Inpatient at intake	9 (30.0)	40 (44.4)	14 (20.6)	10.091	0.006

[a] manic predominant polarity
[b] no predominant polarity
[c] depressive predominant polarity
[d] major depressive episode

5.4.1 IMPACT OF PREDOMINANT POLARITY ON COMORBIDITY AND CLINICAL VARIABLES

The results of the univariate multinomial regression model for clinical variables and comorbid disorders are shown in Table 12. In the adjusted model, the MP group had a lower prevalence of lifetime comorbid anxiety disorders, more often (hypo)manic first phase of the illness, and less frequently MDE as the first phase of the illness relative to the DP group. In the non-adjusted model, in addition to the forementioned variables, also more frequent occurrence of lifetime psychotic symptoms was associated with the MP group (OR=1.1882, 95% CI 1.189-2.891, p=0.007), and more frequent occurrence of comorbid lifetime substance abuse with the NP group (OR=2.113, 95% CI 1.113-4.011, p=0.022).

Table 12. Multinomial univariate logistic regression of baseline lifetime comorbid disorders and clinical variables for polarity groups in the Jorvi Bipolar Study. Depressive polarity group is set as the reference category. All analyses adjusted for age, gender, and bipolar type.

	No polarity			Manic polarity		
Comorbid disorder/ clinical variable	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Any anxiety disorder, lifetime	0.654	0.324–1.319	0.236	0.334	0.125–0.888	0.028
Any substance abuse, lifetime	1.585	0.776–3.234	0.206	0.579	0.213–1.573	0.284
Cluster A personality disorder	1.937	0.534–7.031	0.315	3.314	0.719–15.272	0.124
Cluster B personality disorder	1.679	0.766–3.681	0.196	0.986	0.327–2.971	0.980
Cluster C personality disorder	1.213	0.541–2.723	0.639	0.771	0.234–2.539	0.668
Psychotic symptoms, lifetime	1.045	0.727–1.502	0.812	1.376	0.827–2.290	0.220
First phase MDE[a]	0.589	0.280–1.240	0.163	0.075	0.022–0.261	<0.001
First phase (hypo)manic	1.232	0.469–3.235	0.672	7.829	2.587–23.689	<0.001
Rapid cycling, baseline	1.115	0.770–1.616	0.563	0.738	0.421–1.296	0.290

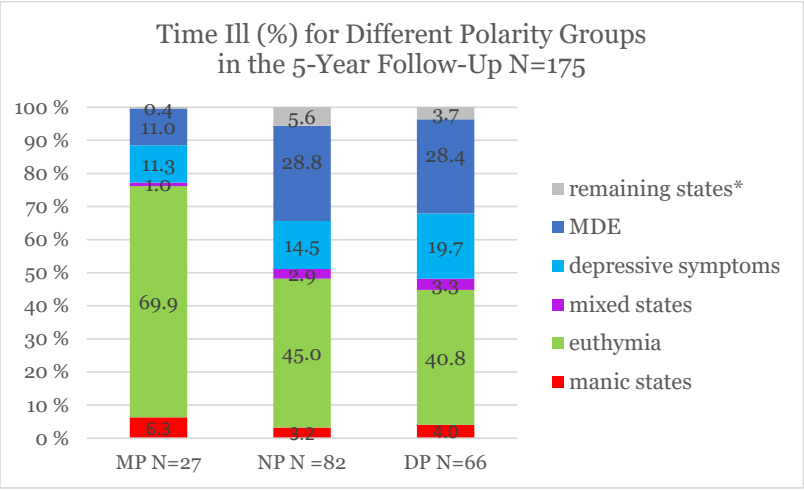
[a]major depressive episode

5.4.2 THE PREDICTIVE VALIDITY OF PREDOMINANT POLARITY IN TIME SPENT ILL AND NUMBER OF PHASES IN FOLLOW-UP

The time spent in different illness states during the 5-year follow-up for the manic, depressive, and no polarity groups is seen in Figure 5. Within the whole sample (N=175), the three groups differed in proportions of time spent in MDEs (median proportions in follow-up 3.5%, 22.8%, and 30.0%, respectively, H=24.407, df=2, p<0.001), in manic states (median proportions in follow-up 3.7%, 1.1%, and 1.0%, respectively, H=7.373, df=2, p=0.025) and in euthymia (median proportions in follow-up 76.7%, 28.2%, and 38.7%, respectively, H=18.731, df=2, p<0.001). All of these differences were statistically significant also among BD I patients (N=80, p-values 0.005, 0.002, and 0.037, respectively), but among BD II patients (N=95), only the difference in time spent in MDEs remained significant (p=0.008).

In post hoc pairwise Kruskall-Wallis comparisons, the MP group spent more time euthymic than the DP group (p<0.001) or NP group (p=0.001), less time in MDEs than the DP group (p<0.001) or NP group (p<0.001), and more time in manic or hypomanic states than the DP group (p=0.019) or NP group (p=0.008).

In Poisson regression models, adjusted for BD type, age, and gender, the DP group had smaller total number of phases in follow-up than the NP group (B=-0.223, p=0.005) and less MDEs than the NP group (B=-0.250, p=0.022). The MP group had more manic phases than the NP group (B=0.519, p<0.001) or DP group (B=0.747, p<0.001), less MDEs than the NP group (B=-0.615, p<0.001) or DP group (B=-0.365, p=0.049), and less mixed phases than the NP group (B=-0.779, p=0.025).



**Remaining states include hypomanic symptoms, cyclothymia, mood episodes caused by substance use, and state not possible to classify. MP=manic polarity, NP=no polarity, DP= depressive polarity*

Figure 5. Time ill for the different polarity groups in the 5-year follow-up of the Jorvi Bipolar Study.

5.4.3 IMPACT OF PREDOMINANT POLARITY ON SUICIDE ATTEMPTS IN FOLLOW-UP

The overall incidence rate of SAs per 1000 patient-years was 126 (95% CI 102-155). The incidence for the MP group was the lowest, 32/1000 person-years (95% CI 12-86), followed by the incidence of 127/1000 person-years for the NP group (95% CI 94-172) and 170/1000 person-years for the DP group (95% CI 126-228) (Figure 6).

