Petri Arvilommi

Treatment, Adherence, and Disability in Bipolar Disorder

ACADEMIC DISSERTATION

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"The endless questioning finally ended.
My psychiatrist looked at me, there was no uncertainty in his voice.
"Manic-depressive illness." I admired his bluntness. I wished him locusts on his
lands and a pox upon his house. Silent, unbelievable rage.
I smiled pleasantly. He smiled back.
The war had just begun."

Kay Redfield Jamison
"An Unquiet Mind" (1995)

Abstract

Petri Arvilommi. Treatment, Adherence, and Disability in Bipolar Disorder.

This study is part of a collaborative bipolar research project between the Unit of Mental Health of the National Institute for Health and Welfare, Helsinki (the former Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki) and the Department of Psychiatry, Jorvi Hospital, Helsinki University Central Hospital (HUCH), Espoo, Finland. The Jorvi Bipolar Study (JoBS) is a prospective, naturalistic cohort study of 191 secondary-level care psychiatric in- and outpatients with a new episode of DSM-IV bipolar disorder (BD).

Overall, the study involved screening 1,630 adult patients (aged 18-59 years) using the Mood Disorder Questionnaire (MDQ) for symptoms of bipolar disorder in the Department of Psychiatry, Jorvi Hospital, from January 1, 2002, to February 28, 2003, for a possible new episode of bipolar disorder. A clinical diagnosis of ICD-10 schizophrenia was an exclusion criterion for screening. The 490 consenting patients were interviewed with a semi-structured interview (SCID-I/P). Thereby, 191 patients were diagnosed with an acute phase of DSM-IV BD and included in the study.

The patients participating were interviewed again 6 and 18 months after baseline. The course of the disease, with timing and durations of different phases, was examined by gathering all available data, which were then combined in the form of a graphical life chart. Observer- and self-reported scales were included at baseline and at both follow-up assessments. Also, the treatments provided were investigated at baseline and at both follow-up interviews.

The aim in the first study was to investigate the adequacy of acute phase pharmacotherapy received by psychiatric in- and outpatients with a research diagnosis of BD I or BD II, including patients with and without a clinical diagnosis of BD. Information about treatments received during the index acute episode was gathered in the interview and from psychiatric records. Definitions of adequate acute-phase pharmacotherapy were based on published treatment guidelines. Only 42% of all 191 patients and 65% of those diagnosed with bipolar disorder received adequate treatment for the acute index phase. Clinical diagnosis of bipolar disorder was the factor most strongly independently associated with adequate treatment. In addition, rapid cycling, polyphasic index episode, or depressive index phase independently predicted inadequate treatment. Outpatients received adequate treatment markedly less often than inpatients. Lack of attention to the longitudinal course of the illness was another major problem area of treatment.

Next, our aim was to investigate the adequacy of the maintenance-phase pharmacotherapy received during the first maintenance phase after an acute episode, following the same patients as in the first study. We defined adequate maintenance-phase pharmacotherapy based on published treatment guidelines. Of

the patients with a maintenance phase in follow-up, adequate maintenance treatment was received by 75% for some time, but by only 61% throughout the maintenance phase and for 69% of the total maintenance time. Having adequate maintenance treatment throughout the maintenance phase was most strongly independently associated with having a clinical diagnosis of BD. In addition, inpatient treatment, rapid cycling, and not having a personality disorder predicted receiving adequate maintenance treatment throughout the maintenance phase.

In addition, we investigated the continuity of attitudes toward and adherence to various types of psychopharmacological and psychosocial treatments among psychiatric in- and outpatients with BD I or II. During the 18-month follow-up, a quarter of the patients using mood stabilizers or atypical antipsychotics discontinued medication by their own decision, and of the medications continued, a third were not used regularly enough to provide a benefit. Overall, more than half of BD patients either discontinued pharmacotherapy or used it irregularly. The highest risk for discontinuing pharmacotherapy was present when the patients were depressed. Also, a quarter of the patients receiving psychosocial treatments did not adhere to the treatment. The main reasons patients gave for nonadherence toward pharmacological treatment were side-effects, lack of motivation, and a negative attitude toward the offered treatment; for individual/supportive psychotherapy, the reasons included practical barriers to coming to sessions and lack of motivation. Rates of nonadherence to mood stabilizers and antipsychotics did not differ, but the predictors did.

Last, we investigated the prevalence and clinical factors predicting the granting of a long-term disability pension for patients with BD. We used register data to gather precise information on the pensions granted and their timing. During the 18-month follow-up after an acute episode, a quarter of the patients belonging to the labor force were granted a disability pension. Higher age, male gender, depressive index episode, comorbidity with generalized anxiety disorder (GAD) or avoidant personality disorder, and a higher number of psychiatric hospital treatments all independently predicted the granting of a disability pension. Moreover, patients' subjective estimations of their vocational ability were surprisingly accurate in forecasting the granting of a future disability pension. In addition, the depression-related cumulative burden and the proportion of time spent in depression during the follow-up were important predictors. However, the predictors may vary depending on the subtype of illness, gender, and age group of the patient.

Keywords: bipolar disorder, treatment, maintenance, adherence, disability, disability pension

Tiivistelmä

Petri Arvilommi. Treatment, Adherence, and Disability in Bipolar Disorder.

Tämä tutkimus on osa Terveyden ja Hyvinvoinnin Laitoksen Mielenterveysyksikön ja Uudenmaan sairaanhoitopiirin Jorvin sairaalan psykiatrian tulosyksikön kaksisuuntaisen mielialahäiriön seurantatutkimusta (Jorvi Bipolar Study, JoBS), jossa seurattiin 191 ajankohtaisesta (DSM-IV) mielialajaksosta kärsivää psykiatrisen erikoissairaanhoidon avohoito- ja sairaalapotilasta. Tutkimusta varten Jorvin psykiatrisessa erikoissairaanhoidossa seulottiin 1.1.2002 alkaen 28.2.2003 saakka 1630 potilasta (iältään 18-59 vuotta), kaksisuuntaisen mielialahäiriön oireiden suhteen. Kliininen ICD-10 skitsofreniadiagnoosi oli poissulkukriteeri seulontaan. Tutkimushaastatteluun suostui 490 potilasta, jotka haastateltiin puolistrukturoidulla haastattelumenetelmällä (SCID-I/P). Tutkimukseen otettiin 191 potilasta, joilla oli diagnosoitu akuutissa vaiheessa oleva kaksisuuntainen mielialahäiriö.

Potilaat haastateltiin uudelleen 6- ja 18- kuukautta tutkimukseen ottamisen jälkeen. Taudin kulku, vaiheiden ajoitus ja kesto tutkittiin keräämällä kaikki käytettävissä oleva tieto, joka koottiin yksityiskohtaiseksi graafiseksi kuvaajaksi, oirekortiksi. Sekä alku- että seurantahaastatteluihin kuului tutkijan ja potilaan täyttämiä tutkimuslomakkeita. Myös määrätyt hoidot tutkittiin sekä alku- että seurantahaastatteluissa.

Tutkimuksen ensimmäinen tavoite oli selvittää miten asianmukaista akuutin vaiheen lääkehoitoa saavat psykiatriset sairaala- ja avohoitopotilaat, joille on asetettu tutkimusdiagnoosiksi kaksisuuntainen mielialahäiriö tyyppi I tai II, mukaan lukien ne potilaat joilla ei ole kliinistä kaksisuuntaisen mielialahäiriön diagnoosia. Asianmukaisen lääkehoidon määritelmät perustuivat hoitosuosituksiin. Vain 42% kaikista 191 potilaasta ja 65% niistä, joilla oli kliininen kaksisuuntaisen mielialahäiriön diagnoosi, saivat asianmukaista hoitoa akuuttivaiheessa. Kliininen diagnoosi oli tärkein asianmukaista hoitoa itsenäisesti ennustava tekijä. Sen lisäksi asianmukaista hoitoa itsenäisesti ennustivat tiheäjaksoisuus, monivaiheinen jakso, ja masennusvaihe. Avohoidossa olevat potilaat saivat asianmukaista hoitoa merkittävästi harvemmin kuin sairaalahoidossa olevat potilaat. Puuttuva huomio taudin pitkittäiseen kulkuun oli merkittävä ongelma-alue.

Seuraavaksi tavoitteena oli selvittää, miten asianmukaista on hoito ensimmäisessä ylläpitojaksossa akuutin vaiheen jälkeen, seuraten samoja potilaita kuin ensimmäisen tutkimuksen akuuttivaiheessa. Asianmukaisen lääkehoidon määritelmät perustuivat hoitosuosituksiin. Niistä joilla oli ylläpitojakso seurannassa, sai 75% asianmukaista lääkehoitoa jonkin aikaa, mutta vain 61% koko ylläpitovaiheen ajan ja 69% ylläpitovaiheen kokonais ajasta. Kliininen diagnoosi ennusti itsenäisesti vahvimmin asianmukaisen lääkehoidon saamista koko ylläpitovaiheen ajan. Kliinisen diagnoosin puuttumisen lisäksi

epäasianmukaista ylläpitovaiheen lääkitystä ennustivat sairaalahoito, tiheäjaksoisuus ja persoonallisuushäiriö.

Seurannan aikana tutkittiin myös eri psykofarmakologisten ja psykososiaalisten hoitojen jatkuvuutta, sekä asenteita ja hoitoon sitoutumista näihin hoitoihin, psykiatrisilla sairaala- ja avohoitopotilailla, joilla oli kaksisuuntainen mielialahäiriö tyyppi I tai II. Neljäsosa niistä potilaista joilla oli mielialaa tasaava tai epätyypillinen psykoosilääke käytössä, lopetti lääkityksen omalla päätöksellään ja niistäkin jotka jatkoivat kolmasosa ei käyttänyt lääkkeitä riittävän säännöllisesti saadakseen siitä hyötyä. Yhteensä yli puolet kaksisuuntaista mielialahäiriötä sairastavista potilaista joko lopetti lääkityksen tai käytti sitä epäsäännöllisesti 18 kuukauden seuranan aikana. Suurin riski lääkkeen lopettamiseen liittyi masennusvaiheisiin. Myös neljäsosa niistä potilasta jotka saivat psykososiaalista hoitoa olivat huonosti hoitoon sitoutuneita. Tärkeimmät potilaiden ilmaisemat syyt huonoon lääkehoitoon sitoutumiseen olivat sivuvaikutukset, puutteellinen motivaatio ja negatiiviset asenteet tarjottua hoitoa kohtaan. Tärkeimmät potilaiden ilmaisemat syyt huonoon yksilö- tai supportiivisen hoitoon sitoutumiseen olivat käytännön esteet ja motivaation puute. Mielialaa tasaavaan tai antipsykoottiseen lääkitykseen sitoutuneiden osuus ei eronnut toisistaan, mutta syyt erosivat.

Lisäksi tutkittiin pitkäaikaiselle työkyvyttömyyseläkkeelle jäämisen syitä ja esiintyvyyttä kaksisuuntaista mielialahäiriötä sairastavilla potilailla. Tutkimuksessa käytettiin rekisteritietoja, jotta saatiin tarkka tieto eläkkeistä ja niiden ajoituksesta. Akuuttia vaihetta seuranneiden 18 kuukauden aikana neljäsosalle työvoimaan kuuluvista potilaista myönnettiin työkyvyttömyyseläke. Työkyvyttömyyseläkkeelle jäämistä ennustivat korkeampi ikä, miessukupuoli, masennus tutkimuksen alkuvaiheessa, samanaikainen yleistynyt ahdistuneisuushäiriö tai estynyt persoonallisuus, sekä suurempi psykiatristen sairaalahoitojen lukumäärä. Lisäksi potilaiden omat arviot työkyvystään alkuhaastattelussa olivat yllättävän tarkkoja ennustamaan työkyvyttömyyseläkkeen myöntämistä. Myös masennuksen osuus seurannan aikana oli tärkeä ennustava tekijä. Ennustavat tekijät kuitenkin vaihtelivat sairauden tyypistä, sukupuolesta ja iästä riippuen.

Avainsanat: kaksisuuntainen mielialahäiriö, hoito, ylläpitohoito, hoitoon sitoutuminen, työkyvyttömyys, työkyvyttömyyseläke

Contents

List of original publications

This thesis is based on the following original articles referred to in the text by their Roman numerals I-IV.

I   Arvilommi P, Suominen KS, Mantere OK, Leppämäki S, Valtonen H, Isometsä ET. Adequacy of treatment received by diagnosed and undiagnosed patients with bipolar I and II disorders. J Clin Psychiatry. 2007 Jan;68(1):102-10.

II   Arvilommi P, Suominen K, Mantere O, Leppämäki S, Valtonen HM, Isometsä E. Maintenance treatment received by patients with bipolar I and II disorders-a naturalistic prospective study. J Affect Disord. 2010 Feb;121(1-2):116-26.

III   Arvilommi P, Suominen K, Mantere O, Leppämäki S, Valtonen H, Isometsä E. Predictors of adherence to psychopharmacological and psychosocial treatment in bipolar I or II disorders - an 18-month prospective study.
J Affect Disord. 2014 Feb;155:110-7.

IV   Arvilommi P, Suominen K, Mantere O, Valtonen H, Leppämäki S, Isometsä E. Predictors of long-term work disability among patients with type I and II bipolar disorder: a prospective 18-month follow-up study.
Bipolar Disord. 2015 Dec;17(8):821-35.

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Abbreviations

ACTH	Adrenocorticotropic hormone
ADHD	Attention deficit hyperactivity disorder
APA	American Psychiatric association
BAI	Beck Anxiety Inventory
BAP	The British Association for Psychopharmacology
BD	Bipolar disorder
BD I	Bipolar disorder type I
BD II	Bipolar disorder type II
BDI	Beck Depression Inventory
BHS	Beck Hopelessness Scale
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBT	Cognitive-behavioral therapy
CDS	Collaborative Depression Study
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
COPD	Chronic obstructive pulmonary disease
CRF	Corticotropin-releasing factor
DALY	Disability Adjusted Life-Year
DIS	Diagnostic Interview Schedule
DMX	Depressive mixed state; a major depressive phase with simultaneous hypomanic symptoms
DMX2	Depressive mixed state; a major depressive phase with two or more (DMX2) simultaneous hypomanic symptoms
DMX3	Depressive mixed state; a major depressive phase with three or more (DMX3) simultaneous hypomanic symptoms
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition

DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DTI	Diffusion tensor imaging
EBC	European Brain Council
ECA	Epidemiological Catchment Area Study
ECNP	The European College of Neuropsychopharmacology
ECT	Electro-convulsive therapy
EMBLEM	European mania in bipolar longitudinal evaluation of medication study
EPI	Eysenck Personality Inventory
FA	Fractional anisotropy
FBPG	Florida Best Practice Psychotherapeutic Medication Guidelines
FCCG	Finnish Current Care Guideline
FFT	Family-focused therapy
fMRI	Functional magnetic resonance imaging
FR	Functional remediation
GAD	Generalized anxiety disorder
GAF	Global Assessment of Functioning Scale
GWAS	Genome wide association study
HAM-D	Hamilton Rating Scale for Depression
HPA	Hypothalamic, Pituitary, Adrenal
HR	Hazard rate
HUCH	Helsinki University Central Hospital
ICD-10	International Classification of Diseases, 10th edition
IPSRT	Interpersonal and social rhythm therapy
IRLE	Interview for Recent Life Events
ISBD	The International Society for Bipolar Disorders
JoBS	Jorvi Bipolar Study
LCM	Life Chart Methodology
LIFE	Longitudinal Interval Follow-up Evaluation
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MDQ	Mood Disorder Questionnaire
MEAF	Mental Health in Early Adulthood in Finland
MINI	Mini-International Neuropsychiatric Interview

MRS	Magnetic resonance spectroscopy
NA	Not applicable
NCS	National Comorbidity Study
NCS-R	National Comorbidity Study Replication
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health
NOS	Not otherwise specified
NS	Not significant
OFC	Olanzapine plus fluoxetine combination
OR	Odds ratio
PE	Psychoeducation
PIF	Psychoses in Finland Study
PTSD	Posttraumatic stress disorder
PSSS-R	Perceived Social Support Scale, revised
RDC	Research diagnostic criteria
SAS-SR	Social Adjustment Scale Self-Report
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 Personality Disorders
SD	Standard deviation
SFBN	Stanley Foundation Bipolar Treatment Outcome Network
SNP	Single nucleotide polymorphism
SOFAS	Social and Occupational Functioning Assessment Scale
SPSS	Statistical Package for the Social Sciences for Windows
SSI	Scale for Suicidal Ideation
SSRI	Serotonin-selective reuptake inhibitor
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
STOP-EM	Systematic Treatment Optimizing Program for Early Mania
VDS	Vantaa Depression Study
WFSBP	World Federation of Societies of Biological Psychiatry

WHO	World Health Organization
WMH	World Mental Health
YMRS	Young Mania Rating Scale

1.   Introduction

Bipolar manic-depressive disorder is arguably both the youngest and possibly also one of the oldest forms of mental illness, and medical conceptions of mania and depression are as old as medicine itself (Goodwin & Jamison, 2007), two of the earliest described human diseases (Angst & Marneros, 2001). From ancient times to the present, an extraordinary consistency has characterized descriptions of these conditions. Few maladies have been represented with such unvarying language. However, while the essential features are recognizable in the medical literature across the centuries, the boundaries that define mania and depression and the relationship between them have changed over time (Goodwin & Jamison, 2007).

Hippocrates (460-337 BC) was the first to systematically describe mania and melancholia (Angst & Marneros, 2001), but these early conceptions were broader than those of today. The medical writers of ancient Greece conceived of mental disorders in terms that sound remarkably modern. They believed that melancholia was a psychological manifestation of an underlying biological disturbance, specifically, a perturbation in brain function (Goodwin & Jamison, 2007). This essentially biological explanation of the cause of melancholia, which survived until the Renaissance, was part of the prevailing understanding of all health as an equilibrium of the four humors – blood, yellow bile, black bile, and phlegm – and all illness as a disturbance of this equilibrium. An excess of black bile was seen as the cause of melancholia, a term that literally means black bile (melas means black and chole means bile). Depression, the clinical term for melancholy, is much more recent in origin and derives from the Latin deprimere (press down or sink down). Mania, in contrast, was usually attributed to an excess of yellow bile (Goodwin & Jamison, 2007). The origin of the term mania is less clear because of its roots in the mytologian area (Angst & Marneros, 2001). Arateus of Cappadocia, who lived in the second century AD, appears to have been the first to bring together the syndromes described in Greek medicine and proposed that mania and melancholia belong together and that mania was a worsening of melancholia, a view that prevailed for centuries (Angst & Marneros, 2001; Goodwin & Jamison, 2007). Aretaeus described a group of patients who "laugh, play, dance night and day, and sometimes go openly to the market crowned, as if victors in some contest of skill" only to be "torpid, dull, and sorrowful" at other times (Burton N., 2012).

From classical Greece until the Middle Ages, mental and physical afflictions were primarily the concern of medical doctors. As illness gradually became the responsibility of priests, the above early insights were submerged. The period that followed was, in retrospect, a dark age, when mental illness was generally attributed to magic, sin, or possession by the devil. Empirical clinical observations without religious overtones did not reappear until the beginning of the seventeenth century (Goodwin & Jamison, 2007).

The explicit conception of manic-depressive illness as a single disease entity dates from the mid-nineteenth century. The French "alienists," Falret and Baillager, independently and almost simultaneously formulated the idea that mania and depression represent different manifestations of a single illness (Angst & Sellaro, 2000; Goodwin & Jamison, 2007). In 1854, Falret described a circular disorder, "la folie circulaire," which for the first time expressly defined an illness in which "this succession of mania and melancholia manifests itself with continuity and in a manner almost regular," with episodes separated by symptom-free intervals (Angst & Sellaro, 2000; Goodwin & Jamison, 2007). In both French diagnoses, the prognosis was considered to be "desperate, terrible and incurable" (Angst & Sellaro, 2000).

In the early 1900s, German psychiatrist Emil Kraepelin (1856–1926) studied the natural course of the disorder and found it to be punctuated by relatively symptom-free intervals. On this basis, he distinguished the disorder from dementia praecox (schizophrenia) and coined the term manic–depressive psychosis to describe it. Kraepelin emphasized that, in contrast to dementia praecox, manic–depressive psychosis had an episodic course and a more benign outcome (Angst & Sellaro, 2000; Goodwin & Jamison, 2007).