In Poisson regression analysis, patients in the MP group had significantly fewer suicide attempts than patients in the DP group (B=-1.660, p=0.001) or the NP group (B=-1.366, p=0.009). When age, BD type, gender, and time spent in high-risk states for suicide attempts (MDE and mixed states) were adjusted, the results remained but were attenuated.

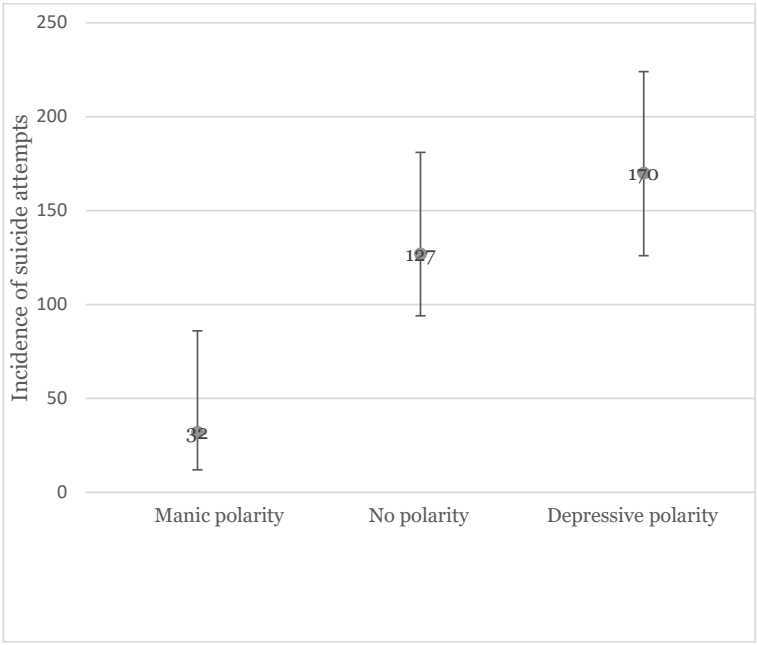


Figure 6. Incidence of suicide attempts in the different polarity groups in the 5-year follow-up of the Jorvi Bipolar Study.

5.4.4 STABILITY OF THE CONCEPT OF PREDOMINANT POLARITY IN FOLLOW-UP

The proportions of predominant polarity varied depending on the time-period used when defining the polarity. When using the pool of phases from the time of the first illness phase (lifetime) to baseline (median time 12.1 years) versus the pool of phases in the 5-year prospective follow-up (median follow-up time 5.3 years), predominant polarity remained the same for 42.7% of the cohort. The polychoric correlation for the stability was found to be 0.407, meaning that a latent polarity continuum explained $0.407^2 \times 100\% \approx 16.6\%$ of the follow-up polarity continuum. When excluding the patients with less than three phases in follow-up, the predominant polarity remained the same for 47% of the patients in the follow-up compared with the time period up to baseline. However, when comparing the predominant polarity defined by the count of phases before baseline with that of the whole illness duration (from the first illness phase lifetime to the end of the 5-year follow-up, excluding the patients with no phases in follow-up), the stability increased to 75.9%.

6 DISCUSSION

6.1 MAIN FINDINGS

In this prospective study, we followed an epidemiologically representative clinical cohort of secondary care BD I and II patients for 5 years. Almost all patients recovered from the index episode (i.e. the episode at intake), but nearly 90 % had at least one recurrent episode during the 5-year follow-up and half had three or more recurrences. The patients were euthymic about half of the follow-up time, in different illness episodes about one-third of the time, and with subthreshold symptoms about one-sixth of the time. When controlling for confounding factors and conducting the analysis at the patient level, there was no difference in the time spent in depressive states between BD I and II patients. In univariate Cox regression analysis, many factors predicted time to full remission and time to first recurrence, but in multivariate analysis only severity of depression and cluster C personality disorder (for time to remission) and the occurrence of lifetime psychotic symptoms (for time to recurrence) were significant predictors.

During the follow-up (median 62.2 months) there were 90 suicide attempts per 718 patients-years by 50/177 patients. Most patients (56%) had one SA, 30% had two SAs, and 14% had three or more SAs. The majority of the attempts (65/90, 72%) took place during MDEs due to markedly more time spent in depression than in other illness states. However, we confirmed our earlier finding from the 18-month follow-up, that the incidence of SAs is highest in mixed states (mixed and depressive mixed combined), over 120-fold that in euthymia, but also very high in MDEs, over 60-fold that in euthymia. The analysis of risk factors during different episodes was possible only for SAs during MDEs because of the statistically too small number of SAs during other phases. During MDE the duration and highest measured severity of depression during follow-up and the presence of cluster C personality disorder at baseline increased the risk of SA.

The dimensional characteristics of the medium-term (18-month) clinical course predicted long-term outcomes in the 5-year follow-up. The strongest predictive relationship was between the proportion of time depressed (including both MDEs and sub-syndromal depressive symptoms) during the initial 18 months and the total time ill over the subsequent time period of up five years. The severity of manic symptoms, reflecting a propensity to full-blown manic episodes, during the initial 18 months was the strongest predictor of hospital admission in the follow-up from 18 months to 5 years. The dimensional severity of manic symptoms during the first 18 months predicted hospital admissions better than BD type, and the prediction remained significant after controlling BD type. The propensity to switch from depression directly to mania (during the first 18 months) without an intervening period

of euthymia was associated with a lower proportion of time ill and a greater likelihood of hospital admission in follow-up from 18 months to 5 years.

About half of the patients had a predominant polarity pattern. In 16 % of the patients, the PP was manic, in 36% depressive and in 48% no predominant polarity could be assigned. The three polarity groups differed in proportions of time spent ill, the MP group spending more time in euthymia, less time in MDEs, and more time in manic states than the DP and NP groups. The incidence of SAs was significantly lower in the MP group than in the other two groups. The MP group had lower prevalence of lifetime comorbid anxiety disorders and more often (hypo)manic first phase of the illness than the DP group, but more often lifetime psychotic symptoms. Overall, including all three polarity groups, the analysis revealed that the MP group had a better prognosis than the other two groups, which resembled each other in many respects.

6.2 DISCUSSION OF METHODS

6.2.1 SCREENING

At baseline, a large number of psychiatric patients (N=1630) treated or seeking treatment in secondary-level care were screened with MDQ. A pilot study of the JoBS (Isometsä et al., 2003) found high sensitivity (0.85), but moderate specificity (0.47) for the MDQ as a screening tool for BD. Based on the pilot study, modification of the cut-off point was implemented and patients without problems due to episodes were included to increase the sensitivity for BD II. The higher sensitivity resulted in a higher number of false positives to be excluded in the subsequent SCID-I interview. Screening enabled inclusion of patients without clinical diagnosis of BD.

6.2.2 REPRESENTATIVENESS OF THE COHORT

The main strength of the study is the epidemiological representativeness of the cohort including both BD I and II patients with an acute episode treated in secondary-level psychiatric care. Screening with MDQ was another major strength of the study, resulting in both clinically diagnosed and undiagnosed patients being included in the cohort. Sampling at the beginning of a new phase enabled assessment of time-related outcome measures such as time to remission and time to recurrence. Inclusion of all types of index episodes allowed analysis of the effect of type of index episode on outcome. It is unlikely that large numbers of BD I patients would fail to contact psychiatric care in an acute phase, but the possibility of being untreated or treated elsewhere is more likely with (undiagnosed) BD II.

6.2.3 DIAGNOSTIC MEASURES

After positive MDQ, the diagnoses of BD and comorbid disorders were assigned by psychiatrists with a minimum of 5 years of clinical experience using SCID-I interview (First et al., 2002). The interrater reliability for the diagnosis of BD was excellent (kappa 1.0 for both BD I and II) – however, the reliability of comorbid diagnoses was not evaluated. Axis II diagnoses were assigned using the SCID-II interview for DSM-IV (First et al., 1997). Since the sampling was done in an acute phase, the possibility of an effect of acute symptomology on the assessment of personality cannot be totally excluded. However, patients were met three times and the assessment was done in a later subacute phase. Furthermore, the diagnoses of personality disorders were based on multiple sources of information.

6.2.4 LIFECHART METHODOLOGY

The most important methodological strength of the study was the use of lifechart methodology, which enabled assessment of time-related outcome measures, such as suicide attempts, and their timing in different illness phases. A method similar but not identical to the Longitudinal Interval Follow-up Evaluation (LIFE) and NIMH lifechart methodology was used, originally planned and used in the Vantaa Depression Study (Melartin et al., 2004). As with LIFE, change points in psychopathologic state of the patient were examined by using probes related to important life events. Unlike LIFE, the lifechart used in JoBS was made directly and strictly comparable with DSM-IV criteria with two exceptions: minimum duration of hypomania was defined at 2 days instead of 4 and the depressive mixed state was defined according to Benazzi and Akiskal (2001). The patients' follow-up time was classified into nine (ten in the 5-year follow-up) different mood periods and euthymia according to DSM-IV plus depressive mixed states. Symptomatic periods not fulfilling the criteria of any mood episodes were recorded as well. Although maximizing the reliability by using all available sources of information including patient records and family members and constructing the lifechart in thorough follow-up interviews, the underreporting of milder illness phases such as short hypomanic or depressive mixed episodes, cannot be excluded. This is the case in any longitudinal study not using daily prospective ratings (Judd et al., 2003d). In addition to lifechart ratings, many subjective and objective measures were used to comprehensively evaluate different domains of risk factors.

At the 5-year interview, due to the retrospective time coverage being significantly longer than at the 6-month and 18-month interviews, a category of time period "not known" was included to avoid bias in situations in which the interviewer could not classify a certain period of the follow-up reliably. However, this category of unknown time period covered only 3% of the whole follow-up time of all interviewed patients at 5 years (Figure 4).

6.2.5 STUDY LIMITATIONS

Despite extensive efforts to reach all patients at the 5-year interview, loss of patients could not be avoided. Of the original cohort, 61.7% of living patients were interviewed at 5 years. Those not interviewed were more often women, younger, had rapid cycling and higher SOFAS scores. However, with respect to many outcome measures such as time to remission or time to recurrence, the 18-month data provided the information, i.e. if the missing patient had already reached remission or had a recurrence by the 18-month follow-up. Only 14/191 patients (7.3%) missed all three follow-up interviews. Overall, although some attrition figures suggest that the missing patients in the main analysis likely had worse outcome (i.e. rapid cycling and higher BDI scores at baseline), the missing patients did not differ in variables such as occurrence of hospitalizations, suicide attempts, or psychotic symptoms.

At 5 years, the bias in patient recollection of milder illness episodes between the 18-month and 5-year interviews is potentially stronger due to longer retrospective time period covered than in earlier interviews, but it is unlikely that major mood episodes or long periods of euthymia were missed. Crude outcome measures were deliberately used to maximize the validity of lifechart data. The study was naturalistic, and thus, the influence of treatment on outcome measures could not be controlled. The size of the cohort was moderate for a long-term study, and statistical power was limited in some analyses. What is regarded as a long-term follow-up in mood disorders is relative, but obviously 5 years is only a small proportion of a lifelong illness course.

In Study II, occurrence of SAs might have biased the recall of depression or mixed states, possibly inflating their association with SAs. Levels of hopelessness, depression and anxiety could be measured only at the time of the interviews, leaving unknown their influence on suicidality on a daily basis. The role of affective temperaments or impulsive-aggressive traits in SAs during MDEs was not measured, but the examination of the role of cluster B personality disorders compensated this deficiency to some extent. The analysis of risk factors of SAs during states other than MDE was not possible because of statistically too small numbers of SAs during these other states. When assessing risk factors for SAs during MDEs, preceding suicidal ideation and attempts as predictors were deliberately excluded to avoid circularity. When entered into the model, both were highly significant indicators of risk for SAs. The vast differences in incidence of suicide attempts during different illness states were accompanied by relatively large confidence intervals.