However, the distinction between patients with only depressive episodes and those with both manic and depressive episodes was not made before 1957 when Leonhard proposed a classification system that went beyond clinical description alone. Leonhard observed that, within the broad category of manic-depressive illness (i.e., recurrent affective illness), some patients had histories of both depression and mania, whereas others had depression only. He then noted that patients with a history of mania (whom he termed bipolar) had a higher incidence of mania in their families than those with recurrent depression only (whom he termed monopolar) (Goodwin & Jamison, 2007). This distinction can be seen as fundamental for the modern emphasis on bipolarity. The work of Leonhard, Angst, Perris, and Winokur led to broad acceptance of the concept of bipolar disorder (BD) by the late 1960s. The bipolar-unipolar distinction was formally incorporated into the American diagnostic system, DSM, third edition (DSM-III) in 1980 (Yildiz et al., 2015).

Although mild cases of mania had been described by earlier observers, Mendel (1881) was the first to define hypomania (Goodwin & Jamison, 2007). Ewald Hecker (1898) was among the first to describe what is now diagnosed as BD II, emphasizing its chronic, fluctuating, ambulatory course characterized by depressions with occasional hypomanic periods. Later, Kraepelin described hypomanic episodes in the course of manic-depressive illness, and Dunner et al. (Dunner et al., 1976) described a specific course pattern in which hypomanic episodes were interspersed with major depressive episodes. Despite the early and seemingly prescient advances, the modern concept of BD II was only defined in the 1970s by Dunner and his colleagues (Judd et al., 2003). In 1976, Dunner, Gershon, and Goodwin suggested the classification of bipolar patients into the categories bipolar I and bipolar II, but it was not until 1994, with the fourth

edition of DSM (DSM-IV), that bipolar disorder type II was included in the official diagnostic system (Yildiz et al., 2015).

So, even though manic-depressive illness has been known for more than 2,000 years, the modern concept of BD is only of some decades. Bipolar disorder poses a challenge in research, and the effort to evaluate and integrate the results of research is filled with difficulties, as nothing could be further from a static condition than bipolar disorder. Whereas most psychiatric conditions vacillate within a single register between symptom exacerbation and various degrees of recovery, those attempting to fully understand bipolar disorder must contend with the fact that exacerbations come in two distinct flavors – manias and depressions – and that often these exacerbations take any of a nearly infinite number of combinations of these two mood disturbances (Maletic & Raison, 2014). Unfortunately, Kraepelins' view of a benign course of BD has proven to be too optimistic and for many patients BD is still a chronic disease with major functional disabilities. So far, new treatments have not changed the picture markedly.

However, with the rapidly increasing number of diverse studies in BD and evolving scientific methods, more than 2,000 years after the discovery of the disease and some decades after the modern concept of BD emerged, we may be nearing a breakthrough in our knowledge of the etiology of BD, which could start a new era in the treatment of this difficult disease.

2. Review of the literature

2.1. Definition of bipolar disorder

Bipolar disorder, or manic depressive illness as it was previously named, is a mental disorder characterized by recurrent episodes of mania, hypomania, mixed states, and depression. Bipolar disorder is divided into type I and II disorders.

2.1.1. Diagnosis of bipolar disorder

Currently, two major classification systems are in use, the DSM-5 (American Psychiatric Association., 2013) and ICD-10 (World Health Organization, 1992), the latter one used in clinical practice in Finland. However, practically all the research has been done according to the former DSM classifications (DSM-III and DSM-IV). The DSM-IV was also used in this thesis. DSM-5 bipolar and related disorders include bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specifier bipolar and related disorder, and unspecified bipolar and related disorder.

The bipolar I disorder criteria represent the modern understanding of the classic manic-depressive disorder or affective psychosis described in the nineteenth century, differing from that classic description only to the extent that neither psychosis nor the lifetime experience of a major depressive episode is a requirement. Bipolar II disorder, requiring the lifetime experience of at least one episode of major depression and at least one hypomanic episode, is no longer thought to be a "milder" condition than bipolar I disorder, largely because of the amount of time individuals with this condition spend in depression and because the instability of mood experienced by individuals with bipolar II disorder is typically accompanied by serious impairment in work and social functioning (American Psychiatric Association., 2013).

2.1.2. Manic episode (DSM-5)

According to DSM-5 (American Psychiatric Association., 2013), a manic episode is defined by a distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy. This period must last at least one week (or less if hospitalization is required). The mood disturbance and increased energy or

activity must be accompanied by at least three (or four if the mood is irritable) of the following symptoms, which have been present to a significant degree and represent a noticeable change from usual behavior: inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressure to keep talking, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity or psychomotor agitation, or excessive involvement in pleasurable activities that have a high potential for painful consequences. The mood disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or psychotic features are present.

2.1.3.   Hypomanic episode (DSM-5)

A hypomanic episode differs from a manic episode in that a duration of only four days is required. In addition, in contrast to a manic episode, a hypomanic episode is not severe enough to cause marked impairment in social or occupational functioning or require hospitalization, and there are no psychotic features. Still, the episode must be associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic and the disturbance in mood and change in functioning must be severe enough to be observable by others. Otherwise, the criteria for hypomanic episode are the same as for manic episode (American Psychiatric Association., 2013).

2.1.4.   Major depressive episode (DSM-5)

The criteria for a major depressive episode in BD are the same as for a major depressive episode in major depressive disorder (MDD). The essential feature of a major depressive episode is a period of at least two weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities. The individual must also experience four (or three if both of the aforementioned essential features are fulfilled) of the following symptoms during the same two-week period that represent a change from previous functioning: significant weight loss or gain, decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feeling of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate or indecisiveness, recurrent thoughts of death, and recurrent suicidal ideation or suicide attempt or a specific plan for committing suicide. The symptoms must also be severe enough to cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (American Psychiatric Association., 2013).

2.1.5. DSM-IV vs. DSM-5

To enhance the accuracy of diagnosis and facilitate earlier detection in clinical settings, the main Criterion A for manic and hypomanic episodes in the DSM-5 includes an emphasis on changes in activity and energy as well as mood.

The DSM-IV diagnosis of "mixed episode" is replaced in the DSM-5 with a mixed-features specifier that can be applied to episodes of major depression, hypomania, or mania. In DSM-IV, a diagnosis of mixed episode required an individual to simultaneously meet all criteria for an episode of major depression and an episode of mania. During its review of the latest research, the DSM-5 Mood Disorders Work Group recognized that individuals rarely meet the full criteria for both episode types at the same time. To be diagnosed with the new specifier in the case of major depression, the new DSM-5 specifier will require the presence of at least three manic/hypomanic symptoms that don't overlap with symptoms of major depression. In the case of mania or hypomania, the specifier will require the presence of at least three symptoms of depression in concert with the episode of mania/hypomania (American Psychiatric Association., 2013).

In the chapter on bipolar and related disorders and the chapter on depressive disorders, a specifier for anxious distress is delineated. This specifier is intended to identify patients with anxiety symptoms that are not part of the bipolar diagnostic criteria (American Psychiatric Association., 2013).

2.2. Epidemiology of bipolar disorder

The lifetime prevalence of BD I is generally assumed to be about 1% (Merikangas et al., 2011). The lifetime prevalence of BD II is estimated to about the same as BD I, even though no reliable population estimates exist because of the challenge of diagnosis of hypomania in general population surveys. An international review of both DSM-IV BD I and BD II population studies yielded an aggregate cross-study lifetime prevalence estimate of 1.2%, ranging from 0.1% in Nigeria to 3.3% in the U.S. (Merikangas et al., 2011). The European College of Neuropsychopharmacology (ECNP)/ European Brain Council (EBC) report 2011 (Wittchen et al., 2011) summarized European studies and found the prevalence of BD to be 0.7% (0.2-1.1%). In a comprehensive nationwide study of all Danish residents, the cumulative incidence at 50 years of age was 0.76% for males and 1.07% for females and lifetime risk was 1.32% for males and 1.84% for females (Pedersen et al., 2014).

The lifetime prevalence of BD I in the recent epidemiological studies has ranged from 0.6% to 3.3%, and the 12-month prevalence from 0.6% to 2.0% (National Epidemiologic Survey on Alcohol and Related Conditions [NESARC], National Comorbidity Study Replication [NCS-R], World Mental Health [WMH]

Survey Initiative) (Grant et al., 2005; Merikangas et al., 2007; Merikangas et al., 2011). In a recent systematic review and meta-analysis of population studies, the pooled lifetime prevalence of BD I was 1.06% (95%CI 0.81-1.31) and the pooled 12-month prevalence was 0.71% (95%CI 0.56-0.86) (Clemente et al., 2015).

Estimation of the prevalence of BD II is difficult due to low reliability of the diagnosis of BD II in population studies. In recent studies, the lifetime prevalence has been 0.4%-1.1% and the 12-month prevalence 0.3%-0.8% (Merikangas et al., 2007; Merikangas et al., 2011). In the systematic review and meta-analysis by Clemente et al. (Clemente et al., 2015), the pooled lifetime prevalence of BD II was 1.57% (95%CI 1.15-1.99) and the 12-month prevalence was 0.50% (95%CI 0.35-0.64).

In Finnish studies, the prevalence of BD has been estimated to be lower than the international prevalence (Suvisaari et al., 2009). The Psychoses in Finland (PIF) Study, based on the Health 2000 Study, found that the lifetime estimate of BD I was 0.24%, increasing to 0.42% if the register diagnoses of BD I were included (Perala et al., 2007). In the Mental Health in Early Adulthood in Finland (MEAF) (N=1963), another study based on the Health 2000 study, the authors found that lifetime prevalence for Finns aged 19 to 34 years was 1.27% (BD I 0.38%, BD II 0.51%, and BD NOS (not otherwise specified) 0.37%) (Suvisaari et al., 2009).

Table 1. Prevalence of bipolar disorder

12-month prevalence of bipolar disorder (I and II)				
ECNP/EBC	0.7%	Wittchen et al. 2011	Europe	
Lifetime prevalence of bipolar I disorder				
NESARC	3.3 %	Grant et al., 2005	United States	N=43093
NCS-R	1.0 %	Merikangas et al., 2007	United States	N=9282
WMH	0.6 %	Merikangas et al., 2011	Americas, Europe, Asia[a]	N=61392
PIF	0.2 %	Perälä et al., 2007	Finland	N=8028
MEAF	0.5 %	Suvisaari et al., 2009	Finland	N=546
12-month prevalence of bipolar I disorder				
NESARC	2.0 %	Grant et al., 2005	United States	N=43093
NCS-R	0.6 %	Merikangas et al., 2007	United States	N=9282
WMH	0.4 %	Merikangas et al., 2011	Americas, Europe, Asia[a]	N=61392
Lifetime prevalence of bipolar II disorder				
NCS-R	1.1 %	Merikangas et al., 2007	United States	N=9282
WMH	0.4 %	Merikangas et al., 2011	Americas, Europe, Asia[a]	N=61392
MEAF	0.7 %	Suvisaari et al., 2009	Finland	N=546
12-month prevalence of bipolar II disorder				
NCS-R	0.8 %	Merikangas et al., 2007	United States	N=9282
WMH	0.3 %	Merikangas et al., 2011	Americas, Europe, Asia[a]	N=61392

[a] 11 countries

2.3.   Comorbidity of bipolar disorder

Comorbidity refers to the co-occurrence of two or more distinct disorders in one person over a defined period of time. Comorbidity of BD may be with another psychiatric disorder or with a disorder from other diagnostic groupings (Angold et al., 1999). Comorbidity in BD is the rule rather than the exception (Goodwin & Jamison, 2007) and is associated with worse outcomes than bipolar disorder alone (NCCMH, 2014)

2.3.1.   Psychiatric comorbidity

The coexistence of other Axis I disorders complicates psychiatric diagnosis and treatment. Conversely, symptom overlap in DSM-IV diagnoses hinders definition and recognition of true comorbidity (Krishnan, 2005). Comorbidity also substantially contributes to the disease burden and economic costs of mood disorders. Numerous studies have shown that comorbidity is associated with earlier onset of bipolar symptoms, greater functional and psychosocial impairment, poor adherence and treatment response, prolonged recovery time, increased risk of suicide attempts and completed suicides, increased utilization of health services, and higher morbidity and mortality (Krishnan, 2005; Lam et al., 2012). The total Axis I lifetime comorbidity has been estimated to range from 60% to 80% (McElroy et al., 2001; Simon et al., 2004; Suppes et al., 2001) to as low as 31% (Vieta et al., 2001).

Simon et al. (Simon et al., 2004) reported the comorbidity rates among the first 1,000 patients entering the STEP-BD study. They found that of the 656 patients 72% met criteria for at least one comorbid disorder, 20% met criteria for two, 15% for three, and 17% for four or more comorbid disorders. In the Stanley Foundation Bipolar Treatment Outcome Network (SFBN) study (McElroy et al., 2001), 65% of the patients met DSM-IV criteria for at least one lifetime comorbid disorder, and 33% met criteria for at least one current comorbid disorder; 42% had two or more and 24% had three or more lifetime comorbid disorders. BD I and BD II patients showed no differences regarding rates of lifetime or current comorbid disorders. Anxiety (42%) and substance use disorders (42%) were the most common comorbid lifetime disorders, followed by eating disorders (6%). Axis I comorbidity was associated with earlier age at onset of affective symptoms, rapid cycling, and worsening severity of episodes over time.

In Finland, Mantere et al. (Mantere et al., 2006) reported that 70% of the patients with BD I and BD II had a current comorbid disorder; on Axis I 60%, Axis II 43%. Anxiety disorders were currently present in 45%, substance use disorders in 20%, and eating disorders in 8% of patients with BD. BD I and BD II did not differ significantly in terms of comorbidity profile. On the basis of the National

Hospital Discharge Register in Finland, Sorvaniemi and Hintikka (Sorvaniemi & Hintikka, 2005) studied the recorded prevalence of psychiatric comorbidity among psychiatric inpatients. Of the 2,687 hospital stays in 1998, psychiatric comorbidity was recorded in 18%. Substance-related disorders (11%) were the most commonly recorded comorbid disorder; personality disorders accounted for 6% and anxiety disorders for 1%. The authors concluded that comorbidity in BD in psychiatric hospitals in Finland goes largely undetected and may have a deteriorating impact on the course of the illness.

Two recent reviews (Nabavi et al., 2015; Pavlova et al., 2015) have estimated the lifetime prevalence of anxiety disorder comorbidity among patients with BD. Anxiety disorders are one of the most common comorbidities in BD and the lifetime prevalence of any anxiety disorder among patients with BD is three times greater than for people without BD (Pavlova et al., 2015). The pooled estimation of any lifetime anxiety disorder was 45% (from 10% to 80%-90%) (Pavlova et al., 2015) and 43% (Nabavi et al., 2015), respectively. The most common anxiety disorders were panic disorder (19% and 17%), generalized anxiety disorder (20% and 14%), social anxiety disorder (20% and 13%), and post-traumatic stress disorder (17% and 11%). The lifetime prevalence of any anxiety disorder did not differ between people with BD I or BD II, but social phobia was more common in those with BD II (Pavlova et al., 2015). Patients with BD also commonly have had more than one lifetime anxiety disorder (Ketter, 2015). In patients with BD, comorbidity with anxiety disorders is associated with more frequent relapses of mood episodes, more severe depressive episodes, a higher prevalence of substance abuse, and an increased risk of suicide attempts, impaired role functioning, and reduced quality of life. It is also associated with earlier onset age as well as treatment resistance (Ketter, 2015). Moreover, anxiety disorders often do not remit with the mood episode and continue to cause functional impairment, even during periods of euthymia (Pavlova et al., 2015).

The lifetime prevalence of substance use disorder in BD is higher than in any other psychiatric illness, with lifetime rates in epidemiological and clinical samples ranging from 40% to 60% (Ostacher et al., 2010) or 19% to 60% (McElroy et al., 2001; Simon et al., 2004; Suppes et al., 2001; Vieta et al., 2000; Vieta et al., 2001). In a recent systematic review and meta-analysis (Di Florio et al., 2014), the overall pooled lifetime prevalence of alcohol use disorders was 35%. Comorbid substance use disorder has been associated with a variety of negative outcomes among BD patients, including greater risk of treatment nonadherence, increased rates of psychiatric hospitalization, low rates of recovery, greater risk of aggression and violence, increased rates of attempted and completed suicide, a less favorable response to conventional treatment (Levin & Hennessy, 2004; McIntyre, Nguyen et al., 2008; Rakofsky & Dunlop, 2013), and all-cause mortality (Hjorthoj et al., 2015).

Comorbidity of attention deficit hyperactivity disorder (ADHD) with BD in adulthood has been estimated at 5% to 20%, and even up to more than 30% if childhood onset ADHD that remitted in adulthood was determined (Brus et al.,

2014; Skirrow et al., 2012), higher than in the general population (2%-5%). In more narrowly defined BD I, comorbidity with ADHD is reported in 5.9% to 8% of cases (Skirrow et al., 2012). Patients with ADHD and BD may present with similar symptoms, including increased energy, distractibility, disorganization, impulsivity, hyperactivity, and rapid speech. Determining whether the patient has either, or possibly both, of these syndromes can be a complex task (Brus et al., 2014; Skirrow et al., 2012). ADHD symptoms are chronic and traitlike and refer to differences from developmental norms, whereas BD symptoms are conceptualized as changes from an individual's usual premorbid state and are episodic in nature (Brus et al., 2014; Skirrow et al., 2012). Comorbidity of BD and ADHD is associated with an earlier age at onset and more chronic and disabling course of BD, as well as more psychiatric comorbidity (Brus et al., 2014).

Fan and Hassell (Fan & Hassell, 2008) reviewed the comorbidity of personality disorder in BD. They found that the prevalence of comorbid personality disorder is highly variable, ranging from 12% to 84% in outpatient studies, and depends on the methodology used, patients included, and the presence of a current mood state. The studies using Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) for patients with BD I or II in euthymic state have found prevalence rates of personality disorder comorbidity from 25% to 50%. Comorbid personality disorder has been associated with a lower medication adherence rate, lower rate of clinical recovery, lower functional level, higher rates of suicidality, and higher rates of substance abuse (Fan & Hassell, 2008). In the Finnish JoBS study, total Axis II comorbidity was 41%, borderline personality disorder and obsessive-compulsive personality disorder being the most common (Mantere et al., 2006).

2.3.2. Medical comorbidity

Patients with BD experience a high incidence of medical comorbidities. These comorbidities contribute to major degrees of morbidity and premature mortality (Post et al., 2015). Traditionally, the high prevalence of medical illness in those with mental health problems has been viewed as a consequence of psychotropic medications and an unhealthy lifestyle. However, recent research has suggested that exposure to psychotropic medication does not necessarily worsen mortality risk in patients with psychiatric illness (Forty et al., 2014). Often it is unclear whether a medical disorder is truly comorbid, a consequence of treatment, or a combination of both (Krishnan, 2005).

Forty et al. (Forty et al., 2014) examined the rates of medical illness in patients with BD (n=1720) to examine the clinical course of BD according to lifetime medical illness burden. The most prevalent medical conditions in the BD sample were migraine headache (24%), asthma (19%), elevated lipids (19%), hypertension (15%), thyroid disease (13%), and osteoarthritis (11%). The authors also compared the rates of medical illness among patients with BD, patients with

MDD (n=1737), and healthy controls (n=1340). They reported that in the logistic regression models patients with BD had asthma and elevated lipids significantly more often than patients with MDD, patients with BD more often had type 2 diabetes, epilepsy, or kidney disease than the control group, patients with BD or MDD had gastric ulcers, hypertension, and osteoarthritis more often than the control group, patients with MDD had multiple sclerosis more often than patients with BD and the control group, and patients with BD had thyroid diseases more often than patients with MDD, who had them more often than the control group.

A recent study by Post et al. (Post et al., 2015) found that of the 876 patients with BD recruited in the SFBN only 21% had no medical comorbidities, while 53% had one to three comorbidities, and the remaining 26% had four or more medical conditions. The most common comorbidities were allergies (38%), migraine headaches (35%), head injury without loss of consciousness (22%), high blood pressure (16%), chronic menstrual irregularities (16%), hypothyroidism (15%), head injury with loss of consciousness (15%), irritable bowel syndrome (13%), arthritis (13%), asthma (13%), and hypotension (11%). Having experienced adversity in childhood (Post et al., 2013), an early age of onset, and a lifetime diagnosis of anxiety disorder remained independently related to the number of medical comorbidities in adulthood.