Study III included only patients who completed both 18-month and 5-year follow-up (N=111). The participants who completed the 5-year follow-up were older and more often men, and consequently, the results may be less generalizable to younger individuals and women. The analyses were limited to two outcomes (hospital admissions and total time ill), and it is possible that different results may have been obtained had additional outcomes been

included (Arvilommi et al., 2015). The effects of relatively uncommon course characteristics were not examined due to limited statistical power.

In Study IV, when defining the polarity, the retrospective counting of former lifetime phases at baseline may be vulnerable to recall bias, but this is a general problem in cross-sectional studies defining predominant polarity. Assignment of dominant polarity may necessitate a sufficient number of illness phases, and as the cohort included patients with very recent onset of illness, and thus, in some cases no or very few retrospective and/or prospective illness phases, spurious findings cannot be totally excluded.

6.3 DISCUSSION OF RESULTS

6.3.1 FIVE-YEAR OUTCOME OF BIPOLAR I AND II DISORDERS: FINDINGS OF THE JORVI BIPOLAR STUDY (STUDY I)

Overall, the patterns of illness course that we perceived in this predominantly outpatient cohort including both BD I and II patients were mostly in line with the previous literature. However, rather than chronicity, if defined as persistence of the index episode, our findings emphasize the recurrent and pleomorphic course of BD. The findings of our study indicate that in both BD I and BD II the illness episodes are highly recurrent and, in accord with large prospective long-term cohort studies of CDS (Judd et al., 2002, Judd et al., 2003b), patients suffer from symptoms about half of the time and illness course is dominated by depressive polarity. Shorter term studies have revealed similar results (Joffe et al., 2004). We found chronicity of the index episode to be more rare (1.3% of subjects) than previous studies from the era preceding the current treatment options and including only BD I patients (Winokur et al., 1994). Consistent with earlier studies on BD I patients (Keller et al., 1993), we found patients with manic index phases to have shorter time to full remission than others, reflecting the often more chronic nature of depression realtive to mania and, as a possible confounding factor, potentially more efficient treatments available for mania than depression (Yatham et al., 2018, Vieta et al., 2018a). Concordant with findings in unipolar depression (Melartin et al., 2004), severity of depression also predicted time to remission.

Based on the findings of earlier literature (Judd et al., 2003d) and previous findings of the JoBS cohort (Mantere et al., 2008), we expected BD II patients to spend more time in depressive states than BD I patients. However, the analysis at the patient level revealed only a small, statistically non-significant difference. Similar tendency to depressive states may appear unlikely in clinical practice, since BD II patients are often treated for depression, whereas the full-blown manic states of BD I patients may seem to dominate their clinical picture. Our finding of no difference in time spent in the depressive states between BD I and BD II patients is consistent with medium-term studies (Joffe et al., 2004, Post et al., 2003), but contrary to earlier long-term

studies (Judd et al., 2003d). Methodological differences are likely to explain some of the discrepancies. Also, based on our 18-month findings of the JoBS cohort, the type of index phase may be a confounding factor in outcome between BD I and BD II (Mantere et al., 2008), and the influence of the type of index episode on outcome becomes diluted over time. An extended time frame may be needed to observe the significance of depression also for the course of BD I.

Research data on the influence of psychiatric comorbidity on long-term outcome of BD is limited. The 18-month findings from the JoBS cohort and the Vantaa Depression Study cohort (N=269) showed that MDD patients had more Axis I comorbid disorders and cluster A and C personality disorders, whereas BD patients had more cluster B personality disorders. In previous 18-month study of the JoBS cohort, no difference in current overall comorbidity between BD I and BD II patients was found, but the prevalence of comorbidity varied strongly with current illness phase (Mantere et al., 2006). Findings of Post et al. (2018) regarding Axis II comorbidity are concordant. The relevance of comorbid anxiety in both unipolar depression and BD is well acknowledged (Goldberg, Fawcett, 2012, Pavlova et al., 2015), and anxiety is known to correlate with long-term depressive morbidity in BD (Coryell et al., 2009, Coryell et al., 2012). In the analyses, we focused on baseline Axis I and II disorders as predictors for the outcome of patients with depressive index phase. In univariate analyses, DSM-IV anxiety disorders overall and, of the discrete disorders, obsessive-compulsive disorder (OCD), were predictors of poor outcome in terms of longer time to full remission. However, in multivariate analysis with such covariates such as cluster C personality disorders and severity of depression, these findings lost statistical significance. Also, it must be noted that the number of comorbid OCD cases among patients with a depressive index phase was small (N=6), which limits the statistical power and increases the risk of spurious findings. Nevertheless, OCD symptoms in BD are common, difficult to treat and according to a recent systematic review (Amerio et al., 2014), often have an episodic course dependent on mood episodes rather than representing a separate disease. In our 5-year analysis, the same kind of pattern applied to comorbid lifetime alcohol dependence; it predicted longer time to full remission in the univariate model, but in the multivariate model comorbid substance use disorders were no longer significant predictors for outcome. Overall, in this study, of all DSM-IV Axis I and II comorbid disorders, only cluster C personality disorders had an independent role in predicting the outcome.

Although comorbid personality disorders are frequent in mood disorders, cluster B and C being most common in BD (Mantere et al., 2006, Friborg et al., 2014), knowledge of the effect of cluster C personality disorder on long-term outcome of BD is sparse. However, cluster C personality disorders are known to have negative influence on the outcome of unipolar depression (Viinamäki et al., 2003, Newton-Howes et al., 2014), and our findings that comorbid cluster C personality disorder and severity of depression predict

longer time to full remission, are concordant with findings in unipolar depression (Melartin et al., 2004, Holma et al., 2008a). The traits of avoidant and obsessive-compulsive personality are strongly related to anxiety disorders and share with them the same predisposing temperament features such as high neuroticism (Jylhä, Melartin & Isometsä, 2009, Ormel et al., 2013). High neuroticism is associated with a higher prevalence of comorbidity in unipolar depression (Jylhä, Melartin & Isometsä, 2009) and patients with BD are unlikely to differ in levels of neuroticism compared with patients with MDD (Jylhä et al., 2010). More research on this topic is needed to clarify the links between BD, neuroticism, and comorbidity.