In the Swedish National Cohort Study of 6,587,036 Swedish adults, including 6,618 with BD, Crump et al. (Crump et al., 2013) reported that after adjusting for age and other sociodemographic factors, patients with BD had an increased risk of diagnosis with influenza or pneumonia, chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disease, and specifically stroke. In contrast, in this study, patients with BD had no increased risk of diagnosis with ischemic heart disease, hypertension, lipid disorders, or cancer. Also, after additional adjustment for substance use disorders, the association between BD and either stroke or COPD diagnosis among men was no longer statistically significant

Thus, the available evidence indicates that several general medical disorders (cardiovascular, metabolic, infectious, neurological, and respiratory) differentially affect the bipolar disorder population (McIntyre et al., 2007). It has been proposed that BD should be viewed as a multisystem disorder, or even a multisystem inflammatory disease (Frank et al., 2015). According to this view, the presence, for example, of medical conditions such as asthma, childhood obesity, and early signs of cardiovascular disease may simply be other manifestations of a multisystem disorder involving both psychiatric and non-psychiatric comorbidities. Also, different disorders may share common genes and comorbidity may be the result of these common genes between disorders (Goh et al., 2007). Moreover, BD has been proposed to be an illness of accelerated aging, with early mortality and risk of developing physical diseases that are more typically seen in the elderly, such as cardiovascular disease, stroke, dementia, cancer, obesity, and type II diabetes mellitus (Lindqvist et al., 2015; Rizzo et al., 2014).

2.4. Etiology and pathogenesis of bipolar disorder

2.4.1. Heredity

The predisposition to fall ill in BD is highly hereditary and often runs in families. In patients with established disease, a family history of mood or psychotic illness is common. Furthermore, a family history of bipolar disorder is an important clinical predictor of a likely bipolar course in patients who present with one or more episodes of depression even before their first episode of mood elation (Craddock & Sklar, 2013). Classical genetic epidemiology with family, twins, and, to a lesser extent, adoption studies has produced overwhelming evidence that genes affect predisposition to bipolar disorder. Indicative figures for the lifetime risks in narrowly defined bipolar disorder in relatives of a bipolar proband are: unrelated member of the general population 0.5%-1.5%; first degree relative 5%-10% (relative risk roughly 8 compared with the risk in the general population); and monozygotic co-twin 40%-70% (relative risk roughly 60) (Craddock & Sklar, 2013). If one identical twin has BD, the other has about an 80% chance of falling ill with a mood disorder. The estimates of heritability of BD are usually around 60% to 90%. Slightly lower estimates of genetic risk have been suggested based on family studies and large population cohorts (Kerner, 2014). The high heritability estimates and high monozygotic concordance rate are convincing indicators of the importance of genetic factors affecting bipolar susceptibility. However, the fact that monozygotic concordance is substantially less than 100% shows that genes alone are not the whole story (Craddock & Sklar, 2013).

Searches for common variants with moderate effect in candidate gene studies of BD have not produced consistent results. Moreover, genome-wide association studies (GWAS) with thousands of samples have not provided evidence that such moderate effect exists. However, common variants of a small effect (Odds Ratio [OR] <1.2) have been demonstrated and replicated (Nurnberger et al., 2014). In these studies, many single nucleotide polymorphisms (SNPs) of genes (e.g., ANK3, CAGNA1C, SYNE1, ODZ4, TRANK1) have emerged as promising candidate genes for BD (Craddock & Sklar, 2013; Kerner, 2014).

Using genes with consistent evidence of association in multiple GWAS, Nurnberger et al. (Nurnberger et al., 2014) identified biological pathways that contribute to risk for bipolar disorder. They found that pathways involved in the genetic predisposition to BD included hormonal regulation, calcium channels, second messenger systems, and glutamate signaling. In addition to these functions, gene expression studies implicated neuronal development pathways as well.

Models of illness are most consistent with multifactorial inheritance (Nurnberger et al., 2014). BD is probably a heterogeneous disease that connects to

many genes, and different genetic deviations can lead to the same kind of disorder phenotypically. Most cases of bipolar disorder involve the interplay of several genes or more complex genetic mechanisms, together with the effects of non-genetic (environmental) risk factors and stochastic factors (Craddock & Sklar, 2013).

2.4.2. Neurobiology

For a complete understanding of the pathophysiology of BD, its neurobiology must be addressed at different physiological levels: molecular, cellular, systems, and behavioral. BD arises from the interaction of multiple susceptibility genes. These genes (and the proteins they code) are undoubtedly related much more closely to specific biochemical processes and thus specific symptoms than to BD as defined by the DSM (Goodwin & Jamison, 2007). Many new methods, new domains, and new results have been found, but their significance is still partly uncertain. Many theories have been developed to integrate the results from different areas, but so far many parts of them have not been proved. From a neurobiological perspective, there is no such thing as bipolar disorder. Rather, almost certainly, many somewhat similar, but subtly different, pathological conditions produce a disease state that we currently diagnose as bipolarity (Maletic & Raison, 2014).

Historically, following the path set by MDD studies, BD was thought to result from an imbalance in monoaminergic neurotransmitter systems. Accordingly, these systems have been investigated in biological and pharmacological studies, and hypotheses involving the noradrenergic, dopaminergic, serotonergic, and cholinergic systems have been developed (Goodwin & Jamison, 2007; Grande et al., 2015). The evidence of monoamine involvement in the etiology of bipolar disorder is for the most part indirect, inconsistent, and lacking replication in larger scale studies (Maletic & Raison, 2014), and despite evidence showing that these circuits are likely to play a part, no singular dysfunction of these neurotransmitter systems has been identified (Grande et al., 2015). However, the monoaminergic hypothesis has not been totally forgotten. Berk et al. (Berk, Dodd et al., 2007) utilized cumulative pharmacological and imaging evidence to put forth the hypothesis of dopaminergic dysfunction in bipolar illness. Cousins et al. (Cousins et al., 2009) also reported that multiple lines of evidence suggest that the dopaminergic system may play a central role in BD. Additionally, van Enkhuizen et al. (van Enkhuizen et al., 2015) recently updated the hypothesis of catecholaminergic-cholinergic balance with recent findings from human and animal studies. They reported that evidence from neuroimaging studies, neuropharmacological interventions, and genetic associations support the notion that increased cholinergic functioning underlies depression, whereas increased activation of catecholamines (dopamine and norepinephrine) underlie mania.

The GABAergic and glutamatergic systems, the major inhibitory and excitatory systems, respectively, are also receiving greater attention and interest (Newberg et al., 2008). Multiple, consistent, and convergent evidence from genetic, postmortem, biochemical, and imaging studies points to a principal role of glutamatergic dysregulation in the etiopathogenesis of bipolar disorder (Maletic & Raison, 2014).

Although traditionally viewed exclusively as a neurochemical disorder, recent evidence suggests that the pathophysiology of BD may involve alterations of signaling cascades, rather than specific alterations in particular neurochemicals per se (Newberg et al., 2008) and it is becoming increasingly evident that current mood-stabilizing agents have actions that extend beyond binding to neuronal membrane surface receptors. Therapeutic actions of psychotropic medications utilized in the treatment of bipolar disorder most likely rely on an interface with intracellular signaling cascades and eventual enduring changes in gene expression, accompanied by alterations in neurotransmission and neuroplasticity (Maletic & Raison, 2014). On the other hand, modulation of synaptic and neural plasticity seems to be important in the circuitry regulating affective and cognitive functions (Grande et al., 2015). Neurotrophins, such as the brain-derived neurotrophic factor, are a family of regulatory factors that mediate the differentiation and survival of neurons, as well as the modulation of synaptic transmission and synaptic plasticity (Newberg et al., 2008). Dendritic spine loss has been noted in post-mortem brain tissue of patients with BD (Grande et al., 2015).

Also, alterations in the hypothalamic, pituitary, adrenal (HPA) axis function in bipolar disorder have been well substantiated. BD is associated with a significant degree of HPA axis hyperactivity, which is most prominent in the manic phase but also persists in remission (Belvederi Murri et al., 2016). Exaggerated release of the corticotropin-releasing factor (CRF) contributes to greater adrenocorticotropic hormone (ACTH) secretion and a subsequent elevation of circulating glucocorticoids (i.e., cortisol) (Maletic & Raison, 2014). Overall, the available evidence suggests that HPA axis abnormalities should *not* be considered an etiological factor or endophenotype of BD, but rather a pathogenetic and pathophysiological mechanism that contributes to shape BD clinical presentation, while increasing the risk of clinical relapses and cognitive deterioration (Belvederi Murri et al., 2016). The cumulative impact of impaired HPA regulation combined with compromised glucocorticoid and insulin receptor activity, aggravated by inflammatory cytokines, might explain the high rate of metabolic syndrome, diabetes, dyslipidemia, and osteoporosis in the bipolar population (Maletic & Raison, 2014; Rosenblat et al., 2014).

Other pathways that can affect neuronal interconnectivity are also under study, including mithochondrial dysfunction and endoplasmic reticulum stress, neuroinflammation, oxidation, apoptosis, and epigenetic changes, particularly histone and DNA methylation (Grande et al., 2015). Convergent evidence from imaging, neurochemical, and genetic studies points to disturbances in bioenergetics and mitochondrial function in the context of bipolar illness (Maletic

& Raison, 2014). BD is also associated with abnormalities in glial cells (Hercher et al., 2014; Maletic & Raison, 2014; Muneer, 2016; Schroeter et al., 2010), whereas the data supporting a role for a primary neuronal pathology in the condition are less convincing (Maletic & Raison, 2014).

Accumulating evidence implicates inflammation as a critical mediator in the pathophysiology of mood disorders (Bhattacharya et al., 2016; Muneer, 2016; Rosenblat et al., 2014), and it has been proposed that BD can be conceptualized as a multi-systemic inflammatory disease (Leboyer et al., 2012). Several studies have reported elevated levels of peripheral inflammatory cytokines in bipolar depressed and manic patients compared with healthy controls (Maletic & Raison, 2014; Muneer, 2016; Rosenblat et al., 2014). Immune dysregulation in bipolar disorder is associated with alterations in monoamine and glutamate signaling, impaired neuroplasticity and neurotrophic support, and changes in glial and neuronal function, most likely contributing to the symptomatic expression and medical comorbidities of this mood disorder (Maletic & Raison, 2014; Muneer, 2016). Overall, the data suggest that successful treatment leading to a euthymic state may reverse inflammation and normalize peripheral levels of inflammatory mediators (Maletic & Raison, 2014), but this has not been seen in all studies (Rosenblat et al., 2014). Combined with autonomic disturbance, increased platelet/endothelial aggregation, and unhealthful lifestyle, elevated inflammation may contribute to a substantially increased risk of respiratory and gastrointestinal disorders, cerebrovascular and cardiovascular disease, and migraines in the bipolar population (Leboyer et al., 2012; Maletic & Raison, 2014; Rosenblat et al., 2014). However, not all patients suffering from mood disorders have an inflammatory component (Bhattacharya et al., 2016).

2.4.3. Structure and function in brain imaging studies

New findings have emerged with modern methodologies although there is still a paucity of longitudinal studies and studies of different mood states. The main findings from structural neuroimaging studies have been summarized in recent reviews (Abe et al., 2015; Arnone et al., 2009; Emsell & McDonald, 2009; Hanford et al., 2016; Lim et al., 2013; Phillips & Swartz, 2014) supporting the main themes from functional neuroimaging studies. The authors have found cortical changes, mainly decreased gray matter volume, decreased white matter volume, and decreased cortical thickness in prefrontal, anterior temporal, and insula cortices. Also, decreased gray matter volume, in particular in the right ventrolateral prefrontal cortex and orbitofrontal cortex, has been found. The main subcortical findings have been a decreased volume of amygdala and hippocampus, as well as altered striatal volumes. The main white matter tract findings from diffusion tensor imaging (DTI) studies have been an altered fractional anisotropy (FA) and increased radial diffusivity in frontally situated white matter, supporting the main themes from functional neuroimaging studies. Some structural imaging

differences have been found between patients with BD I and BD II (Abe et al., 2015). However, according to Hanford et al. (Hanford et al., 2016), there is little support for the idea that cortical changes precede the onset of BD.

The advances in neuroimaging techniques have produced prolific neuroimaging research in BD. Although discrepancies exist among neuroimaging research reports, a common hypothesis has been found, namely, that bipolar disorder arises from abnormalities within brain systems that modulate emotional behavior. Strakowski et al. (Strakowski et al., 2012) hypothesized that developmental failure to establish healthy ventral prefrontal-amygdala networks underlies the onset of mania and ultimately, with progressive changes throughout these networks over time, a bipolar course of illness.

Phillips and Swartz (Phillips & Swartz, 2014) provided a new conceptualization of neural circuitry abnormalities in bipolar disorder based on the most consistent themes emerging from neuroimaging research. They stated that emotional over-reactivity and emotion dysregulation are characteristic symptoms of bipolar disorder. According to them, a large number of functional neuroimaging studies has examined (and found abnormalities in) the emotion-regulation neural circuitry function in patients with BD during performance of emotion-processing and emotion-regulation tasks.   These studies indicated abnormalities in adults with BD in prefrontal cortical-amygdala-centered emotion-regulating circuitry and prefrontal cortical-striatal reward circuitry. They suggested four main themes connected with these abnormalities that emerged from neuroimaging studies.

The first theme is that abnormally decreased ventrolateral prefrontal cortex activity and abnormally decreased ventrolateral prefrontal cortex-amygdala functional connectivity exist during different positive and negative emotion-processing tasks, emotion-regulation tasks, and response inhibition. The second theme, built on the first, is a pattern of abnormally increased amygdala, striatal, and medial prefrontal cortical activity and decreased functional connectivity between amygdala and prefrontal cortex to positive emotional stimuli (especially happy faces). These findings may reflect an underlying attentional bias to positive emotional stimuli in bipolar disorder, predisposing to mania. A third theme is abnormally increased activity in emotion-processing circuitry, including amygdala, orbitofrontal cortex, and temporal cortex during non-emotional cognitive task performance in bipolar disorder. These findings suggest heightened perception of emotional salience in non-emotional contexts in bipolar disorder. The last theme is related to the fact that another feature of bipolar disorder is heightened reward sensitivity, indicated by behavioral and event-related-potential studies. Accordingly, the findings from neuroimaging studies have demonstrated abnormally increased left ventrolateral prefrontal cortex and orbitofrontal cortex and ventral striatum activity during reward processing (Phillips & Swartz, 2014).

Phillips et al. (Phillips & Swartz, 2014) suggested that BD can be conceptualized in neural circuity terms as parallel dysfunction in prefrontal cortical (especially ventrolateral prefrontal cortex and orbitofrontal cortex)-

hippocampal-amygdala emotion-processing and emotion-regulation circuits bilaterally, along with an "overactive" left-sided ventral striatal-ventrolateral prefrontal cortex reward processing circuitry that may, together, result in characteristic behavioral abnormalities associated with the disorder – emotional lability, emotional dysregulation, and reward sensitivity.

2.4.4. Sleep and circadian rhythms

Rhythm disruption is a core feature of BD, and it has been hypothesized that disturbances in the circadian timing system play a fundamental role in the etiology of BD (Gonzalez, 2014), with multiple lines of evidence supporting the conceptualization of bipolar disorder as a disorder of circadian rhythms (Soreca, 2014). Sleep disturbances are central to the symptoms of mood disorders, so much that hypersomnia and insomnia are diagnostic criteria for depression and mania (Frank et al., 2015). Altered endocrine and neurotransmitter diurnal rhythms in bipolar disorder have also been described. The secretion of several neurotransmitters is subject to circadian regulation and appears to be altered in bipolar disorders. In contrast to large-scale GWAS which have not established an association between CLOCK genes and bipolar disorder, smaller linkage studies, while lacking adequate replication, have noted an association between several circadian genes, including TIMELESS, ARNTL1, PER3, NR1D1, CLOCK, and GSK-3 beta, and bipolar illness (Maletic & Raison, 2014).

Many lines of evidence suggest that circadian disturbances are not likely to be a secondary epiphenomenon of bipolar illness given that they are present during mania and depression, in euthymic state, and in healthy relatives of bipolar patients (Maletic & Raison, 2014). However, the possibility still exists that the rhythm disturbances are a secondary epiphenomenon, rather than there being a primary dysfunction in the timing system itself (Gonzalez, 2014). It has also been suggested that multisystemic involvement in bipolar disorder, with high rates of psychiatric and medical comorbidity, may be a consequence of the underlying circadian pathology (Soreca, 2014). Even though compelling evidence suggests biological rhythm disruption in BD, no consensus has been reached as to the exact nature of these disturbances (Gonzalez, 2014).

2.4.5. Psychosocial factors

Although much recent research has focused on biological factors, several psychosocial factors have also been identified that may be relevant to understanding the development and progression of bipolar disorder or a particular individual's presentation (NCCMH, 2014). Even the most heritable psychiatric disorders, including bipolar disorder, are thought to have a multifactorial origin, with genetic and non-genetic factors probably interacting. These gene-

environment interactions assume that environmental factors are major causes of the disorder, whereas genes affect the level of susceptibility to these factors (Etain et al., 2008). Also, antecedent factors, such as childhood maltreatment, may act as predisposing factors for developing the disorder, whereas concurrent factors such as social class, social support, and self-esteem, or variation in self-esteem, may act as course modifiers or precipitants for episodes (NCCMH, 2014).

Several environmental factors have been identified as potentially involved in this disorder, including early childhood trauma, stressful life events, virus infections, cannabis use, obstetric complications, and even very distant environmental factors, such as solar cycles (Etain et al., 2008). A potential role for psychosocial stressors in both the etiology and exacerbation of acute episodes has been identified in bipolar disorder (Hosang et al., 2010), with stressful life events being one of the strongest predictors of relapse in BD, and impairment in the stress response has been recognized as a core feature of BD clinical expression (Brietzke et al., 2012). The relationship between stressful life events and development of BD appears to be age/or developmental stage dependent. Childhood abuse and neglect have been postulated to affect endocrine systems, producing permanent reprogramming of the HPA axis (Lai & Huang, 2011), leading to systemic and neurological consequences, including dysfunction in the prefrontal cortex, amygdale, hippocampus, gonadal hormones, and immune system. The effect of stress in increasing the risk of BD is progressively diminished as the person gets older, suggesting the existence of critical windows for this effect (Brietzke et al., 2012). Also, several other biological pathways, including neuroplasticity, inflammation, and circadian system, are proposed to play a role in mediating the impact of childhood trauma on risk of developing BD or a more severe form of the disorder (Aas et al., 2016). Preliminary results have demonstrated that candidate genes belonging to these pathways help moderate the effects of childhood trauma on age at onset and suicidality in BD (Aas et al., 2016).

Several lines of evidence suggest that childhood trauma not only predisposes subjects to bipolar disorder, but also modulates the clinical expression and course of the disease (Etain et al., 2008). In a large study, Gilman et al. (Gilman et al., 2015) investigated the role of childhood adversities and adulthood stressors in liability for bipolar disorder using data from NESARC (n=33 375). They analyzed risk for initial-onset and recurrent DSM-IV manic episodes. Stressors characterized as personal losses, financial and interpersonal problems, and economic difficulties were associated with 1.5 to 3-fold increases in the risk of both first-onset and recurrent manic episodes during a three-year follow-up period. Moreover, a history of childhood abuse and sexual maltreatment was associated with the risk of both first-onset and recurrent manic episodes independent of adulthood stressors. Adulthood stressors were more likely to precipitate first-onset mania among individuals with a history of childhood physical abuse or neglect. Sexual maltreatment, in contrast, was such a powerful predictor of bipolar disorder that stressful life events in adulthood did not further increase the risk of mania among adults who experienced this type of adversity.