Our finding that lifetime psychotic symptoms predicted shorter time to first recurrence in patients with a depressive index phase (also after controlling for BD type and severity of depression) are concordant with findings of a 10-year follow-up study of BD I patients, where the occurrence of concurrent delusional symptoms was associated with poor prognosis (Turvey et al., 1999b). Similarly, in a 12-year follow-up of both BD I and II patients, the group with psychotic features spent the highest proportion of time ill and had the highest recurrence rate (Tondo, Vazquez & Baldessarini, 2017). Former psychotic symptoms in the current study may be related to either depression with psychotic features or manic psychosis and can therefore be considered (only) as an indicator of the severity of the illness in general. However, the association may be more diverse than that, and thus, the definite implications on the basis of this cohort remain obscure.

Only 49.2% of the euthymic patients were working or studying at the time of the 5-year interview. This is in line with previous studies showing that syndromal recovery does not correlate with functional recovery in BD (Tohen et al., 2003).

6.3.2 INCIDENCE AND PREDICTORS OF SUICIDE ATTEMPTS IN BIPOLAR I AND II DISORDERS: A 5-YEAR FOLLOW-UP STUDY (STUDY II)

The long-term follow-up of the Jorvi Bipolar Study reveiled that suicide attempts in BD take place almost exclusively during illness episodes. The main finding of the study on suicide attempts was the vast differences in incidences of SAs during different illness states. These large variations in incidence of suicide attempts being dependent on the illness state are consistent with findings in an earlier 18-month follow-up of the JoBS cohort (Valtonen et al., 2008, Holma et al., 2014) as well as with previous lifechart-based studies on unipolar depression in psychiatric care (Holma et al., 2010) and in primary health care (Riihimäki et al., 2014), which found that SAs cluster in MDEs. Concordant with our findings, a large American multicenter medium-term follow-up study of BD patients reported that the proportion of days depressed in the past year were associated with both SAs and completed suicides (Marangell et al., 2006). Furthermore, a prospective post-discharge study of

unipolar patients (Oquendo et al., 2002) found that in a 2-year follow-up the presence of MDE increased the risk of suicide attempt up to 7-fold. Somewhat surprisingly, Tondo et al. (2016) observed in their meta-analysis that the incidence of SAs in BD continued to decrease the longer the time at risk. The same pattern was found in the cumulative incidence of suicides in the Danish register-based study of suicides in mental disorders (Nordentoft, Mortensen & Pedersen, 2011), which noted that the incidence of suicides in BD plateaus towards the end of the follow-up. The findings of the current study are in line with the forementioned results and provide possible reasons for the plateau pattern of incidence of SAs in BD. The overall incidence of SA's in our cohort more than halved during the follow-up period from 18 months to 5 years relative to that of the first 18 months of the follow-up (84/1000 and 192/1000 patient-years, respectively). Towards the end of the follow-up, patients spend a much smaller proportion of follow-up time in high-risk states, which is a probable explanation for the decrease in incidence rates of suicide attempts by the end of follow-up. During the follow-up period from 18 months to 5 years, the proportion of time spent in MDE was only 20.6%, whereas during the first 18 months of follow-up it was 33.5 %. The proportions of time spent in mixed states were 1.9% and 4.1%, respectively. The declining total incidence of SAs at longer time at risk is a logical consequence of BD patients spending less time in high-risk states in longer follow-up.

Whether or not the patterns of incidence of suicides in BD are similar to that of suicide attempts is not known, but there is some research supporting this presumption. The results of a psychological autopsy study of suicides in BD are consistent with our incidence findings (Isometsä et al., 1994). Furthermore, large temporal variations in risk of suicide after discharge from a psychiatric hospital among BD patients have been found (Qin, Nordentoft, 2005), and the risk of post-discharge suicide varies by the type of index episode (Isometsä, Sund & Pirkola, 2014). As the potency of risk variation by illness state that we found (up to 120-fold) was an order of magnitude higher than those of any high-risk trait characteristic (rarely over 6-fold), we conclude that it is likely more important to recognize the high-risk states and reduce the time spent in them than to identify potential trait predictors for SAs. Contrary to many high-risk trait characteristics, clinical high-risk states are also potentially more modifiable by treatment. Thus, in clinical practice, recognition and treatment of the high-risk mixed and depressive states form the cornerstone of suicide prevention in BD.

Risk factors for SAs may differ from risk factors for suicide in BD (Schaffer, et al., 2015b), but a previous deliberate self-harm is a known predictor of suicide, and the risk may remain for decades after a SA (Suominen et al., 2004). A Swedish register-based study found that after previous self-harm, among psychiatric diagnoses, BD implied the highest risk of suicide. Of those with BD who used other methods than self-poisoning for their index SA, one-fifth committed suicide after 3-9 years (Runeson et al., 2016).

A previous report of the JoBS study on suicidal behavior in BD reported the risk factors during specific high-risk states of MDE and mixed episodes (Valtonen et al., 2007). Our study revealed that during MDEs, the duration of the MDE, the severity of depression, and the presence of cluster C personality disorder increase the risk of SA. Concordant results were found in the study of three prospective cohorts of bipolar and depressive disorder patients: comorbid personality disorder increased the risk of SA to about 2-fold (Jylhä et al., 2016). The excess risk was mostly due to patients with comorbid disorder spending more time in depressive episodes than those without this comorbidity, but there were direct risk-modifying effects as well. Risk factors for SAs in BD may exert their effects in multiple ways, either indirectly influencing the time spent ill or directly affecting the risk during high-risk states (Jylhä et al., 2016, Jylhä et al., 2016). However, a suicidal act is almost invariably a result of multiple rather than single risk factors operating simultaneously (van Heeringen, 2012). The risk factors that we found in univariate logistic regression analyses (i.e. when ignoring data on timing of SAs) were in accord with those noted in recent meta-analyses (Schaffer et al., 2015a, 2015b, 2015c). In multivariate analysis, younger age, hopelessness, neuroticism, and severity of depression remained significant predictors of SAs. Due to the small number of SAs during mixed states, the factors moderating the risk during these states could not be analyzed. Contrary to our expectations, we did not find cluster B personality disorder (Schaffer et al., 2015b) or female gender (Tondo et al., 2016) to predict SAs in BD patients when depressed.