Childhood physical abuse and sexual abuse seem to be the strongest predictors of unfavorable clinical characteristics in bipolar disorders (Etain et al., 2013). In BD, there are indications that childhood trauma is associated with a more severe form of the disease, including earlier age at onset of illness, a rapid cycling course, greater proneness toward depression, more psychotic features, higher number of lifetime mood episodes, and suicide ideation and attempts (Aas et al., 2016; Etain et al., 2013; Larsson et al., 2013). Etain et al. (Etain et al., 2013) also found a clear dose-response effect of abuse on all of these clinical variables, in the direction of associating increased trauma with more severe clinical expression. The influence of childhood trauma on the clinical expression of bipolar disorder may involve two types of link. For suicidal behavior, substance misuse, and psychotic features, childhood trauma may have a direct and probably non-specific effect, as this effect seems to be independent of the psychiatric disorder. Nevertheless, this direct link may be reinforced by an earlier onset of the disease (as childhood trauma is linked with earlier onset of BD and earlier onset of BD is linked with suicidal behavior, substance misuse, and psychotic features). For other clinical components, the effects of childhood trauma may be mediated by an earlier age at onset (e.g., rapid cycling or comorbid panic disorder) (Etain et al., 2008).

However, no study has so far definitely demonstrated causality between childhood trauma and bipolar disorder (Larsson et al., 2013). Although there has been a long-standing suspicion that social stressors contribute to the risk of bipolar disorder, the limited evidence that exists is not strong enough to support causation, despite evidence from twin studies indicating that environmental factors account for approximately a quarter to a third of the population variance in bipolar disorder (Gilman et al., 2015). There is the unresolved chicken and egg debate (Etain et al., 2008). The high incidence and severity of childhood trauma in bipolar disorder was initially seen as causal. Another interpretation is also possible, namely, that being predisposed to bipolar disorder may increase the likelihood of experiencing trauma during childhood. According to this hypothesis, high trauma scores may be a consequence of childhood behavioral disturbances linked to an early onset of BD, to prodromal features of adulthood onset BD, or to early comorbid disorders and may lead to dysfunctional attitudes in parents. Alternatively, the genetic characteristics and psychopathology of the parents might lead both to disease in the offspring and to an increase in the likelihood of childhood trauma. In this interpretation, the genetic substrate of the parents leads to both the abuse and to the illness in children. Presently, the most reliable predictor for BD remains a positive family history for BD. Apart from a positive family history, stressful life events are associated with the onset of first as well as subsequent mood episodes in BD (Hosang et al., 2012; Kemner et al., 2015; Koenders et al., 2014).

2.4.6.   Neuroprogression

The term neuroprogression has been increasingly used to define the pathological reorganization of the central nervous system along the course of severe mental disorders. This reorganization could arise as a result of several insults, such as inflammation and oxidative stress. In BD, neural substrate reactivity is changed by repeated mood episodes, ultimately promoting a brain rewiring that leads to an increased vulnerability to life stress (Gama et al., 2013).

However, illness trajectories in BD are largely variable and it seems that illness progression is not a general rule in BD (Passos et al., 2016). Martino et al. (Martino et al., 2016) have written a critical review of the clinical evidence supporting the concept of neuroprogression in BD. They stated that since the emergence of the staging models (Berk et al., 2007; Kapczinski et al., 2009), copious amounts of narrative reviews have proposed BD as a neuroprogressive illness in which there is a higher risk of recurrence and cognitive impairment as well as poorer response to treatment and functional outcome as a function of previous episodes, as one of the pillars of the notion. After reviewing the studies reported on these topics, they concluded that clinical evidence supporting the concept of neuroprogression in BD is scarce and limited. Because in the studies only a part of the patients (around 20% to 40%) have been reported to have each of these measures of neuroprogression, they speculated that the same subgroup of about a third of patients may have most of these features: increased risk of recurrence and cognitive deficits, as well as poorer response to treatment and psychosocial functioning. So that it would not necessarily be a question of neuroprogression, rather that they are different kinds of patients from the start.

At the moment, multimodal neuroimaging techniques such as DTI, functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS) do not clearly support a neuroprogression model in BD. However, additional studies that take a lifespan and longitudinal perspective are needed to address this area of controversy definitively (Sajatovic et al., 2015).

2.5.   Course and outcome of bipolar disorder

2.5.1.   Age at onset

Patients generally experience their first manic episode in their early twenties, although this can occur at any stage of life, from childhood to old age (Treuer & Tohen, 2010). Goodwin and Jameson (Goodwin & Jamison, 2007) reviewed 15 studies published between 1990 and 2003 and derived a weighted mean of 22 years. Baldessarini et al. (Baldessarini et al., 2010) reported pooled data from 1,566 patients with BD from six international sites (5 European, 1 US) to compare ages in subgroups. They found that median age of onset was 25 years (≤13 years

3%, >13-19.9 years 22%, ≥ 20-29.9 years 37%, ≥ 30 years 38%). Juvenile onset (age≤ 20) involved 25%, and childhood onset (age ≤ 13) 3%, of cases. Median age at onset in BD II was six years later than in BD type I (24 years vs. 30 years). Post et al. (Post et al., 2008) examined the incidence of childhood onset BD in the US and Europe in 543 patients with BD (type not reported). In their sample, 61% of the US patients had their onset of BD prior to age 19, double the rate for the European sites (30%). In the European sites, the mean age at onset was 25.2 years vs. 19.4 for the US sites. In a Norwegian sample of 225 patients with BD I or II, the onset age was 6% for age ≤12 years, 32% for 13-18 years, 43% for 19-29, and 19% for >30 years (Larsson et al., 2010). The mean age was 22.8 years. In the Finnish JoBS, the mean age of onset was 21.2 years (Mantere et al., 2004) and 30% of the patients had an age of onset <18 years (Suominen et al., 2007).

Although the rates of recovery from index episodes are high (70%–100%) among children and adolescents with BD, of those who recover, up to 80% will experience one or more syndromal recurrences over a period of two to five years, particularly depressive episodes and multiple subsyndromal recurrences. Compared with adult BD studies, youth with BD spend more time symptomatic and with mixed/rapid cycling, subsyndromal symptoms, and with more mood changes (Birmaher, 2013). Evidence also suggests that experiencing (hypo)manic symptoms is a common adolescent phenomenon that infrequently predicts mental health use, the probability increasing linearly with the number of manic symptoms. Thus, (hypo)manic symptoms may be conceived as partially pertaining to normal adolescent behavior (Tijssen et al., 2010).

BD considerably affects the normal psychosocial development of a child and increases the risk of academic, social, and interpersonal problems (e.g., family, peer, work); it is also linked to an increased risk of suicidality, substance use, and poor health utilization (Birmaher, 2013). Earlier onset of BD is also an important predictor of a more severe clinical course and poorer outcome, as well as a longer time to correct diagnosis (Larsson et al., 2010; Suominen et al., 2007).

At the other end of life, epidemiological studies report that types I and II BD affect 0.5% to 1.0% of older adults, and it is estimated that 5% to 10% of individuals with BD will be aged ≥50 at the time of the first manic or hypomanic episode (Sajatovic et al., 2015). BD becomes less common with age; in the geriatric population (>65 years), it is about a third (0.1-0.4%) as common as in younger populations (Dols et al., 2014; Sajatovic et al., 2015). Mania or hypomania that first appears in later life (after age 40) usually follows many years of repeated episodes of unipolar depression or is secondary to other factors such as steroid medication, infection, neuroendocrine disturbance, or neurological problems. However, only 15% of people with bipolar disorder presenting for the first time to mental health services are precipitated by a medical problem (NCCMH, 2014).

2.5.2.   Frequency of episodes (cycle length)

Variation in cycle length (the time from the onset of one episode to the onset of the next) reflects primarily variation in the length of the symptom-free interval because the duration of episodes tends to be relatively constant in a given individual (Goodwin & Jamison, 2007). Studies have found differing results concerning the hypothesis of progressive shortening of euthymic phases or cycle lengths with more recurrences. About 40% of reports found a decreasing length of euthymic phases, but in most reports there was either no significant change or the course was random (Baldessarini et al., 2012). Some studies have found a decreasing length of euthymic phases mainly in the first three episodes, with unchanging euthymic phases of about one per year for further episodes (Goodwin & Jamison, 2007). According to long-term follow-up studies, there seems to be no 'burnout', declining of the frequency of cycles with age (Angst et al., 2003; Goodwin & Jamison, 2007).

2.5.3.   Onset, duration, and polarity of episodes

Often, the onset of manic episodes is abrupt, developing over a few days. Depressive episodes develop more gradually, over weeks, although bipolar depressive episodes are more abrupt in onset than unipolar depressive episodes (Goodwin & Jamison, 2007). In the Finnish JoBS study, only half of the patients with BD reported having had discrete prodromal symptoms. The first prodromal symptom was mostly congruent with mood (e.g., decreased need to sleep before manic and hypomanic episodes and fatigue, loss of interest before depressed mood). For most patients (80%), the prodromal symptoms lasted more than a week, thus potentially allowing time for intervention (Mantere et al., 2008b).

Before introduction of effective treatments, the reported duration of manic episodes was between 4 and 13 months and a mean length of depressive episodes between 4 and 8 months (Angst & Sellaro, 2000; Fagiolini et al., 2013). The studies conducted after effective medication has been available have shown decreased duration of episodes, with a mean time to recovery from 6 to 17 weeks, with depression lasting longer than manias in some studies (Goodwin & Jamison, 2007). However, the recovery of treated mania, even very early in the course of BD, can still require three to six months before the patient no longer meets standard diagnostic criteria for an acute episode (syndromal remission); it can take even longer to reach symptomatic remission, defined as the presence of minimal symptoms, and still longer to attain the beginning of recovery, defined as remission sustained for at least two months. Time to remission is even longer following repeated recurrences.

The polarity of the index episode can predict the polarity of subsequent episodes. Different definitions have been proposed for predominant polarity

across studies, from the simple definition of having more lifetime episodes of a given polarity to the later concept of having at least two-thirds of lifetime episodes in a given polarity (Carvalho et al., 2014). Patients with a depressive predominant polarity are most likely to attempt suicide, have depressive onset, and be diagnosed with BD II that follows a seasonal pattern. Conversely, with manic-predominant polarity, drug misuse is common and patients usually present at a young age with a manic episode and have BD I (Grande et al., 2015). Predominant polarity may influence response to acute treatment for bipolar depression and should be considered when selecting maintenance treatment for BD (Carvalho et al., 2014).

2.5.4. Long-term outcome

2.5.4.1. Course and outcome

Traditionally, BD has been thought of as an episodic condition characterized by periods of hypomania/mania and depression (Vazquez et al., 2015). However, studies have shown that for most patients BD is a recurrent, lifelong illness with high risk of disability and excess mortality, and evidence is accumulating to suggest that this condition is associated with significant chronicity (Judd et al., 2002; Judd et al., 2003; Mantere et al., 2008a; Pallaskorpi et al., 2015; Perlis et al., 2006; Post et al., 2003; Tohen et al., 2003). For a large proportion of patients with BD, residual subsyndromal symptoms persist between major syndromal episodes, and studies have shown that many patients with BD are symptomatic for approximately 50% of the time over follow-up periods greater than 10 years. Unfortunately, despite many treatment options with demonstrated short-term efficacy, evidence concerning long-term treatment effectiveness in BD remains limited (Vazquez et al., 2015).

2.5.4.2. Rates of remission and relapse

One way to study the burden of BD is through the timing and rates of remission/recovery and relapse/recurrence. The risk of recurrence in the 12 months after a mood episode is especially high (50% in one year, 75% at four years and, afterwards, 10% per year) compared with other psychiatric disorders. So, the rate of relapse in those who make a full recovery from the index episode and have not relapsed in four years is about 10% per year; unfortunately, very few with residual symptoms from the index episode reach four years without having at least one further episode (NCCMH, 2014).

2.5.4.2.1. First manic episode follow-up studies

In the McLean-Harvard First-Episode Mania Study, Tohen et al. (Tohen et al., 2003) followed 166 patients with BD for two to four years after their first

hospitalization for a manic or mixed episode. Most patients (n=125, 75%) were in their first lifetime affective episode, but 41 (25%) had experienced prior episodes of depression that did not require hospitalization. By two years, most subjects achieved syndromal recovery (98%, with 50% achieving recovery by 5.4 weeks), and 72% achieved symptomatic recovery, but only 43% achieved functional recovery (returned to their occupational and residential status in the year before intake). Within two years of syndromal recovery, 40% experienced a new episode of mania (20%) or depression (20%), and 19% switched phases without recovery.

In the Systematic Treatment Optimizing Program for Early Mania (STOP-EM), Gignac et al. (Gignac et al., 2015a) followed a cohort of 81 patients with a first episode of mixed or manic episode for four years. They reported high remission and recovery rates: At 6 months, remission and recovery rates were 99% and 91%, respectively, and all patients remitted by 12 months and all recovered by 18 months. Within a year of remission, 58% of patients had a recurrence of their mood disorder, and by four years a recurrence rate of 74% was observed. First recurrences were predominantly depressive, and patients who had a recurrence of their mood disorder within the first year had significantly higher rate of recurrences over the follow-up period.

Gignac et al. (Gignac et al., 2015b) also performed a systematic review and meta-analysis of the former prospectively characterized cohorts of 734 patients with a first episode of mania. They reported a syndromal recovery rate of 84% at six months and 88% at one year. While most patients achieved syndromal recovery, only 62% had achieved a period of symptomatic recovery within one year. Recurrence rates were 26% within six months, 41% by one year, and 60% by four years (so 40% did not have a recurrence in four years).

2.5.4.2.2. Follow-up studies of unselected populations

Perlis et al. (Perlis et al., 2006) reported the primary outcomes from STEP-BD. From 1,469 participants symptomatic at study entry, 858 (58%) subsequently achieved recovery. During up to two years of follow-up, 49% of these individuals experienced recurrences, with more than twice as many developing depressive episodes (35%) as those who developed manic, hypomanic, or mixed episodes (14%). Residual depressive or manic symptoms at recovery and the proportion of days depressed or anxious in the preceding year were significantly associated with shorter time to depressive recurrence. Residual manic symptoms at recovery and proportions of days of elevated mood in the preceding year were significantly associated with shorter time to manic, hypomanic, or mixed recurrence.

Simhandl et al. (Simhandl et al., 2014) reported the results of a prospective four-year naturalistic follow-up of 300 consecutively admitted hospitalized patients with BD I and BD II and found that 68% of the patients relapsed within four years. Pallaskorpi et al. (Pallaskorpi et al., 2015) reported the five-year outcome of the JoBS cohort. Nearly all subjects had recovered from the index episode (96% had reached full remission of at least two months), but almost all

(90%) had a recurrence and almost half (48%) experienced three or more recurrences.

Vazquez et al. (Vazquez et al., 2015) made a systematic comparison of long-term prospective, naturalistic studies (10 studies, with 3,904 patients with BD, 86% BD I, followed up to 2.1 years) versus randomized controlled trials (RCTs). Among the 10 naturalistic studies analyzed, the overall recurrence risk averaged 55% (from 40% to 66%), and the annualized recurrence rates averaged 26%/year (from 20%/years to 31%/year) with clinically determined treatments. Most subjects in these clinical trials (70%) presented with depressive index episodes, and a majority (56%) of their first recurrent episodes during two-year follow-up was also depressive.

2.5.4.3. Time with symptoms

Another way to examine the burden of BD is to analyze the proportion of time ill. The evidence shows the disabling nature of BD, with patients having symptoms about half of the time followed. According to the results, BD II is not a milder form of BD; in some ways, it is even worse than BD I.

Judd et al. (Judd et al., 2002; Judd et al., 2003) reported the results of the National Institute of Mental Health Collaborative Depression Study (CDS), a prospective long-term follow-up of 146 patients with BD I and 86 patients with BD II. Patients with BD I were symptomatically ill 47% of weeks throughout a mean of 12.8 years of follow-up. Depressive symptoms predominated over manic/hypomanic symptoms; patients experienced three times more depressive than manic symptoms (32% vs. 9% of total follow-up weeks). Subsyndromal and minor depressive/dysthymic symptoms were much more prevalent than major depressive-level symptoms (23% vs. 9% of weeks). Overall, most symptomatic weeks involved subsyndromal, minor depressive, and hypomanic symptoms (74%). Only 12% of all follow-up weeks were spent with symptoms at the threshold for major depression or mania. Patients with BD II were symptomatically ill for more than half of the follow-up weeks (54%). They experienced 39 times more depressive symptoms (50% of all follow-up weeks) than hypomanic symptoms (1% of all follow-up weeks). Subsyndromal, minor depressive/dysthymic, and hypomanic symptoms combined were three times more prevalent than full major depressive-level symptoms (41% vs. 13% of all follow-up weeks).

Post et al. (Post et al., 2003) reported morbidity in 258 bipolar outpatients followed for one year in the SFBN. Patients were treated naturalistically with a mean of four psychotropic medications during the year. Despite comprehensive pharmacological treatment, two-thirds of the patients were substantially affected by their illness; 26% was ill for more than three fourths of the year, and 41% was intermittently ill with major affective episodes. Patients experienced symptoms almost half (47%) of the year, with manic symptoms 11% of the time and depressive symptoms 33% of the time. Only 9% of the patients had no episodes,

28% had one to three episodes, 32% had four to eight episodes, and 31% of the population had more than eight episodes in the year.

In another SFBN study (Kupka et al., 2007), clinician-adjusted self-ratings of mood were completed daily for one year for naturalistic treated outpatients with BD I (n=405) or BD II (n=102). The percentages of time spent ill for BD I vs. BD II were; euthymia 48% vs. 50%, depression 36% vs. 37%, hypomania 12% vs. 10%, mania 1% vs. 0%, and rapid cycling 4% vs. 3%. The study confirmed that depression is the most common illness state in BD outpatients receiving naturalistic treatment, but the more depressive course of BD II than BD I seen in Judd et al.'s long-term follow-up was not seen in this study. Based on the Finnish JoBS study, Mantere et al. (Mantere et al., 2008a) reported the outcome results of 18 months' follow-up. Patients with BD II spent a higher proportion of time ill (48% vs. 38%) and 40% more time in depressive states (58% vs. 42%) than BD I patients. Pallaskorpi et al. (Pallaskorpi et al., 2015) studied the five-year outcome of the same cohort and reported that, contrary to the 18-month follow-up and similar to the findings of Kupka et al., there were no differences in the time spent in depressive states between patients with BD I and BD II. They found that the patients spent almost a third of the time in illness episodes and about a sixth of the time with subthreshold symptoms. Half the time, they were euthymic.

2.6.   Disability in BD

Functioning is a complex concept that involves many different domains, including the capacity work, study, live independently, and engage in recreational activities and interpersonal relationships (Zarate et al., 2000). Functional recovery is defined as the return to premorbid levels of psychosocial activity (Strakowski et al., 1998). In most studies, functional recovery has been described as the ability to achieve the level of functioning prior to the most recent episode (Martinez-Aran et al., 2007).

2.6.1.   Burden of bipolar disorder

In the era prior to modern pharmacotherapy, Kreapelin (1921) described a relatively good long-term outcome of manic-depressive illness, with periodic manic or depressive episodes typically followed by a return to what was considered normal functioning (Rosa, Sanchez-Moreno et al., 2007). However, modern outcome studies have found that most bipolar patients evidence high rates of functional impairment (Zarate et al., 2000). Psychosocial functioning in BD runs the full gamut of human potential. Whereas some people with BD accomplish historical landmarks in human achievement, others experience significant difficulties in managing the tasks of daily living (Levy & Manove, 2012).

Poor premorbid functioning tends to present early in the course of BD. Although many patients with BD regain psychosocial functioning upon symptomatic remission, the majority of patients suffer significant and persistent interpersonal, social, and vocational impairment, often despite adequate control of affective symptoms (Andreou & Bozikas, 2013). Disappointingly, despite several new treatment options, the proportion of patients with BD who are able to retain their premorbid levels of social and vocational functioning has not increased since the 1970s (Dickerson et al., 2010).

Bipolar disorder is among the 20 leading causes of disability worldwide, just below schizophrenia (Vos et al., 2012), and imposes a tremendous burden on patients and the health care system (Dean et al., 2004). At the individual level, disability and costs of BD are greater than in major depressive disorder, although MDD has a larger impact on the general population due to its higher prevalence (Goldberg & Harrow, 2011; Kessler et al., 2006; McIntyre, Wilkins et al., 2008). Long-term follow-up studies of patients with BD have indicated strikingly high levels of sustained morbidity, on the order of 30% to 50% of time observed, mostly accounted for by depressive-dysthymic-dysphoric morbidity that persists or recurs despite treatment (Huxley & Baldessarini, 2007). Several studies have also confirmed that 30% to 60% of bipolar patients, even if in syndromic remission, fail to regain full functioning in occupational and social domains (MacQueen et al., 2001). Even patients who achieve full clinical remission show difficulties in reaching a complete functional recovery, that is, returning to their premorbid level of functioning (Sanchez-Moreno et al., 2009). In the McLean-Harvard First-Episode Mania Study, Tohen et al. (Tohen et al., 2003) followed 166 patients with BD for two to four years after their first hospitalization for a manic or mixed episode. Within two to four years of first lifetime hospitalization for mania, all but 2% of patients' experienced syndromal recovery, but 28% remained symptomatic, with only 43% achieving functional recovery.

2.6.2.   BD and vocational ability

Work is an important part of functioning and vocational disability affects the patient, his or her nearest, and society as a whole in many ways. Work is highly valued by people with mental illness and return to work is seen as integral to their notion of recovery (Gilbert & Marwaha, 2013). High rates of unemployment, absenteeism, failure to return to work following acute episodes, and work impairment are frequent (Dean et al., 2004). According to a recent review (Marwaha et al., 2013), most studies (follow-up from 6 months to 15 years) with samples of people with established BD have suggested that approximately 40% to 60% is employed, while the employment rate in the general population in Europe ranges from 62% to 66% and in the US from 66% to 74%. About 30% to 40% of patients with BD have significant difficulties in work performance, and 40% to 50% may suffer a slide in their occupational status over time. Also, Morselli et al.

(Morselli et al., 2004) found that for each of the European nations studied, the percentage of unemployed people in the BD group was significantly above the mean level of unemployment in each country. Reed et al. (Reed et al., 2010) reported the results of a prospective study of 1,795 patients with a manic or mixed episode followed up for two years (European mania in bipolar longitudinal evaluation of medication study [EMBLEM]). Most (69%) of the patients had high work impairment in the year prior to the acute episode. Impairment in work ability at two years was found in 42% of the patients, and 15% was unable to work due to mental illness.

The reasons for the poor vocational outcome of patients with BD are not well understood. Studies have focused on work impairment in terms of long-term employment, occupational functioning, absenteeism due to emotional problems and somatic complaints, and poor work performance (Dean et al., 2004). Studies have searched explanations from demographic, clinical, and neurocognitive risk factors, and many of these have been associated with disability (Huxley & Baldessarini, 2007; Sanchez-Moreno et al., 2009; Tse et al., 2014).

Many factors have also been associated with vocational outcome, but they vary between studies and have been difficult to replicate, in part due to methodological differences in assessing functional outcome and the populations studied (Martinez-Aran et al., 2007). Symptoms of illness phases, also subsyndromal symptoms, affect functioning, even if hypomanic symptoms sometimes temporarily involve a higher level of functioning (Altshuler et al., 2006; Judd et al., 2005; Rosa et al., 2010; Simon et al., 2007). Also, the number of hospitalizations, as a proxy for overall severity of the illness, has been found to predict work disability (Tse et al., 2014). However, as even patients who achieve clinical remission show difficulties in returning to their premorbid level of functioning (Sanchez-Moreno et al., 2009), other reasons must also exist. The factors most consistently associated with functional impairment in patients with BD after episode remission include residual depressive symptoms (Altshuler et al., 2006; Bonnin et al., 2010; Bonnin et al., 2012; Gitlin et al., 2011; Judd et al., 2005; Rosa et al., 2009) and specific deficits in cognitive functioning (Andreou & Bozikas, 2013; Martinez-Aran et al., 2007; Mur et al., 2009; Wingo et al., 2009), but additional explanations for the disability in patients with BD in remission have also been sought. In recent studies, Yan-Meier et al. (Yan-Meier et al., 2011) found stressful life events in the prior three months, Strejilevich et al. (Strejilevich et al., 2013) found mood instability, Jimenez et al. (Jimenez et al., 2012) found impulsivity, and Gershon et al. (Gershon & Eidelman, 2015) found inter-episode intensity and instability to be associated with functional impairment. So, in addition to cross-sectional severity, longitudinal course of illness, and cognitive functioning, other clinical factors may influence the ability to work.

2.6.3. Long-term vocational disability and disability pension

Patients with BD who are on disability pension or long sick leave likely suffer from the most severe forms of work disability due to their illness. Nevertheless, despite their marked public health and economic relevance, only a few cross-sectional studies (Grande et al., 2013; Gutierrez-Rojas et al., 2011; Schoeyen et al., 2013) have specifically investigated risk factors for disability pensions and/or long sick leaves among patients with BD. The predictors of receiving a disability pension in these studies were Axis II comorbidity, number of manic episodes, being without a stable partner, and older age (Grande et al., 2013), previous repeated manic episodes, three or more hospitalizations, and current depressive symptoms, lower educational attainment (Gutierrez-Rojas et al., 2011), the preceding number of hospitalizations for depressive episodes and illness duration (Schoeyen et al., 2013). The factors that are correlated to current work status and true predictors of future disability pension may differ because in cross-sectional studies causes and consequences are difficult to differentiate. A cross-sectional design also precludes specifying the timing and conditions under which the pension was granted.

2.7. Mortality

An increasing body of research has shown that BD is associated with premature mortality. Where previously it was believed this was mostly attributable to unnatural causes such as suicide, homicide, or accident, patients with BD are also at risk of premature death from a range of medical illnesses (Hayes et al., 2015).

In a large national cohort study (Crump et al., 2013), women and men with BD had, respectively, 2.3-fold and 2.0-fold increased mortality and died 9.0 (mean age, 73.4 vs. 82.4 years) and 8.5 (mean age 68.9 vs. 77.4 years) years earlier on average than the rest of the population. This life expectancy difference was not fully explained by unnatural deaths. Patients with BD had an increased risk of death from ischaemic heart disease, diabetes, COPD, influenza or pneumonia, unintentional injury, and suicide for both women and men and cancer for women only. After adjusting for age and other sociodemographic factors, the risk of death from suicide was 10-fold among women and 8-fold among men with BD compared with other women or men. Although the highest hazard ratios were for suicide, the leading causes of death were cardiovascular disease and cancer, as in the general population. Substance use disorders explained only a modest part of these findings. The authors also found that these associations between BD and mortality from chronic diseases (ischaemic heart disease, diabetes, COPD, or cancer) were much weaker among persons with an earlier diagnosis of these conditions, suggesting that timely medical diagnosis and treatment may effectively reduce mortality among patients with BD to approach that of the general population. Another nationwide register study from Denmark (Kessing et al., 2015) found that

for a typical male or female patient with BD aged 25 to 45 years, the remaining life expectancy was decreased by 12.0-8.7 years and 10.6-8.3 years, respectively.

A recent systematic review and meta-analysis by Hayes et al. (Hayes et al., 2015) showed that all-cause mortality in BD is double that expected in the general population. Natural deaths are more than 1.5 times greater in BD than in the general population; these natural deaths include an almost double the risk of death from circulatory illnesses (e.g., heart attacks, strokes) and three times the risk of death from respiratory illness (e.g., COPD, asthma). Unnatural deaths are around seven times more common, with an increased risk of suicide of around 14 times and other violent deaths (e.g., accidents, homicides) almost four times as likely. There is no evidence that all-cause mortality for patients with BD has improved over time (from the 1950s) relative to the general population, despite the modern treatments since then.

A review by the International Society for Bipolar Disorders (ISBD) Task Force on Suicide in BD (Schaffer et al., 2015) found that the pooled suicide rate in bipolar disorder is 164 per 100,000 person-years. Sex-specific data on suicide rates identified a 1.7:1 ratio in men compared to women. People with bipolar disorder accounted for 3.4% to 14% of all suicide deaths, with self-poisoning and hanging being the most common methods. According to the reviewed epidemiological studies, 23% to 26% of people with bipolar disorder attempt suicide, with higher rates in clinical samples. In the Finnish JoBS study, 80% of patients had suicidal behavior and 51% had attempted suicide during their lifetime (Valtonen et al., 2005).

2.8. Treatment of bipolar disorder

2.8.1. Pharmacotherapy

The treatment of BD can be divided into acute phase treatment, in which the aim is symptomatic recovery with stable eythymic mood, and maintenance phase treatment, in which the aims are relapse prevention, reduction of subtreshold symptoms, and enhanced social and occupational functioning (Geddes & Miklowitz, 2013). The basic treatments for BD have been mood stabilizers (lithium, valproate, carbamazepine, lamotrigine) and antipsychotics (traditional and atypical antipsychotics) accompanied by appropriate psychosocial treatment. Over the last 10 to 15 years, there has been a substantive increase in the number of treatments for each phase of BD that have been well established in large, methodologically sound trials (Ostacher et al., 2015). However, overall, advances in drug treatment remain quite modest. On the other hand, substantial progress has been made in the development and assessment of adjunctive psychosocial interventions (Geddes & Miklowitz, 2013).

Because of the difficulty in choosing the right treatment, guidelines have been developed; these are "systematically developed statements that assist

clinicians and service users in making decisions about appropriate treatment for specific conditions" (NCCMH, 2014). They are derived from the best available research evidence, using predetermined and systematic methods to identify and evaluate the evidence relating to the specific condition in question. The following recommendations are mainly based on recent practice guidelines: Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with BD 2005 (Yatham et al., 2005) and updates 2009 (Yatham et al., 2009) and 2013 (Yatham et al., 2013); World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of BD, update 2009 on the treatment of acute mania (Grunze et al., 2009), update 2010 on the treatment of acute bipolar depression (Grunze et al., 2010), and update 2012 on the long-term treatment of BD (Grunze et al., 2013); British Association for Psychopharmacology (BAP), Evidence-based Guidelines for Treating BD, revised second edition 2009 (Goodwin & Consensus Group of the British Association for Psychopharmacology, 2009); Finnish Current Care Guideline for BD (FCCG), update 2013 (Workgroup for Finnish Current Care Guideline, Bipolar Disorder, 2013); National Institute for Health and Care Excellence (NICE) clinical guideline for BD 2014 (NICE, 2014), update 2016; Florida Best Practice Psychotherapeutic Medication Guidelines (FBPG) for Adults with BD, 2015 (Ostacher et al., 2015); and in some parts also the American Psychiatric Association (APA) practice guideline for the treatment of patients with BD, 2002 (APA, 2002).

2.8.1.1. Pharmacologic treatment of manic episodes

For patients experiencing a manic or mixed episode, the primary goal of treatment is the control of symptoms to allow a return to normal levels of psychosocial functioning. The rapid control of agitation, aggression, and impulsivity is particularly important to ensure the safety of patients and those around them (APA, 2002). The acutely manic bipolar patient may present in an agitated state that acts as a barrier to therapy, interrupts the physician-patient alliance, and creates a disruptive, even hazardous, environment. Oral therapy should be offered first whenever possible as it can be as effective as intramuscular agents. Intramuscular injections may be used for patients who refuse oral therapy. According to the CANMAT update 2013, intramuscular olanzapine, ziprasidone, and aripiprazole or a combination of intramuscular haloperidol and a benzodiazepin should be considered. Benzodiazepines may be used as adjuncts to sedate acutely agitated patients.

Acute mania is the phase best studied. A significant number of treatment options are available with solid evidence to support them (Fountoulakis et al., 2012). Lithium, carbamazepine, valproate, haloperidole, and atypical antipsychotics (quetiapine, olanzapine, risperidone, aripiprazole, ziprasidone, asenapine, and paliperidone) have been shown to be efficacious against mania (Smith et al., 2007). The practice guideline recommendations for the first and

second line of monotherapy are represented in table 1. When choosing medication, one should consider the types of symptoms of mania the patient has (e.g., euphoric, mixed, psychotic) and their severity, previous experiences and patient preference, long-term treatment, modifying medical factors, and safety profile (WFSBP, 2009).

Lithium is recommended as a first-line treatment for acute mania in most guidelines (APA 2002, WFSBP 2009, BAP 2009, CANMAT 2013, FBPG 2015), but NICE 2016 recommends it only if the patient is already taking it or as an add-on to the first-line antipsychotic. The usefulness of lithium in acute mania may be limited by the need for regular plasma level checks to avoid toxicity, as well as by its side-effect profile and contraindications. Its potentially slower onset of action together with the low levels of sedative properties often makes it necessary to combine it with a tranquilizing agent at treatment initiation (WFSBP 2009).

Valproate is also recommended as a first-line treatment for acute mania in most guidelines (APA 2002, WFSBP 2009, BAP 2009, CANMAT 2013, FBPG 2015), but, as with lithium, NICE 2016 recommends valproate only if the patient is already taking it or as an add-on to the first-line antipsyhotic. The safety margin of valproate is relatively large, allowing rapid titration ("dose loading") and a subsequent earlier onset of action (WFSBP 2009). The use of valproate is limited by the risk of teratogenicity, including developmental delay in children exposed to it in utero, and a high risk of unplanned pregnancy in women with BD (Geddes & Miklowitz, 2013). Therefore, it is important that the potential harm to developing fetuses be discussed with women and their families (CANMAT 2013, FBPG 2015), in addition to discussion of the use of effective contraception (APA 2002, WFSBP 2009, BAP 2009, FCCG 2013, CANMAT 2013, FBPG 2015). The NICE 2016 guideline recommends against offering valproate to women of childbearing potential for acute or maintenance treatment.

A substantial amount of data demonstrates that carbamazepine has efficacy similar to lithium and valproate (WFSBP 2009, CANMAT 2005), but because of safety, tolerability, and interactions with other medications, it is rarely advocated for first-line treatment (usually recommended as a second-line treatment) (APA 2002, WFSBP 2009, BAP 2009, CANMAT 2013, FBPG 2015). In the FCCG for Bipolar Disorder 2013, which only lists medications by efficiency, it is listed among the ones that are efficient for mania. The NICE 2016 guideline does not list carbamazepine among the medications recommended for mania.

Several second-generation or atypical antipsychotics, including olanzapine, quetiapine, risperidone, aripiprazole, asenapine, and zipraridone (FCCG 2013) and paliperidone (CANMAT 2013, FBPG 2015) have been found to be effective against mania. Few trials directly assessing the comparative efficacy of different second-generation or atypical antipsychotics exist, but a mixed treatment meta-analysis compared 13 agents studied in 68 randomized controlled trials (16,073 participants) (Cipriani et al., 2011). This review found substantial and clinically important differences in terms of both efficacy and tolerability between agents. According to this review, antipsychotic drugs seem to be better than

anticonvulsants and lithium in the treatment of manic episodes, and olanzapine, risperidone, and the first-generation antipsychotic haloperidol had the best profile of agents included (Geddes & Miklowitz, 2013). Most guidelines recommend atypical antipsychotics as a first-line treatment. Of the (atypical) antipsychotics, the NICE 2016 guideline recommends only olanzapine, risperidone, and quetiapine and the first-generation antipsychotic haloperidol against mania. Paliperidone, a metabolite of risperidone, is recommended as first-line treatment in CANMAT 2013 and as second-line treatment in FBPG 2015. The major concern with especially olanzapine, but to a lesser extent also quetiapine and risperidone, is weight gain and metabolic problems. Because of these safety concerns, the FBPG 2015 guideline sets olanzapine to a lower level (1B) and the BAP 2009 guideline sets both olanzapine and quetiapine to level 2.

Table 1. First- and second-line treatment recommendations for acute manic phase according to practice guidelines.

Practice guideline	Manic phase							
	Li	Val	Car	Lam	SGA	OFC	FGA	AD
BAP 2009	+	++	+		++[1]		+	D/C
WFSBP 2009	+/++	++	+		++[2]		+[8]	
CANMAT 2013	++	++	+		++[3]		+[8]	D/C
FCCG 2013	++	++	++		++[4]		++[8]	
NICE 2016	+[5]	+[5]			++[6]		++[8]	
FBPG 2015	++	++	+		++[7]		+[8]	

[1]aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, [2]aripiprazole, risperidone, ziprasidone; olanzapine as second line because of safety concerns, quetiapine and asenapine also as second line. [3]aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, asenapine, paliperidone, [4]aripiprazole, asenapine, quetiapine, olanzapine, risperidone, ziprasidone, [5]add-on antipsychotic, [6]olanzapine, quetiapine, risperidone, [7]aripiprazole, asenapine, quetiapine, risperidone, ziprasidone; olanzapine 1B because of safety concerns, [8]haloperidol. SGA=Second generation antipsychotic, FGA=First generation anti-psychotic, OFC=Olanzapine+fluoxetine, D/C=discontinue.

Of the first-generation antipsychotics, haloperidol has been shown to be effective against mania (WFSBP 2009) and is recommended as a first-line treatment in NICE 2016 and a 1B level treatment in FBPG 2015, and it is listed among the agents effective against mania in FCCG 2013. Because of the neurological side-effects (extrapyramidal motor symptoms and tardive dyskinesia), it is rated second line in the other guidelines (WFSBP 2009, BAP 2009, CANMAT 2013).

2.8.1.2. Pharmacologic treatment of mixed episodes

The simultaneous presentation of manic and depressive symptoms poses significant treatment challenges. Data suggest that patients who are in a mixed state are less likely to achieve remission and take longer to do so (CANMAT 2005). Suicide risk also appears to be high (Valtonen et al., 2008). Mixed episodes are not included in the DSM-5; instead, it has a mixed features specifier which can apply to the current manic, hypomanic, or depressive episode in BD I or II or MDD. For mixed episodes, APA 2002, BAP 2009, and NICE 2016 guidelines recommend the same medications as for a manic phase. According to CANMAT 2005, lithium may not be as effective in mixed states as it is in classic mania, while valproate and atypical antipsychotics appear to be equally effective in both. The FCCG 2013 recommends aripiprazole, carbamazepine, olanzapine, risperidone, tsiprasidone, and valproate for mixed episodes. The more recent guideline, FBPG 2015, which was written during a period of transition from DSM-IV to DSM-5, gives no recommendations for the treatment of manic or hypomanic episodes with a mixed specifier as there is no evidence for treatments in these phases.

2.8.1.3. Pharmacologic treatment of hypomanic episodes

Untreated hypomania may be associated with major financial, legal, and psychosocial problems, without ever commanding medical attention, but virtually no studies have been carried out to assess effective treatments. Treatment approaches for acute hypomania have typically mimicked those for manic episodes (CANMAT 2005). Hypomania may be the prelude to full-blown mania in individual patients, in which case treatment should be as for mania. Otherwise, hypomania is not a common point for the initiation of new treatment. In case the patient is receiving prophylactic treatment with an antimanic agent, the best recommendation is to check the plasma level of the medication and, depending on the result, increase the dosage. If no further prophylaxis is planned, short-term treatment with either valproate or an atypical antipsychotic may be the best choice, as both are well tolerated and have a good safety profile and relatively rapid onset of action, minimizing the danger that hypomania develops into mania within the next days. In this respect, it is also important to intervene early against sleep loss as this may be an important factor for developing full-blown mania (WFSBP 2009). The FCCG 2013 recommends increasing the dosage of the maintenance treatment against mania, discontinuing antidepressant medication that predisposes to hypomania, and using atypical antipsychotics for a short period.

2.8.1.4. Pharmacologic treatment of depressive episodes

Patients with BD, especially patients with BD II, spend much more time in depressive phases than in any other acute phase and so treatment of depression is

of major importance. The depressive phase of bipolar disorder is chronic in 20% of patients and causes more disability and decreased quality of life than any other phase of the illness. Even subsyndromal depressive symptoms are associated with functional impairment. In rapid cycling bipolar patients, depressive episodes are more refractory to treatment than hypomanic or manic episodes. Suicidal acts are a major concern in patients with bipolar disorder and are associated with severe depressive and mixed phases of illness, higher depression scores, and a greater number of severe depressive episodes (CANMAT 2005). However, unfortunately, the treatment of bipolar depression is a major challenge, with few treatments of proven efficacy and, in particular, substantial controversy about the role of antidepressant drugs (Geddes & Miklowitz, 2013).

Table 2. First- and second-line treatment recommendations for acute bipolar depression according to practice guidelines.