6.3.3 CLINICAL COURSE PREDICTS LONG-TERM OUTCOMES OF BIPOLAR DISORDER (STUDY III)

Consistent with previous results that the illness course of both BD I and II is dominated by depressive symptoms (Judd et al., 2002), we found based on the analysis of dimensional course characteristics that the strongest predictive association was between the proportion of time depressed (including both subsyndromal depressive symptoms and major depressive episodes) during the initial 18 months and the total time ill over the subsequent 4-year follow-up. In turn, severity of manic symptoms during the first 18 months was the strongest predictor of hospital admissions during the next four years. Noteworthy is that the dimensional severity of manic symptoms predicted hospital admission better than the BD type, also when controlling for BD type in the analysis. These findings imply that specific clinical course characteristics (time depressed and dimensional measure of manic symptom severity) may have implications for service planning, considering that the total time ill is known to be linked to functional and occupational deficiencies in BD (Judd et al., 2005, Grande et al., 2013, Arvilommi et al., 2015, Forte et al., 2015) and hospital admissions account for a notable proportion of care costs

associated with BD (Das Gupta, Guest, 2002, Hong et al., 2010, Kessing et al., 2013, Hidalgo-Mazzei et al., 2015).

In addition to the abovementioned strong associations between specific course characteristics and outcome, some additional features of clinical course emerged as significant predictors of long-term outcome. The propensity to switch from depression directly to mania without an intervening period of euthymia was found to be associated with a lower proportion of time ill in follow-up, but, at the same time, with a greater likelihood of hospital admission. Patients with a depression-to-mania switching pattern may not respond to lithium treatment in an optimal manner (Koukopoulos, Sani, 2014), and a different treatment approach may be needed to prevent such transitions and reduce the risk of hospital admission in patients with this illness course (Kessing et al., 2013).

In our study, the dimensional course characteristics predicted the long-term outcomes, but the categorical typology grouping patients into distinct course classes (Uher et al., 2013) or the distinction between BD I and BD II did not. The fact that the two main classes from the earlier 18-month analysis did not predict the outcomes may be due to their typology being more related to the presence of manic symptoms (which predicted the total time ill only weakly) than the burden of depression (which appeared to be a stronger predictor of total time ill), and, on the other hand, to an inherent limitation of categorical measures when relative to dimensional indicators (Prisciandaro, Roberts, 2009). Along with the historical distinction of bipolar subtypes, continuous course descriptors of BD may be utilized in research and clinical practice. The highly variable illness courses of BD patients with regard to frequency, duration and polarity of the episodes is a challenge in clinical practice, and utilization of clinical course characteristics may help in differentiating the patients who need treatment focused on bipolar depression and functional rehabilitation, and those who primarily need active prevention of manic episodes and risk of hospitalization (Kessing et al., 2013).

6.3.4 PREDOMINANT POLARITY IN BIPOLAR I AND II DISORDERS: A 5-YEAR FOLLOW-UP STUDY (STUDY IV)

Although predominant polarity has been extensively investigated in cross-sectional and retrospective designs, few prospective studies exist on the effect of PP on outcome of BD (Carvalho et al., 2014, Belizario, Silva & Lafer, 2018). To our knowledge, no previous studies including both BD I and II patients have examined the predictive validity in terms of time spent ill. In our prospective 5-year follow-up, we found that patients in manic, depressive, and no-polarity predominant polarity groups differed in their clinical outcome. Patients in the MP group seemed to have better prognosis than those in the DP and NP groups in many respects. The MP group spent more time in euthymia, less time in MDEs, and expectedly more time in manic states than the other two groups. However, higher frequency of hospitalizations was not

discovered among the MP group, probably because there are multiple indications besides full-blown mania (e.g. psychotic depression) for hospitalization among BD patients. The differences in time ill were significant also in the subgroups of BD I patients, but for the BD II group the findings remained only for time spent in MDEs, almost reaching significance also for time spent euthymic. In accord with the prospective studies of Gonzales-Pinto et al. (2010) and Belizario et al. (2018), we found that the MP group had a smaller number of MDEs and more manic phases in follow-up than the other two groups. Possibly reflecting the inverse ratios of manic versus depressive phases between the DP and MP groups in follow-up, differences in the total number of phases were found only between the DP group and the NP group. The intermediate NP group had more illness phases in follow-up overall, as well as more MDEs specifically, but no difference between the groups was observed in time spent ill. Theoretically, this implies that the NP group might more often switch phases, but contrary to the study of Vieta et al. (2009), we found no difference in the occurrence of rapid cycling between the three groups at baseline.

Previous studies have shown that MP is associated with lifetime psychotic symptoms (Popovic et al., 2014) and first illness episode with psychotic features (Baldessarini et al., 2012b, Popovic et al., 2014). Our result of the MP group having more lifetime psychotic symptoms, due to either psychotic mania or psychotic depression, is concordant with previous findings. When interpreting the results, it must be noted that the effect of treatment could not be controlled in our study. There are probably more effective treatment options for manic states than for depressive states (Yatham et al., 2018, Vieta et al., 2018a) indicating that the contribution of the treatment to the more favorable outcome of the MP group cannot be excluded. However, if this is the case, it only reflects clinical reality.

The reliability of the concept of PP has only rarely been tested in prospective settings. We found a lower consistency between retrospective and prospective polarity assignment than Belizario et al. (2018), and the classification was strongly influenced by the time frame used; only 43% of the patients remained in the same polarity group in retrospective (up to baseline) evaluation versus prospective (5-year follow-up) evaluation. The consistency improved slightly (up to 47%) by excluding cases with less than three phases during follow-up. However, classification of PP remained the same in 76% of cases when those assigned at baseline were compared with those at the end of follow-up (when observing the whole illness history to the end of follow-up). Our findings indicate that the evaluation of PP can be reliably undertaken only after some illness phases have passed. This is a weakness from the clinical point of view since the evaluation should be done as early as possible during the illness course in order to help the clinician to design treatment and to prevent chronicity. Numerous studies have shown that the polarity of the first illness episode predicts the polarity of subsequent episodes (Janiri et al., 2017, Daban et al., 2006, Rosa et al., 2008, Forty et al., 2009, Mazzarini et al., 2009,

Baldessarini et al., 2012a, Popovic et al., 2014, Azorin, Adida & Belzeaux, 2015). In accord with these studies, we found an association between the PP and the polarity of the first illness episode. This might be a useful predictor to be utilized early in the course of BD when the number of past illness phases is scant and evaluation of PP reliably not possible. Future studies are needed to elucidate the optimal time frame for evaluation of PP.

In our study, PP predicted several-fold differences in incidence of suicide attempts during the follow-up. Although we did not find an association between lifetime history of SAs and PP, our finding of the MP group having less SAs in follow-up is in accord with most earlier literature (Colom et al., 2006, Gonzalez-Pinto et al., 2010, Popovic et al., 2014), but contrary to a recent prospective study, which found a higher number of SAs among the MP group (Belizario, Silva & Lafer, 2018). The incidence of SAs was found to exist along a continuum from the MP group to the DP group, with the NP group situated between these two groups (Figure 6). The MP group had less SAs than the NP and DP groups, which did not differ significantly from each other. Baldessarini et al. (2012b) noted that when mixed states were combined with the depressive category in the definition of PP, the association of the DP group with SAs almost doubled. The vast differences discovered in the incidences of SAs during different illness states, with mixed phases having the highest risk (Valtonen et al., 2008), is a credible explanation for this alteration. Dividing the mixed states as we did when defining the polarity (Table 8, definition 5), is in accordance with the DSM-5 classification (American Psychiatric Association, 2013), but might challenge the generalization of some findings with regard to previous or future studies if no consensus for methods is found. However, exclusion of mixed phases from the definition of PP (Table 8, definition 2) in the sensitivity analysis had only a minor influence on the main findings in our study.

Only a few studies, often with negative findings, exist on the occurrence of comorbid disorders related to PP. The fact that some of the earlier studies combined anxiety disorders and substance abuse disorders to form the one covariate “Axis I disorders” might serve as an explanation for their negative results since these two disorders may have contradictory associations with predominant polarity. According to our study, there are associations between psychiatric comorbidity and PP. Consistent with finding of Azorin et al. (2015), we found the MP group to have less frequent occurrence of lifetime comorbid anxiety disorders than the DP group. This is in line with our previous finding at 18-months suggesting that depression and anxiety covary strongly over the course of BD (Mantere et al., 2010). The same kind of pattern between comorbid SUD and manic symptoms along the illness course of BD has been observed (Mantere et al., 2010), and the SUDs before the first illness episode of BD have been associated with MP (Colom et al., 2006, Popovic et al., 2014). However, the results for substance use in regard to PP are conflicting. Janiri et al. (2017) found that BD patients without SUDs more often had MP, while BD patients with alcohol use disorder or polysubstance use more often had

DP. In our study, we found no difference in the occurrence of lifetime comorbid SUDs between the MP and DP groups. Prospective studies that take into account the current mood state are needed to examine the relationship between SUDs and predominant polarity.

The intermediate no polarity group has rarely received attention in earlier literature (Belizario, Silva & Lafer, 2018, Vidal-Rubio et al., 2018). The definition of PP considers only the ratio of the illness episodes, not their numbers. As a result, in theory, patients in this intermediate no polarity group could have a more severe course of illness with regard to factors such as time ill, number of episodes, rapid cycling and occurrence of comorbid disorders. Our findings do not support this presumption. Instead, the NP group resembled the DP group in many respects. However, the occurrence of lifetime comorbid substance abuse disorders was more frequent in the NP group than in the DP group in the non-adjusted model. Subjects in the NP group were also more often inpatients at intake. No difference was found in time spent in manic states, MDEs, or euthymia during the follow-up between these two groups. Nor was there a difference in the lifetime number of phases before baseline when the duration of illness history was adjusted. However, in the follow-up the NP group had more MDEs and more phases altogether than the DP group. Overall, based on our findings, MP might be a more powerful predictor of (better) illness course than DP, which seems to be only partly distinguishable from the NP group. In clinical practice, patients with a depressive illness course need even more prompt evaluation for suicidality, the presence of mixed features highlighting this need and also having potential prognostic and therapeutic implications (Pacchiarotti et al., 2011, Pacchiarotti et al., 2013).

7 CONCLUSIONS AND FUTURE IMPLICATIONS

7.1 CONCLUSIONS

BD is a recurrent and pleomorphic illness. The illness course is variable not only between but also within patients. In the long run, patients spend about half of their time symptomless and half symptomatic with a varying degree of symptoms. Chronicity, if defined as an uninterrupted persistence of illness, seems to be rare, but multiple subsequent episodes along the illness-course are the norm. According to our study, subgroups of BD I and II may differ only marginally in proneness to depressive states in long-term. When depressed, severity of depression, former occurrence of psychotic symptoms and comorbid cluster C personality disorder were found to be predictive of worse outcome.