Practice guideline	Depressive phase							
	Li	Val	Car	Lam	SGA	OFC	FGA	AD
BAP 2009	(+)	(+)		++	++[2]			+[3]
WFSBP 2010					++[2]	+		
CANMAT 2013	++	+	(+)	++	++[1]	++		+[4]
FCCG 2013	+	(+)		+	++[2]	+		+[4]
NICE 2016				+	++[1]	++		
FBPG 2015	+			+	++[1]	+		

[1]quetiapine; lurasidone (Canmat as second line, FBPG), olanzapine monotherapy as second line (NICE) or third line (CANMAT), [2]quetiapine, [3]together with an antimanic agent in BD I and with caution in BD II if without antimanic agent, [4]combined with mood stabilizer, SGA=Second generation antipsychotic, FGA=First generation antipsychotic, OFC=Olanzapine+fluoxetine.

For the management of bipolar depression, WFSBP 2010 concludes that no choice of first step in treating BD shows unequivocal benefits. They give no overwhelming preference for any single treatment, but quetiapine is the only one recommended on grade 1. They see previous response as one of the strongest predictors of treatment success. Lithium may be used if it has been ongoing, after checking the serum levels. Lamotrigin may be started if lithium optimization is unsuccessful. The CANMAT 2013 guideline recommends lithium, lamotrigine, and quetiapine monotherapy, as well as olanzapine plus selective serotonin reuptake inhibitor (SSRI), and lithium or valproate plus SSRI/bupropion as first-line options. The 2016 NICE guideline recommends olanzapine plus fluoxetine combination (OFC) or quetiapine monotherapy or, if the person prefers, either olanzapine or lamotrigin monotherapy. The second level, if there is no response to OFC or

quetiapine, is lamotrigine monotherapy. If the patient is already on lithium or valproate, the recommendation is to check the plasma levels, increasing the dose if necessary and adding one of the first-line treatments. In the FBPG 2015 guideline, quatiapine (BD I or II) or lurasidone (BD I) monotherapy or as adjunctive to lithium or valproate (BD I) have the highest level (1A) recommendation for BD I (with quetiapine the only specific treatment recommended for any phase of BD II). OFC is recommended at level 1B because of the safety concerns associated with olanzapine's metabolic effects. Lithium, lamotrigine, and a combination of lithium plus lamotrigine are level 2 recommendations because the evidence for them is not as strong as for the ones listed for level 1.

2.8.1.5.   Pharmacologic maintenance treatment

There is no doubt that all patients need aftercare for some months with continuation treatment after acute symptoms have resolved. This period can last from a few months to a year. However, no controlled prospective studies indicate when long-term prophylaxis (beyond aftercare) becomes compulsory (WFSBP 2012). Most recent guidelines (BAP 2009, CANMAT 2013, NICE 2016, FBPG 2015) do not specify when long-term prophylactic treatment becomes necessary. The WFSBP 2012 does not make an explicit recommendation, as there is a lack of studies to rely on, but it refers to the Dutch guideline (Nolen et al., 2008), which considers the number of episodes and variables such as positive family history of BD suggestive of an increased genetic risk. For patients with a first episode of not-severe mania, without a first-degree family history of BD, the guideline does not recommend maintenance treatment. However, they recommend considering maintenance treatment for patients with a first episode (mania) and positive first-degree family history of BD or if the episode of mania has been severe; they also recommend maintenance treatment for patients with a second episode (at least one manic episode) without a positive first-degree family history. They recommend maintenance treatment for patients with a third (or more) episode of which at least one is (hypo)mania and for patients with a second episode (at least one manic episode) and a positive first-degree family history and/or severe episode. The FCCG 2013 recommends starting maintenance treatment always when the diagnosis of BD is made. For patients with BD I, it recommends permanent maintenance treatment; the same recommendation is also made for patients with BD II if there has been marked suicidality, psychotic depressive episodes, or significant functional disability or if there have been many episodes. In other cases with BD II, and if the patient has been in remission for many years, slowly discontinuing the maintenance treatment can be considered. However, whatever the advice from doctors, the limiting consideration at this stage is often the attitude of the patient and the family, underlining the necessity of psychoeducation (WFSBP 2013).

CANMAT 2013 recommends lithium, valproate, olanzapine, and quetiapine, as well as lamotrigine (primarily for prevention of depression), aripiprazole, and

long-acting risperidone as first-line monotherapy treatments for maintenance treatment of BD. Quetiapine, long-acting risperidone, aripiprazole, and ziprasidone are also recommended as adjunctive to lithium or valproate as first-line treatments. WFSBP 2012 recommends lithium, quetiapine, aripiprazole, and lamotrigine as first-line treatments. Olanzapine and risperidone have been downgraded to second-level treatments because of safety issues (weight gain with both, and also metabolic issues with olanzapine and hyperprolactinemia with risperidone). NICE 2016 recommends' taking into account drugs that have been effective during episodes of mania or depression and discussing with the patient whether he or she wants to continue this treatment or switch to lithium. Lithium is recommended as the first-line maintenance treatment and, if ineffective, adding valproate is recommended. If lithium is poorly tolerated or not suitable, NICE 2016 recommends' valproate or olanzapine monotherapy, or quetiapine if it has been effective during the acute phase. FBPG 2015 recommends lithium, quetiapine, aripiprazole, and lamotrigine (evidence strongest for prevention of depression, usually as adjunct) and long-acting risperidone as first-line monotherapy treatments (Level 1A). Olanzapine monotherapy is only recommended for 1B level because of concerns about weight gain and metabolic syndrome.

Table 3. First- and second-line treatment recommendations for maintenance phase according to practice guidelines.

Practice guideline	Maintenance phase							
	Li	Val	Car	Lam	SGA	OFC	FGA	AD
APA 2002	++	++	+	+				
BAP 2009	++	+	+	+	+[1]			(+)
WFSBP 2010	++			++	++[2]/+[3]			
CANMAT 2013	++	++	+	++	++[4]			
FCCG 2013	++	++			++[6]			
NICE 2016	++	+			+[5]			
FBPG 2015	++			++	++[6]			

[1]aripiprazole, quetiapine, olanzapine, risperidone, ziprasidone, [2]aripiprazole, quetiapine, [3]olanzapine, risperidone, [4]olanzapine, quetiapine, risperidone LAI, aripiprazole; paliperidone second line; asenapine third line, [5]olanzapine, quetiapine, [6]quetipine, aripiprazole, risperidone LAI; olanzapine level 1B because of safety concerns, SGA=Second generation antipsychotic, FGA=First generation antipsychotic, OFC=Olanzapine+fluoxetine.

2.8.1.6. Pharmacologic treatment of BD II

The only recommendation for the pharmacological treatment of BD II in the FBPG 2015 is quetiapine monotherapy for BD II depression. It states that they did not want to extend the recommendations for BD I to the treatment of BD II as the evidence does not support doing so. BAP 2009 follows the same line. The other recent guideline (NICE 2016) does not separate BD into type I and II so the same recommendations apply for both types. The CANMAT 2013 guideline has recommendations also for BD II depression. It recommends quetiapine monotherapy as the only first-line treatment, whereas lithium, lamotrigine, and valproate monotherapy as well as lithium or valproate in combination with an antidepressant, lithium combined with valproate, and atypical antipsychotics combined with antidepressants are recommended as second-line treatments. The CANMAT recommendations for BD II maintenance treatment are lithium, lamotrigine, and quetiapine as first line-treatments and valproate monotherapy, lithium, valproate or atypical antipsyhotic combined with antidepressant, adjunctive quetiapine, adjunctive lamotrigine, combination of two of lithium, valproate, or atypical antipsychotic as second-line treatments. According to FCCG 2013, quetiapine is efficient in acute bipolar II depression, but it is uncertain if lamotrigin is efficient. Adding antidepressants to mood stabilizers may be of use if there are no concurrent hypomanic symptoms. The guideline recommends quetiapine as a first-line treatment for maintenance treatment in BD II and lithium, lamotrigin, valproate, and carbamazepine as second-line treatments.

2.8.1.7. Electro-convulsive therapy

Electro-convulsive therapy (ECT) is highly effective for treatment-resistant acute mood episodes, particularly in patients with psychotic or catatonic features (Grande et al., 2015; Schoeyen et al., 2015). The BAP 2009 guideline recommends considering ECT for depressive BD patients with high suicidal risk, psychosis, severe depression during pregnancy, or life threatening inanition and for manic patients who are severely ill and/or whose mania is treatment resistant, patients who express a preference for ECT, and patients with severe mania during pregnancy. The CANMAT 2013 guideline recommends ECT as a third-line treatment for BD depression, but for earlier consideration in patients who have psychotic bipolar depression, in those at high risk for suicide, and in those with significant medical complications due to not drinking and eating. For manic patients, the CANMAT 2013 guideline recommends ECT as a second-line treatment.

2.8.2. Psychosocial interventions

The development of effective psychological interventions for bipolar disorder is relatively recent. Historically, individuals with this diagnosis were seen as poor

candidates for psychotherapy because of potentially challenging interactions with therapists. However, there has been a growing awareness that psychological factors play an important role in bipolar disorder and that treatment approaches addressing these factors can improve clinical outcomes (NCCMH, 2014).

Although pharmacotherapy is the mainstay of treatment for bipolar disorder, medication offers only partial relief for patients. Treatment with pharmacological interventions alone is associated with disappointingly low rates of remission, high rates of recurrence, residual symptoms, and psychosocial impairment (Swartz & Swanson, 2014). Substantial progress has been made in the development and assessment of adjunctive psychosocial interventions (Geddes & Miklowitz, 2013) and bipolar-specific therapy is increasingly recommended as an essential component of illness management (Swartz & Swanson, 2014).

A number of psychological interventions is available for which there is a current evidence base (NCCMH, 2014). Evidence-based models of psychotherapy include cognitive-behavioral therapy, family-focused therapy, interpersonal and social rhythm therapy, group psychoeducation, and systematic care management (Geddes & Miklowitz, 2013). A common aim of these approaches is to provide the service user with a set of mood regulation and self-management skills to address the challenges of living with bipolar disorder more effectively after the psychological intervention. The main approaches currently employed for bipolar disorder are family interventions, cognitive behavioral therapy, interpersonal and social rhythm therapy, and psychoeducation. Oud et al. (Oud et al., 2016) in a very recent systematic review and meta-analysis of psychological interventions for adults with BD recommended the use of psychological interventions in the treatment of people with BD to reduce relapse rates and to reduce depressive symptoms. They reported that, although there is insufficient evidence to recommend one specific treatment over the others, the best evidence is for individual, structured psychological interventions, with weaker evidence for group and family interventions and collaborative care.

2.8.2.1.   Family-focused therapy and other family interventions

A reciprocal relationship exists between BD and the family and BD affects not only the patients but also their relatives. Specific family attitudes/interactions affect the course of BD and, equally, the illness itself has a strong impact on family functioning, caregivers' burden, and caregivers' health. Several studies have suggested that the emotional atmosphere of the family during the post-discharge period may be an important predictor of the illness outcome in BD. A variety of family psychoeducation programs has been developed for BD. Although they differ in many respects (e.g., multifamily, single-family, relatives only, inclusion/exclusion of patient, duration and intensity of treatment, clinical state of the patient), most of the approaches involve giving support to the relatives encouraging self-care, psychoeducation about the illness and its management, and training in communication and problem solving (Reinares et al., 2016).

Despite differences in format, target population, duration, setting, and period of implementation, most studies support the benefits of adjunctive family intervention (single-family and multifamily approaches) on both the patient outcomes and caregiver well-being. While positive findings have been reported when treatment starts after discharge or the patient is in remission, discrepant findings have been reported when adjunctive family intervention was introduced in the acute phase, although the treatment seems to be useful to improve depression for at least a subgroup of patients (Reinares et al., 2014). For patients with family members who are willing and able to participate in treatment, family therapy is an excellent option. Families with greater levels of impairment may derive additional benefit from family therapy when it is delivered either as individual or multifamily group therapy (Swartz & Swanson, 2014).

Family-focused therapy (FFT) is based on the frequently replicated association between criticism and hostility in caregivers (so-called expressed emotion) and an increased likelihood of relapse in mood disorders and schizophrenia. FFT involves the patient and caregivers (parents or spouse) in up to 21 sessions of psychoeducation, communication skills training, and problem-solving skills training. Studies have shown that adjunctive family interventions have the potential to lengthen periods of stability and alleviate residual symptoms in maintenance care (Geddes & Miklowitz, 2013). Compared with psychoeducation only, FFT hastens recovery and confers additional protection against recurrence (Swartz & Swanson, 2014). The benefits of FFT have been shown to extend to at least the two-years follow-up, being particularly useful for depressive symptoms and improving adherence, and compared to individual treatment, people having had FFT have a lower number of relapses and lower risk of hospitalization in the two-year post-treatment follow-up (Reinares et al., 2016).

2.8.2.2. Cognitive behavioral therapy

Cognitive-behavioral therapy (CBT) presumes that recurrences of mood disorder are determined by pessimistic thinking in response to life events and core dysfunctional beliefs about the self, the world, and the future. CBT to treat depression has been adapted for patients with bipolar disorder with recognition that manic episodes are often associated with excessively optimistic thinking (Geddes & Miklowitz, 2013). CBT for BD adds additional modules of psychoeducation, strategies for coping with prodromes, activities for regulating sleep and routines, and approaches to managing long-term sequelae of the illness (Swartz & Swanson, 2014).

The evidence for adjunctive CBT for relapse prevention is inconclusive (Geddes & Miklowitz, 2013). Several trials have analyzed the impact of adjunctive CBT but mixed findings have been reported, highlighting the need to study under what conditions CBT works in BD (Reinares et al., 2014). Miziou et al. (Miziou et al., 2015) concluded that the available data so far give limited support for the usefulness of CBT during the acute phase of bipolar depression as adjunctive

treatment in patients with BD, but definitely not for the maintenance phase. During the maintenance phase, booster sessions might be necessary, but the data are generally negative. Probably, patients at earlier stages of the illness might benefit more from CBT. Reinares et al. (Reinares et al., 2014) took a somewhat more optimistic view of the outcome of CBT in BD. They stated that, on the whole, the impact of adjunctive CBT seems to be particularly useful in prevention of depression, especially in recovered and less recurrent patients, although booster sessions might be needed to maintain the benefits of the intervention (Reinares et al., 2014).

2.8.2.3. Interpersonal and social rhythm therapy

Substantial evidence exists that mood instability in bipolar disorder is related to changes in circadian rhythms. The relation between sleep and mood disturbances seems to be bidirectional (Geddes & Miklowitz, 2013). Interpersonal and social rhythm therapy (IPSRT), an adaptation of interpersonal psychotherapy for depression, uses a problem-solving approach to interpersonal problems by encouraging patients to maintain and regulate daily routines and sleep and wake rhythms (Geddes & Miklowitz, 2013).

Overall, there are no convincing data on the usefulness of IPSRT during the maintenance phase of BD. However, some data suggest that if applied early and particularly during the acute phase, IPSRT might prolong the time to relapse (Miziou et al., 2015; Reinares et al., 2014). Interestingly, it appears that administering it in the acute phase of treatment confers the greatest advantage to patients. IPSRT also shows promise as monotherapy (i.e., without medication) for BD II depression (Swartz & Swanson, 2014). In their systematic review and meta-analysis, Oud et al. (Oud et al., 2016) found no evidence of benefit from IPSRT.

2.8.2.4. Psychoeducation

In view of the many patients who could benefit from psychoeducation (PE), group approaches following a predesigned curriculum have been proposed. The Barcelona approach emphasizes awareness of illness, treatment adherence, early detection of recurrences, and sleep and wake regularity (Geddes & Miklowitz, 2013).

Recent reviews have drawn somewhat differing conclusions of the outcome of PE. Reinares et al. (Reinares et al., 2014) concluded that the six-month group PE seems to have long-lasting prophylactic effects over all sorts of episodes, time spent ill, and hospitalization per patient in individuals with BD who were euthymic at recruitment. Also, Swartz et al. (Swartz & Swanson, 2014) reported that treatment with a PE group (both 21- and 6-session formats) conferred benefits for those with bipolar disorder including longer time to recurrence, decreased rates of hospitalization, and improved symptoms over time. Miziou et al. (Miziou et al., 2015) more critically stated that even though interventions of the six-month group

PE seem to exert a long-lasting prophylactic effect, this was restricted to manic episodes and to patients in the earlier stages of the disease who had achieved remission before the intervention started. Similarly, Bond and Anderson (Bond & Anderson, 2015) concluded that PE appears to be effective in preventing relapse in BD, with the strongest evidence for reducing overall and manic relapse. The greatest effect was found in the group format, which also had a longer follow-up and more hours of therapy. However, no consistent effect on mood symptoms, quality of life, or functioning were found, although PE improved medication adherence and short-term knowledge about medication. Both Miziou et al. (Miziou et al., 2015) and Reinares et al. (Reinares et al., 2014) stated that the data suggest group PE to be less efficacious in patients with a higher number of previous episodes. According to Swartz and Swanson (Swartz & Swanson, 2014) the advantages of PE are less apparent when a PE group is compared with a more active comparator than treatment as usual. For instance, outcomes with 6-session PE did not differ from 20-session individual CBT. Similarly, both 21-session PE and functional remediation (FR) groups were associated with improvement in global functioning, although those assigned to FR fared even better than those assigned to PE. The authors stated that these studies raise the possibility that a stepped-care approach to bipolar disorder may be indicated, that is, treating patients with the less costly/burdensome group PE prior to adding CBT or functional remediation for those who do not achieve an adequate benefit with PE alone.

2.9. Adequacy of treatment received

2.9.1. Adequacy of acute phase treatment

Treatment of BD focuses on acute stabilization, in which the goal is to bring patients with mania or depression to a symptomatic recovery with euthymic mood (Geddes & Miklowitz, 2013). Because of the difficulty of choosing the right treatment, there are clinical guidelines, "systematically developed statements that assist clinicians and service users in making decisions about appropriate treatment for specific conditions," (NCCMH, 2014). However, for many reasons, the recommendations for how to treat patients with BD are not always followed and a gap exists between optimal and actual pharmacotherapy treatments. Reports of several clinical studies (Blanco et al., 2002; Frye et al., 2005; Lim et al., 2001; Simon et al., 2004) have indicated that the treatment recommendations of practice guidelines and treatments prescribed to patient in practice differ, often markedly. The treatment of patients with BD in accordance with guidelines varies widely throughout studies, ranging from 50% to 80% (Paterniti & Bisserbe, 2013). Perlis et al. (Perlis, 2007) found that 34% of psychiatrists reported not having

recourse to guidelines on a regular basis to treat BD, whereas only a very small percentage identified guidelines as their primary source of information.

For example, Simon et al. (Simon et al., 2004) reported that of the first 1,000 participants in the STEP-BD study, only for 59% did the pharmacotherapy meet the criteria for "minimally adequate" mood stabilizer use. In another study, Lim et al. (Lim et al., 2001) examined medications at discharge of 1,471 patients admitted to a hospital with BD I mania or depression and found that only 1 in 3 patients with psychotic features, and 1 in 6 without psychotic features, received medication consistent with the 2000 Expert Consensus Guidelines for bipolar disorder. A third study by Blanco et al. (Blanco et al., 2002) analyzed 865 visits to a psychiatrist by patients with bipolar disorder which were recorded in the National Ambulatory Medical Care Survey database between 1992 and 1999. They found that more than a third of the visits did not include a prescription for any mood stabilizer, but antidepressants had been prescribed during almost half the visits and in about half of these visits without a prescription for a mood stabilizer. Actually, treatment practices that are not recommended and even rejected by virtually all guidelines, such as antidepressant monotherapy without a mood stabilizer (Blanco et al., 2002; Frye et al., 2005; Ghaemi et al., 1999; Lim et al., 2001) seem surprisingly common.

However, some studies have reported somewhat better adherence to practice guideline recommendations. For example, in a survey of French psychiatrists, Verdoux et al. (Verdoux et al., 1996) reported that 82% of bipolar outpatients had at least one mood stabilizer, and 68% had at least one antipsychotic. In another study, Ahmed et al. (Ahmed & Anderson, 2001) reviewed case notes of outpatients with a clinical diagnosis of bipolar affective disorder and found that 75% had a mood stabilizer and 20% had antipsychotics alone or, in 43% of patients, combined with a mood stabilizer. However, the dosage of mood stabilizers was often inadequate. Lloyd et al. (Lloyd et al., 2003) investigated the charts of patients under the care of four hospitals in northeast England and found that 85% had a mood stabilizer. Antidepressants were prescribed for 23% of patients, combined with a mood stabilizer in all but three cases. Farrelly et al. (Farrelly et al., 2006) reviewed the case notes of 84 consecutive patients attending the Cambridge Mental Health Service outpatient clinics and reported that the treatment was consistent with the BAP 2003 guidelines in 72% of episodes. In all, the treatment was not optimal in any of these reports and actually in many cases the treatments seem to have been clearly inadequate for the majority of bipolar patients. More recently, Paterniti et al. (Paterniti & Bisserbe, 2013) reported pharmacotherapy and concordance with treatment guidelines in a survey of 113 BD patients who had been referred to tertiary care services in Canada in 2006-2009. They found that all patients with BD I and 90% of the BD II group were given at least one psychotropic treatment. Antidepressants were the most frequently (for more than 60% of patients) prescribed class of psychotropics. At least one CANMAT 2009 guideline-concordant treatment was received by 74% of

patients when considering only the type of treatment and by 68% if also the dosage is considered.

2.9.2. Adequacy of maintenance phase treatment

BD is an inherently recurrent disorder, requiring maintenance preventive treatments in the vast majority of patients. For virtually all patients with BD, the question of maintenance treatment is when, not if (Gitlin & Frye, 2012). Nearly every patient with BD will experience recurrent episodes during their lifetime; patients having only one episode are rare at best (Gitlin & Frye, 2012; Goodwin & Jamison, 2007; Perlis et al., 2006). Recurrent episodes carry with them an increased risk of suicide, accumulating social problems, possible cognitive decline, and high costs (Goodwin & Jamison, 2007). Controlled clinical studies have shown significantly better outcomes in patients with BD on maintenance treatment with mood stabilizers (Gitlin & Frye, 2012; Goodwin & Jamison, 2007; Maj et al., 1998). In addition to the syndromal states, adequate maintenance treatment also prevents development of subsyndromal states (Frye et al., 2006; Keller et al., 1992; Marangell, 2004), which are often prodromes of escalating recurrent episodes (Perlis et al., 2006) and involve other problems, including functional disability (Altshuler et al., 2002; MacQueen et al., 2003; Marangell et al., 2009). The core goal in the treatment of BD should be prevention of new illness episodes (Belmaker, 2007). Thus, practice guidelines consistently recommend maintenance treatment after the acute phase. Unfortunately, the treatments provided for patients with BD are often short-term and episode-focused (Bowden & Singh, 2005). In this context, it is important to understand the factors that affect prescribing of maintenance treatment in actual clinical practice.

An obstacle in this field of study is lack of complete consensus on how the longitudinal treatment phases of BD should be defined. The basic controversial issue is whether or not a distinct continuation phase should be included, precisely when it should end, and, consequently, when the maintenance phase should start. Long-term treatment in mood disorders, originally developed for MDD, has traditionally been divided into continuation and maintenance treatments (Grunze et al., 2013), which are, in turn, associated with the starting points "remission" and "recovery," respectively. Even though these concepts of recurrence and relapse (and the corresponding treatment phases) are theoretically meaningful, they can only be identified under certain circumstances. Therefore, DSM-IV and ICD-10 have adopted a wholly pragmatic set of definitions, separating two episodes by an interval of at least eight weeks of remission, implying that the continuation phase ends after eight weeks of continuous absence of symptoms (Grunze et al., 2013). Another difficulty in comparing studies is that, even though major studies have investigated long-term treatment received by patients with BD, it often remains ambiguous whether the treatment provided is for chronic symptoms or true maintenance phase treatment.

A study of the German centers of the SFBN (Dittmann et al., 2002) found that of the 111 patients in their 2.5-year follow-up, almost all (97.3%) were on at least one mood stabilizer during follow-up, and a high proportion of patients received long-term treatment (for at least six months) with antidepressants (42.3%) or typical antipsychotics (24.5%). The EMBLEM study is a two-year prospective, observational study on the treatment and outcome of patients who are treated for a manic or mixed episode. That study found that during one-year follow-up, rapid cycling patients were more likely to receive antidepressants and lamotrigine (Cruz et al., 2008). The exact treatment phase (acute or maintenance) was not reported in these studies. However, in the STEP-BD study (Ghaemi et al., 2006), a cross-sectional intake treatment data during different phases for the first 500 patients taken in the study, they reported the treatments received in the maintenance phase; the authors stated that most of the agents used in the acute phases of BD were similarly used in the maintenance phase of treatment.

In Britain, Farrelly et al. (Farrelly et al., 2006) reviewed the case notes of 84 consecutive patients attending the Cambridge Mental Health Service outpatient clinics. They reported that during the two-year study period, 82% of patients were maintained on long-term preventative treatments with mood stabilizers, and eight patients continuously took antidepressants throughout the study period. Also in this study, the treatment phase during the follow-up was not specified, so it may have included both acute and maintenance phases. In addition, several other major studies have investigated the treatments received by patients with BD (Ahmed & Anderson, 2001; Anderson et al., 2004; Blanco et al., 2002; Farrelly et al., 2006; Frangou et al., 2002; Lloyd et al., 2003; Simon et al., 2004; Verdoux et al., 1996). Even though most of them are informative, they suffer from important limitations regarding evaluation of maintenance phase treatment.

Most of these studies have not clearly defined the treatment phase (acute or maintenance) investigated (Ahmed & Anderson, 2001; Anderson et al., 2004; Cruz et al., 2008; Dittmann et al., 2002; Farrelly et al., 2006; Lloyd et al., 2003; Simon et al., 2004; Verdoux et al., 1996); patients have often been sampled exclusively from specialty clinics (Al Jurdi et al., 2008; Dittmann et al., 2002; Ghaemi et al., 2006). In other cases, only patients with BD I are included (Cruz et al., 2008; Frangou et al., 2002) or the diagnosis is made based on a patient register or on a clinical diagnosis alone (Ahmed & Anderson, 2001; Anderson et al., 2004; Farrelly et al., 2006; Frangou et al., 2002; Lloyd et al., 2003; Verdoux et al., 1996), leaving the validity of the diagnosis uncertain. All of the former studies have included only clinically diagnosed bipolar patients, which gives an overly optimistic view of the true clinical epidemiology of treatment of BD.

2.10. Adherence

Pharmacotherapy is the foundation of treatment for BD, but the recommendations of practice guidelines do not always actualize in the clinical reality. Adequate treatments may be offered, but only treatments taken have an effect, and effectiveness of pharmacological treatment is undermined by poor adherence. Rates of long-term nonadherence in BD have ranged from 20% to 66%, with a mean of 41% (Lingam & Scott, 2002). These rates seem not to have changed significantly since the introduction of new pharmacological agents (Berk et al., 2010; Lingam & Scott, 2002). Rates of nonadherence in schizophrenia have been in the same range (Sendt et al., 2015) as for other long-term diseases (Osterberg & Blaschke, 2005). Adherence rates are typically higher among patients with acute conditions, as compared to those with chronic conditions.

Poor adherence is the single most important factor in poor treatment response among patients with BD (Goodwin & Jamison, 2007). Even though effective treatments for BD are available, their realization is problematic. The difference between efficacy and effectiveness has been largely attributed to treatment nonadherence (Guscott & Taylor, 1994). The consequences of nonadherence to pharmacotherapy are profound and can be life-threatening, equivalent to those of untreated or inadequately treated manic-depressive illness (Goodwin & Jamison, 2007). So, the potential benefits of pharmacological treatment on recovery, preventing relapse, and reducing mortality are significantly undermined by poor adherence (Berk et al., 2010). Studies have reported nonadherence to be associated with decreased likelihood of achieving remission and recovery, increased rates of relapse and hospital readmissions, increased risk of suicidal behavior, and greater healthcare costs (Hong et al., 2011; Velligan et al., 2009). The potential problems with adherence also make it very difficult, if not impossible, for the prescribing clinician to assess whether the lack of response is related to the medication regimen itself or poor adherence. Thus, the physician may continue to prescribe additional medications for patients who are not showing desired improvement, although the real cause for the lack of response may be that patients are not taking medications as prescribed (Velligan et al., 2009). Unfortunately, clinicians are poor judges of adherence and routinely underestimate the rates of nonadherence among their patients (Baldessarini et al., 2008; Stephenson et al., 2012).

However, unlike non-responsiveness to treatment, nonadherence is potentially reversible through experience, education, learning, and psychotherapy (Goodwin & Jamison, 2007), as reported in recent reviews (Berk et al., 2010; Colom et al., 2005; Crowe et al., 2012). MacDonald et al. (MacDonald et al., 2016) reported a systematic review and meta-analysis of randomized controlled trials of interventions to support adherence to medication in BD during the last 30 years. They found strong evidence that interventions can improve medication adherence (the pooled OR was 2.27 [95% CI 1.45-3.56]). The effects appeared to be durable and studies with two-year follow-up still reported positive effects on adherence.

Brief interventions tending to specifically focus on adherence were more effective in improving adherence than longer interventions where medication adherence was combined with other aspects of self-management. Most of the interventions involved psychoeducational techniques which appeared to be effective. However, in a review of effectiveness of interventions to improve medication adherence in BD, Crowe et al. (Crowe et al., 2012) reported that most of the studies included in their review found that although their interventions did not improve adherence they did improve clinical outcomes.

The World Health Organization (WHO) defines adherence as "the extent to which a person's behaviour – taking medication, following diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider" (WHO, 2003). The term adherence is preferred to compliance because adherence emphasizes active patient participation in a treatment formed through therapeutic alliance or shared decision making in a patient-centered model of healthcare (Busby & Sajatovic, 2010).

On a purely practical level, adherence involves a number of behaviors including assessing treatment, obtaining medications, understanding and following instructions about taking and monitoring medications, and remembering to take medications. Nondherence may be 'voluntary', or intentional, when the person decides not to adhere to treatment, or 'involuntary', where the lack of adherence is unintentional, (e.g., forgetting to take the medication) (Berk et al., 2010).

Nonadherence can occur through four types of errors: (1) omission, not starting the drug at all, or once started, failing to take it, (2) dosage, taking too much or too little, (3) timing, failure to follow directions about when to take the drug, for how long, or when to change levels, and (4) purpose of commission, taking the drug for the wrong reasons (Goodwin & Jamison, 2007). It has been noted that patients may modify rather than completely accept or abandon treatment regimens (Berk et al., 2010) and patterns of nonadherence may vary over time and from patient to patient. Non-adherent behavior can take different forms: *Full nonadherence* refers to the patients' complete failure to adhere to the physician's directions in the self-administration of any medication. *Selective nonadherence* means nonadherence to only some kind of medication. *Intermittent adherence*, probably the most common pattern, includes, for example, abandoning treatment for certain periods, such as a weekend, before an important meeting or appointment or the patient adhering for a period of time, then stopping, but starting again after a recurrence. In *late adherence*, patients show initial resistance to accepting that they have BD and deny their need for treatment, but after repeated relapses begin to recognize the relationship between stopping the medication and recurrence of their illness. In *late nonadherence*, after two or three years of full adherence, some patients start to discontinue their maintenance treatment. *Abuse* involves taking more medication than prescribed (Colom et al., 2005; Goodwin & Jamison, 2007). These factors indicate that adherence is

dynamic, varying in a number of ways, and thus requiring repeated discussions throughout treatment (Berk et al., 2010).

Although adherence to pharmacotherapy among patients with BD has been explored for decades, the number of studies remains limited, and most of them have investigated adherence to lithium; only more recent studies have examined other medications. Very few studies have reported adherence to psychosocial treatment in patients with BD, mainly examining therapy drop-outs (Busby & Sajatovic, 2010) or non-attendance or non-participation (Cakir et al., 2009; Even et al., 2007). For example, Cakir et al. (Cakir et al., 2009) investigated patients' motivation to attend a six-week psychoeducational program and found 72% of patients to be adherent (i.e., attending at least 75% of scheduled appointments). The risk factors for nonadherence to psychosocial treatments in patients with BD are poorly known.

Studies have reported many risk factors to be associated with nonadherence in patients with BD, but only a few have been constantly associated with pharmacotherapy nonadherence. Like in the recent reviews by Busby and Sajatovic (Busby & Sajatovic, 2010) and Leclerc et al. (Leclerc et al., 2013), these factors may be divided into those related to patient characteristics (e.g., younger age, being single, substance abuse, lower level of education, negative attitude to medication), disease (e.g., mixed episode, rapid cycling), treatment (e.g., side-effects, number of medications), and health care system (e.g., lower access to care, fewer resources). The relative importance of each of these domains is not well known, but of obvious importance for improving care outcomes. In the STEP-BD study (Perlis et al., 2010), which is one of the biggest studies of patients with BD, the authors reported that clinical features associated with poor adherence (missing at least 25% of total doses) included younger age, single marital status, earlier onset, history of suicide attempts, rapid cycling, and current anxiety or alcohol use disorder; the study included 3,640 subjects who completed at least one follow-up visit. In another study, Sajatovic et al. (Sajatovic et al., 2009) investigated a community mental health clinic sample of 140 BD patients and defined nonadherence as missing 30% or more of prescribed medication. In that study, the only clinical predictor for nonadherence was substance use comorbidity. Moreover, nonadherence was associated with negative attitudes toward mood-stabilizing pharmacotherapy and difficulty in managing to take medication in the context of one's daily schedule. Recent studies on adherence among patients with BD have reported an association of residual depressive symptoms (Belzeaux et al., 2013), non-planning impulsivity (the inability of an individual to weigh the long-term as opposed to immediate results of his or her action) (Belzeaux et al., 2015), illness insight (Novick et al., 2015), and perceived therapeutic alliance and treatment environment (Sylvia et al., 2013) with nonadherence among patients with BD. The effect of cognitive functioning on adherence in BD has been rarely studied, however, according to the the study by Jonsdottir et al. (Jonsdottir et al., 2013) neurocognitive impairment is not a risk factor for nonadherence in BD.

A major difficulty for progress in this field is that major methodological differences exist in definitions of adherence and assessment methods; thus, rates of adherence may vary widely merely due to methodological factors. Most studies have used subjective or indirect methods to assess adherence (e.g., reports from patients, providers, or significant others; chart review), and few have used direct or objective methods (e.g., pill count, blood/urine analysis, electronic monitoring, refill records) (Velligan et al., 2009). Adherence to medication recommendations can be reported in a continuing (fraction or percentage of medication taken or not taken) or categorical fashion (adherent vs. non-adherent) (Busby & Sajatovic, 2010). It remains to be determined exactly what level of adherence is necessary for positive clinical outcomes under different medication regimens and in different settings of BD. As there is no objective or generally accepted cutoff (% taken) for adherence in BD, studies have used different definitions, and it is difficult, if not impossible, to compare studies which may have chosen different levels of adherence (Busby & Sajatovic, 2010). Most of the experts in the Expert Consensus Guideline on adherence problems in serious mental illnesses (Velligan et al., 2009) considered that an appropriate cutoff for adherence in BD is 20% or less medication not taken. This 80%/20% cutoff is used in many studies. Some studies have divided the non-adherent group into partial, usually ≥50% and <80% medication taken, as also recommended by experts (Velligan et al., 2009) and total, <50% medication taken, nonadherence. Unfortunately, there is currently no ideal operationalization or measure of adherence (Berk et al., 2010), and different types of assessment cover different aspects of behavior (Velligan et al., 2009).

3. AIM OF THE STUDY

The aim of this 18-month follow-up study was to investigate the treatments received (during the acute and maintenance phase), adherence to treatments, and predictors of long-term disability of BD I and II patients with an acute phase at intake in secondary-level psychiatric care.

The specific aims of the study were to:

1. Investigate the adequacy of acute-phase pharmacotherapy received in a representative secondary-level sample of psychiatric in- and outpatients with a research diagnosis of bipolar I or II disorder.
2. Investigate the adequacy of maintenance-phase pharmacotherapy received in a representative secondary-level sample of psychiatric in- and outpatients with a research diagnosis of bipolar I or II disorder.
3. Investigate the continuity of, attitudes toward, and adherence to various types of psychopharmacological and psychosocial treatments among psychiatric in- and outpatients with BD I or II.
4. Investigate the prevalence of disability pensions at baseline and predictors for being granted a disability pension during an 18-month follow-up of the patients in the labor force at baseline.

4.   Materials and methods

4.1.   General study design

The JoBS is a collaborative bipolar research project between the Unit of Mental Health of the National Institute for Health and Welfare, Helsinki (the former Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki) and the Department of Psychiatry, Jorvi Hospital, Helsinki University Central Hospital (HUCH), Espoo, Finland. The Department of Psychiatry of Jorvi Hospital provides secondary-care in- and outpatient psychiatric services to all citizens of Espoo, Kauniainen, and Kirkkonummi (261,116 inhabitants in 2002). The Ethics Committee of HUCH approved the study protocol.

4.2.   Screening

The first phase of patient sampling for the JoBS cohort involved screening all in- and outpatients at the Department of Psychiatry of Jorvi Hospital who currently had a possible new phase of DSM-IV BD from January 1, 2002, to February 28, 2003. During that period, every patient between the ages 18 and 59 years, who (1) was seeking treatment, (2) had been referred, or (3) had already received care and was now showing signs of deteriorating clinical state, or a change in mood in case of mania or hypomania, was screened with the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000). Patients were also included as positive, despite a negative MDQ screen, if suspected to have BD due to a clinical diagnosis of BD or pertinent symptoms. A clinical diagnosis of ICD-10 schizophrenia was an exclusion criterion for screening. The response to MDQ item 3 ("problems due to episodes") was ignored based on the pilot study of the JoBS (Isometsa et al., 2003). The sampling procedure is presented in Figure 1. After receiving a positive MDQ screen, or after suspicion of BD, the patients were fully informed about the study project and written informed consent was requested. In all, 1,630 patients were screened, 546 of whom proved to be MDQ-positive or suspected bipolar (Figure 1). Of 546 eligible patients, 49 declined a face-to-face interview and 7 could not be contacted.

4.3. Baseline evaluation

4.3.1. Diagnostic measures

In the second phase of sampling, the 490 participating patients were interviewed face-to-face to make a diagnosis. The diagnosticians were all psychiatrists (Outi Mantere, Hanna Valtonen, Petri Arvilommi, Kirsi Suominen, Sami Leppämäki, Marita Pippingsköld), and weekly meetings were held to solve diagnostic problems. Using the Structured Clinical Interview for DSM-IV Disorders, researcher version with psychotic screen (SCID-I/P) (First et al., 2002), supplemented with a section for diagnosing mixed episodes, they evaluated whether the patient fulfilled the criteria for diagnosis of BD. All psychiatric and medical records were available, and if the diagnosis was uncertain, attending personnel, family members, or other informants were contacted. The final study group included in the analyses comprised 191 DSM-IV bipolar I and II patients with a current phase. The index episode was defined according to DSM-IV criteria and could be monophasic or polyphasic. We also included as bipolar II those bipolar NOS patients with hypomania of two-three days, or depressive mixed states (DMX3=three or more simultaneous intra-episode hypomanic symptoms present for at least 50% of the time during a major depressive episode) as defined by Benazzi and Akiskal (Benazzi & Akiskal, 2001), that clearly belonged to the bipolar II group. To test diagnostic reliability, we used videotaped interviews that were then blindly assessed by another diagnostician. In the 20 randomly selected, videotaped diagnostic interviews, agreement was complete (the kappa coefficient for BD overall was 1.0; also specifically, for BD I it was 1.0 and BD II it was 1.0). To assess comorbid diagnoses on axis II, we used the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) (First et al., 1997).