BD is associated with one of the highest risk of suicide among the psychiatric disorders. As suicide attempts are highly predictive of completed suicide and more prevalent as an outcome than suicide, it is feasible to evaluate them as a predictor for long-term outcome. Possibly more than half of BD patients attempt suicide during their lifetime and over one-quarter during long-term follow-up. According to this study, nearly all SAs in BD take place during illness episodes. The incidence rates of SAs are highly variable depending on the illness state, the risk being highest during mixed states but also very high during MDEs. The variations in incidence rates between euthymia and illness phase seem to be far larger than the potency of trait characteristics as risk factors. This suggests that the question of "when" rather than "who" might be more relevant when predicting the suicide risk in BD. Interestingly, the incidence of SAs in BD seems to decline with longer time at risk. The probable explanation is that towards the end of follow-up patients spend a smaller proportion of time in high-risk states and more time with subthreshold symptoms or in remission.

Course specifiers of BD have been established to help in predicting the highly variable course of BD. Predominant polarity is not included as a course specifier in DSM-5, but may still provide a feasible tool in evaluating the variety of long-term illness courses of BD patients. According to this study, patients with manic predominant polarity seem to have a better long-term prognosis overall than the other two groups (depressive predominant polarity and no-polarity) in terms of time euthymic, incidence of suicide attempts and prevalence of psychiatric comorbidity. The depressive and the no-polarity groups may be only partly distinguishable from each other. However, the classification status of predominant polarity seems to be only moderately stable over subsequent time periods of long-term follow-up.

The long-term outcomes of BD range from lasting remission to chronic disabling mood symptoms. Classification of BD into type I and II may have only limited ability to predict outcomes with regard to time ill and hospitalizations in the long run. In this study, a clinical course characterized by depressive symptoms predicted more time ill in long-term follow-up, while severity of manic symptoms predicted the probability of hospital admissions. Dimensional descriptors of clinical course, such as duration of depression, severity of mania, and tendency to switch from depression to mania, may help in predicting the long-term illness course and in designing treatment.

7.2 CLINICAL AND RESEARCH IMPLICATIONS

When evaluating and treating BD patients in clinical practice, the cross-sectional approach is clearly inadequate. Retrospective evaluation should always be implemented, and ideally, the clinician should attempt to predict the prospective aspects of the illness, such as polarity of mood episodes and risk of suicidal acts, on the basis of former trajectories. This is a demanding professional task. Established subtypes of BD I and II and course specifiers defined in diagnostic classifications may offer some help in predicting the course of an individual patient, but the illness trajectories are highly variable also among the subtypes of BD I and BD II. Using a systematic lifechart may help considerably when defining the former illness course of a BD patient. This applies not only to the polarity, frequency, and duration of mood episodes but also to predisposing factors such as psychosocial stressors. Lifechart is a valuable tool also in evaluating suicide attempts during different mood episodes, as well as other potentially modifiable factors such as availability of and adherence to psychopharmacological and psychosocial treatments.

The presence of psychiatric and/or medical comorbidity seems to be more the rule than the exception in BD and has an effect on both outcome and treatment choices. Thus, evaluation of comorbid disorders, including personality disorders, should always be done when treating BD patients in any mood episodes and also when encountering them in a euthymic state, bearing in mind that the presence of comorbid disorders may vary depending on the current mood state. When depressed, former psychotic symptoms, features suggestive of the presence of cluster C personality disorder, high score in a depression scale, and prolonged depression should induce even more prompt monitoring of the patient.

It seems that the risk of suicide attempt in BD is highly dependent on the illness state, mixed states having the highest risk, but the risk is also very high in MDEs. In clinical practice, it is crucial to actively recognize and treat these illness states to prevent suicide attempts and suicides. Patients with mixed symptoms may not be able to spontaneously describe their state at a syndromal level, and the vital task of the clinician is to actively map these mixed symptoms, especially in depressive patients with high anxiety levels.

Recognizing the high-risk states and reducing time spent in them by intensive treatment is probably the most effective way to prevent suicidal acts in BD patients. Altough clinical attention regarding suicidal behavior in personality disorders is often intuitively directed to the presence of cluster B personality disorder, according to this study, also clinical recognition of cluster C personality disorders in BD patients is essential for suicide prevention.

Patients with BD differ markedly in their relative predominance of episodes during the long-term illness course. Furthermore, the severity, duration, sequence, and frequency of episodes may seem to vary in a chaotic manner between and within the patients. These differences may have important implications when planning both pharmacological and psychosocial treatment, especially with regard to treating and preventing mania and depression. Furthermore, some illness trajectories, such as recurrent need for hospitalization may be linked to not only considerable distress of patients but also overall healthcare expenses. Clinical tools to assist in evaluation and prediction of such factors are needed. Firmly established BD I and II distinction accounts (only) for the peak severity of manic symptoms whereas clinically often utilized rapid cycling accounts (only) for the frequency of episodes. The concept of predominant polarity seems to have long-term predictive validity, and evaluation of relative predominance of episode polarity with regard to past illness history - although potentially somewhat arduous in busy clinical practice - may assist the clinician in distinguishing different prognostic groups of BD. Established dimensional (as opposed to categorical) course characteristics may provide tools to facilitate appropriate care pathways for patients in a relatively early phase of the illness; those with a greater burden of depression should be offered treatment focused on depression and functional rehabilitation, and those with a propensity to manic episodes should be targeted with active relapse prevention to avoid further hospitalizations. The concept of predominant polarity and forementioned dimensional course characteristics may be more useful than the distinction of bipolar subtypes in predicting the long-term outcome of BD. However, given the severe harm related to manic states, and BD subtypes being strongly tied to treatment recommendations, distinction into type I and type II cannot be dismissed in clinical practice.

Since significantly fewer BD patients recover at a functional than syndromal level, further studies should address the long-term course of BD by evaluating it also from the perspective of functional outcome. Putative links between neurobiological and genetic factors and long-term outcome of BD remain to be elucidated in future decades. With regard to suicide attempts, future prospective studies should clarify the factors moderating risk during high-risk states. The predictive validity of established course characteristics and predominant polarity should be replicated in future prospective studies, and the possible links with course characteristics tested also with outcome measures other than time ill and hospital admissions. Future studies should

also assess associations between predominant polarity, course characteristics, and long-term treatment response in BD patients.

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