4.3.2. Observer and self-report scales

In the third phase, the current symptomatology of the index episode was evaluated. The Young Mania Rating Scale (YMRS) (Young et al., 1978) was used to assess the severity of mania, and the 17-item Hamilton Depression Scale (HAM-D) (Hamilton, 1960) and the self-reported 21-item Beck Depression Inventory (BDI) (Beck et al., 1961) were used to assess the severity of depression. Other self-reported scales, in addition to BDI, included the Beck Anxiety Inventory (BAI) (Beck et al., 1988) to assess the level of anxiety, the Scale for Suicidal Ideation (SSI) (Beck et al., 1979) for suicidal behavior, and Beck Hopelessness Scale (BHS) (Beck et al., 1974). Moreover, the self-report scales included the Interview for Recent Life Events (IRLE) (Paykel, 1997) and the Perceived Social Support Scale Revised (PSSS-R) (Blumenthal et al., 1987), the Social Adjustment Scale Self-

Report (SAS-SR) (Weissman & Bothwell, 1976), and the Eysenck Personality Inventory (EPI) (Eysenck HJ, 1964). The Social and Occupational Functioning Assessment Scale for DSM-IV (SOFAS) (Goldman et al., 1992) was used to assess the functional level. Some delay occurred from screening to estimating symptom scores in the first interview, which especially in the case of short hypomanias meant that the patient had often passed the index phase. In the analysis of symptom severity, these latter patients were omitted.

Figure 1. Screening of eligible bipolar patients in the Jorvi Bipolar Study
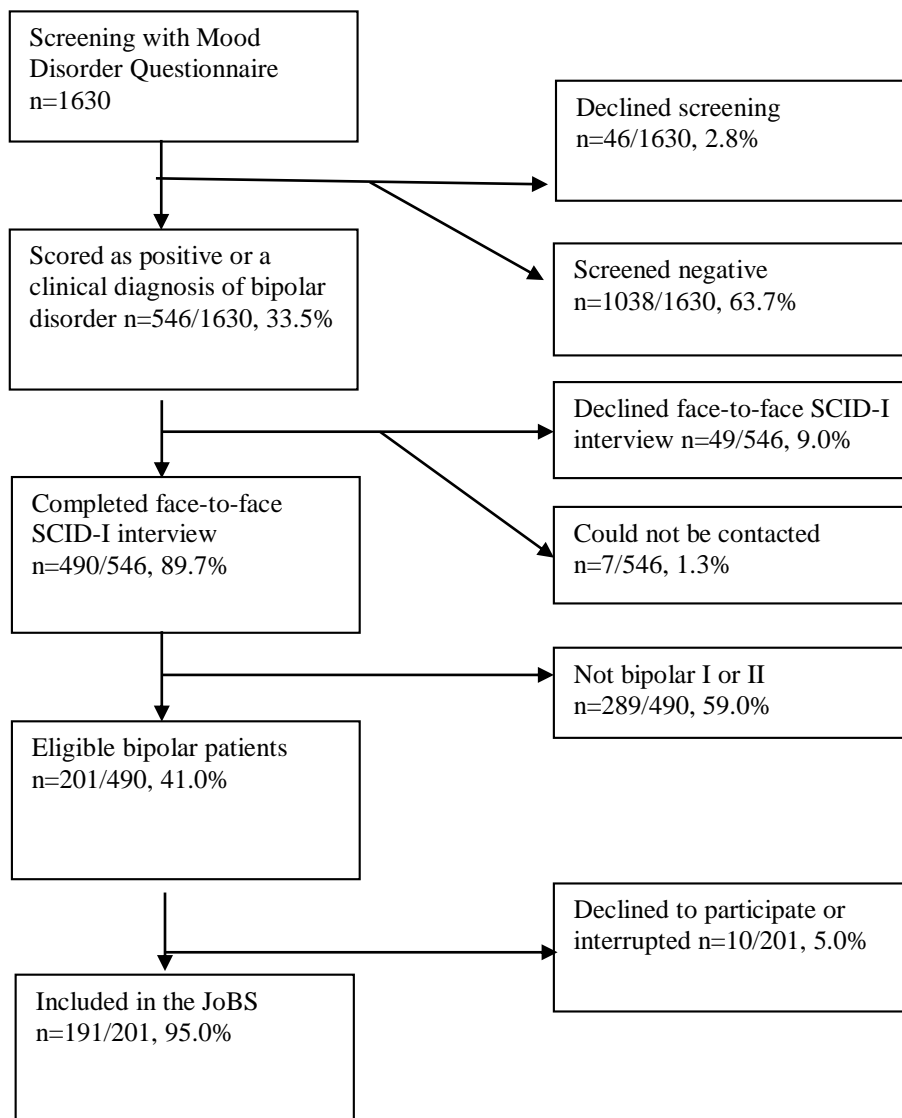
4.3.3. Other characteristics

We also collected information on demographic characteristics and variables for prior illness history and preceding treatment using a graphic retrospective life chart. Age at illness onset was defined as the time of onset of the first mood episode fulfilling the DSM-IV criteria. A polyphasic episode was defined as an episode consisting of more than one distinct phase (depressive, hypomanic, manic, mixed, or depressive mixed phase). The index episode and index phase were defined as the episode or phase, respectively, when the patients were included in the study.

4.4. Follow-up procedure

4.4.1. Study drop-outs

Of the 191 subjects with a current phase initially included in the study, at six months, 5 (2.6%) declined to participate, 15 (7.9%) were missing, and 171 (89.5%) were interviewed. Of the missing patients, reliable information was available for five in patient records. At 18 months, of the original sample of 191 patients, 3 were known to have died, 6 more refused to be interviewed, 142/188 (75.5%) were interviewed in person, and 5/188 were interviewed by phone. For 13 patients, information from patient records was sufficient to construct a life chart, and another 3 patients with too short (less than one year) follow-up were excluded. Thus, 160/188 patients (85.1%) were included in the 18-month analyses. Of BD II patients, seven converted to BD I due to mania, three due to a mixed phase during the follow-up (between beginning of index phase and 18-month follow-up). In analyses, all patients were categorized according to their baseline diagnosis. In addition, based on a similar clinical picture, eight BD NOS patients at intake were included in the analysis as BD II patients. Of these BD NOS patients, seven were followed up for 18 months, with two (29%) converting to BD II (Mantere et al., 2004).

4.4.2. Follow-up assessment and life-chart methodology

The patients participating were interviewed again 6- and 18-months after baseline. The course of the disease, with timing and durations of different phases, was examined by gathering all available data, which were then combined in the form of a graphical life chart, analogous to the life chart used in the Vantaa Depression Study (VDS) (Melartin et al., 2004) and based on DSM-IV criteria. Repeated SCID-I/P interviews and all observer- and self-reported scales were included at

both follow-up assessments. All medical and psychiatric records were available. In addition to information from symptom ratings and visits to attending personnel, change points in the psychopathologic states were also inquired about using probes related to important life events to improve the accuracy of the assessment. The onset of the index phase and the index episode were evaluated retrospectively.

We defined an episode according to the DSM-IV criteria and this could be monophasic or polyphasic. Accordingly, a phase in this study refers to a monophasic episode or a single phase of a polyphasic episode and, similarly, an episode refers to a monophasic or polyphasic episode. A depressive, manic, or mixed phase was defined as in DSM-IV; a hypomanic phase had a minimum duration of two days (Akiskal & Benazzi, 2005; Angst, 1998; Judd et al., 2003). Depressive mixed phases (=three or more simultaneous intra-episode hypomanic symptoms present for at least 50% of the time during a major depressive episode), as defined by Benazzi and Akiskal (Benazzi & Akiskal, 2001), were also evaluated. States of subsyndromal symptoms (including prodromal and residual symptoms) were rated when the patient was not euthymic and did not fulfill the criteria of a phase; durations of more than one week for hypomanic symptoms and more than two weeks for depressive symptoms and cyclothymia were required. A state of euthymic mood was used when the duration of euthymia was longer than two weeks.

Time after the beginning of the index phase was divided into three periods: (1) mood episode, (2) partial remission, or (3) full remission. In partial remission, the full criteria of a DSM-IV mood episode were not met, but some symptoms were present. In full remission, no DSM symptoms were present. The patient had reached remission if during at least two consecutive months the criteria for a mood episode were not met (DSM-IV). Relapse was defined as a return of a mood episode after a period of less than two months with symptoms below the mood episode threshold. Recurrence was defined as the emergence of symptoms sufficiently severe to satisfy criteria for a new mood episode after at least two consecutive months of partial or full remission.

4.4.3. Definition of maintenance phase

We defined maintenance treatment, and thus the maintenance phase, as starting on the day when the time with full criteria of a phase ended and ending on the day when the criteria for a relapse or recurrence were met, or at the last follow-up interview. Thus, the maintenance phase could include states of either full or partial remission. We based the discrimination of different phases on the life chart. We focused only on the first maintenance phase (lasting ≥ two weeks) after the index episode.

4.5. Data collection and definitions concerning treatment

We gathered data on all regularly used medicines and psychosocial treatments. Treatment was defined as ongoing as long as it was provided or prescribed according to psychiatric records, while termination was the date when treatment was first documented as not ongoing or reported as terminated by the patient with no later contact with a professional.

4.5.1. Adequate acute-phase pharmacotherapy (study I)

We defined adequate acute-phase pharmacotherapy based on published treatment guidelines (APA, 2002; Goodwin & Young, 2003; Grunze et al., 2002; Grunze et al., 2003; Sachs et al., 2000) and regardless of dosage, serum concentrations, or duration of treatments: (1) Adequate treatment for bipolar depression was defined as monotherapy with lithium or lamotrigine, or combinations of lithium, valproate, carbamazepine, or olanzapine with an antidepressant; a combination of lamotrigine with an antidepressant was interpreted as inadequate for patients with BD I, (2) adequate treatment for mania was defined as monotherapy and combinations of lithium, valproate, carbamazepine, atypical antipsychotics, or haloperidol; the treatment was interpreted as inadequate if an antidepressant was used, (3) adequate treatment for hypomania was defined the same as for mania, (4) adequate treatment for mixed state was defined the same as for mania except that treatment was interpreted as inadequate if a conventional antipsychotic was used, (5) adequate treatment for depressive mixed state was defined the same as for mixed state, and (6) adequate treatment for rapid cycling was defined as monotherapy or combinations of lithium, valproate, or carbamazepine. Treatment with lamotrigine was interpreted as adequate for BD II patients. Treatment of rapid cycling was classified as inadequate if an antidepressant was used.

4.5.2. Adequate maintenance phase pharmacotherapy (study II)

We defined adequate maintenance-phase pharmacotherapy also based on published treatment guidelines (APA, 2002; Goodwin, 2003; Grunze et al., 2004; Keck et al., 2004; Yatham et al., 2005). To be defined as adequate, the maintenance treatment had to include lithium, valproate, carbamazepine, or olanzapine. Monotherapy with lamotrigine was defined as adequate in BD II. We defined the treatments regardless of dosage or serum concentrations. Antidepressants were not included in the definition of adequate maintenance treatment, but we reported their use separately. We defined mood stabilizers as

follows: lithium, valproate, carbamazepine, oxcarbazepine, and lamotrigine. Atypical antipsychotics included olanzapine, risperidone, quetiapine, and aripiprazole.

4.5.3. Methods concerning continuity and adherence (study III)

Treatments provided were investigated at baseline and at both follow-up interviews. Psychotherapeutic support comprised regular appointments with a mental health professional aimed at helping the patient by discussing his or her problems (weekly psychotherapy excluded). Psychotherapy was defined as weekly therapy sessions for four or more weeks with a qualified, certified therapist. Continuity of psychotherapeutic and medical treatment was assessed by interviewing patients and investigating all medical and psychiatric records. The treatment phase was defined as a continuous time of treatment starting on the day the treatment was prescribed and ending on the day it was agreed to end, as reflected in psychiatric records. If treatment had been ongoing before baseline, it was considered as started at the time of the first baseline evaluation.

Self-reported treatment adherence was investigated by interviewing patients during follow-ups. Using all the information available, the interviewer determined whether the patient had come to sessions/been on medication (1) regularly (treatment compliance is adequate with respect to treatment goals), (2) somewhat irregularly (it is unclear whether this would affect treatment goals), (3) very irregularly (the treatment did not proceed according to plan), (4) not at all (the provided treatment could not be implemented), and (5) the question is not relevant (treatment was not provided). Patients fulfilling the requirements of the first response were *defined as adherent to treatment*. All other patients were considered nonadherent to that treatment.

Attitudes toward psychotherapeutic treatments and medications were assessed by interviewing the patients during follow-up and giving the following Likert-scale response options: Attitudes toward treatment are (1) very positive, (2) positive, (3) neutral, (4) negative, (5) very negative, (6) so negative that it prevents using the treatment, or (7) could not answer. The attitudes were investigated regardless of having actually received the treatment in question.

4.5.4. Methods concerning disability pension (study IV)

Information on disability pensions granted to subjects belonging to the JoBS cohort was obtained from interviews, patient records, and registers of the Social Insurance Institution of Finland and the Finnish Centre for Pensions. In Finland, employees aged under 63–65 years become eligible for disability pension after receiving a daily allowance from sickness insurance for 300 days during a two-year period (counted at six days per week) if they are still considered incapable of

working because of an illness. The 300 days usually comprise several consecutive shorter sick leave periods. Medical certificates issued by a psychiatrist for work disability allowances are referred to and granted by the Social Insurance Institution of Finland and by other pension providers; records on all pensions granted in Finland are collected by the Finnish Centre for Pensions. A part-time pension may also be granted. In this study, all forms of disability pension, whether temporary or permanent, full-time or part-time, were treated as one group. Homemakers and individuals working part-time were treated as working. Patients who had been granted a disability pension before baseline were excluded from the prospective analyses of the cohort followed up because the endpoint had in their case already occurred. Information on disability pensions for this study was obtained from the registers up to the time of the 18-month follow-up if it had been realized or up to 18 months after baseline if the 18-month follow-up data were missing.

4.6. Statistical methods

Studies I and II

In the study I and study II, we first counted the frequencies of different pharmacological agents and their combinations during the index acute phase (study I) and at the beginning, the end, and during the first maintenance phase after the index episode (study II).

Then we compared the crude frequency differences of a wide range of variables, including the following clinical and background variables: gender, bipolar subtype, type of index phase, treatment setting, rapid cycling, type of episode (mono- or polyphasic), bipolar diagnosis before index phase in study I, and gender, bipolar subtype, last phase before remission, rapid cycling, clinical bipolar diagnosis before maintenance phase, hospital treatment during index phase, and any personality disorder in study II. We used Pearson's chi-squared test and Fisher's exact test at the same time points for different pharmacological agents and their combinations at study intake in study I and at different time points in the maintenance phase in study II; we also used them for proportions of patients receiving adequate treatment at study intake in study I and at different time points during the maintenance phase in study II. In Study II, using Pearson's chi-squared test, we also compared the frequency differences in gender, age, bipolar subtype, marital status, education, work status, any lifetime anxiety disorder, any lifetime substance use disorder, psychotic symptoms lifetime, clinical diagnosis of BD before maintenance phase, rapid cycling, hospital treatment during lifetime, for uninterrupted adequate maintenance treatment.

Finally, we performed logistic regression analyses with adequacy of index phase treatment as the independent variable separately for all the patients and for

those with a clinical diagnosis of BD at study intake (study I). We used age, gender, bipolar subtype, index phase, rapid cycling, treatment setting, type of index episode (mono- or polyphasic), any lifetime anxiety disorder, any lifetime substance use disorder, any personality disorder, and the number of hospital treatments as dependent variables in study I. In study II, we made regression analysis for adequate maintenance treatment received throughout the maintenance phase as the independent variable, separately for all the patients having a maintenance phase during the follow-up and for those with a clinical diagnosis of BD before the maintenance phase and age, gender, bipolar subtype, the last phase before the maintenance phase, rapid cycling, treatment setting in the phase before the maintenance phase, any lifetime or current anxiety or substance use disorder, any personality disorder, and clinical diagnosis of BD before maintenance phase as dependent variables, to assess the variables independently related to adequate treatment while controlling for potential confounding factors.

Study III

In the third study, we used the Pearson chi-squared test to evaluate categorical and non-parametric data and the Mann–Whitney or Kruskall–Wallis test to compare continuous variables not normally distributed. To compare adherence (dichotomized as adherent/nonadherent) of the same patient at the 6- and 18-month interviews, we used the McNemar test, and to compare attitudes of the same patient at the 6- and 18-month interviews we used the Marginal Homogeneity Test. The one-sample binomial test was used to compare the observed and expected proportions of medications autonomously discontinued in different phases with the proportion of time spent in each phase. To compare the attitudes of the same patients toward different types of treatments (different medications, psychosocial treatments, electro-convulsive treatments), we used the related samples Cochran Q test. We used Spearman's correlation to analyze the correlations of adherence and attitudes between treatment groups. Finally, to adjust for confounding factors, three logistic regression models were created with nonadherence to mood stabilizers, nonadherence to antipsychotics, and nonadherence to psychotherapy/supportive psychotherapy as dependent variables, adjusting for age, gender, and bipolar subtype in all models; all the significant factors in the univariate analysis and factors that were considered clinically or theoretically important as independent variables were used.

Study IV

In the fourth study, we used the Pearson's chi-squared test for nominal variable comparisons and analyzed normally distributed continuous variables by two-sample t-tests and non-normally distributed variables using the Mann-Whitney U- and Kruskal-Wallis tests.

For univariate and multivariate analyses to predict the time interval to the date that the pension was granted, we used Cox proportional hazards models. We included all of the hypothesized predictors and other variables significant or almost significant (p<0.10) in the univariate analyses, including age, gender, duration of disease, perceived working ability, type of index episode, number of depressive phases, number of manic/hypomanic phases, comorbidity with anxiety or substance use disorders currently or during lifetime, comorbidity with personality disorder, and number of hospital treatments in the multivariate analyses. Since we were specifically interested in examining the possible effect of comorbidities on being granted a disability pension, we included all diagnoses of anxiety disorders and personality disorders in the multivariate analysis regardless of their significance in the univariate analyses. We also made separate models incorporating information from the 18-month follow-up, including time and proportion of time in different phases during the follow-up. To assess intercorrelations between the predictors, we computed Spearman bivariate correlations. Kaplan-Meyer curves and log-rank tests were also used to demonstrate subgroup differences.

We conducted separate analyses by splitting the data for the 151 patients by bipolar subtype (BD I vs. BD II), age (<40 vs. ≥40 years at baseline), and gender. We made Cox regression models for each of these six subgroups, adjusting for the remaining variables (age, gender, and bipolar subtype) and used the same predictors that were significant in the first model.

5. RESULTS

5.1. Adequacy of acute phase pharmacotherapy in BD (Study I)

5.1.1. Mood stabilizers and atypical antipsychotics

Only just over a half (107/191, 56%) of the patients had received one or multiple mood stabilizers during the index acute phase. Having received mood stabilizers was in univariate analyses associated with several factors. Patients with BD I had them more often than those with BD II (63/90 [70%] vs. 44/101 [44%], p<0.001), men more often than women (61/90 [68%] vs. 46/101 [46%], p=0.002), and inpatients more often than outpatients (48/65 [74%] vs. 59/126 [47%], p<0.001). Patients with a clinical diagnosis of BD mostly had a mood stabilizer, whereas patients without the diagnosis very rarely (102/117 [87%] vs. 5/74 [7%], p<0.001). Somewhat unexpectedly, patients with rapid cycling had mood stabilizers less often than non-rapid cycling patients (27/62 [44%] vs. 80/129 [62%], p=0.016). Valproate was the most commonly prescribed mood stabilizer, the proportion being nearly three times the proportion of lithium treatment (28/117 [66%] vs. 79/117 [24%]) among clinically diagnosed patients with BD.

Atypical antipsychotics were prescribed to 16% (31/191) of patients. The patients treated with atypical antipsychotics had mainly BD I (28/31, 90%), were equally often in depressive (15/31, 48%) or manic (14/31, 45%) phases, and had a clinical diagnosis of BD (29/31, 94%). Only three patients had monotherapy with atypicals, whereas most of the patients with atypicals had combinations with mood stabilizers or antidepressants.

5.1.2. Antidepressants

Overall, half (94/191, 49%) of the patients had an antidepressant. Patients with BD II had them more often than patients with BD I (63/101 [62%] vs. 31/90 [34%], p<0.001), patients without a clinical diagnosis of BD more often than patients with the diagnosis (51/74 [70%] vs. 43/117 [37%], p<0.001), and patients with a polyphasic last episode more often than those with a monophasic last episode (57/98 [58%] vs. 37/93 [40%], p=0.032). Most of the depressive (73/106 [69%]) and half of the depressive mixed patients (13/26 [50%]) had an antidepressant. Even a fourth (5/21 [24%]) of hypomanic patients received antidepressants.

In all, 26% of all patients, and half (53%) of the patients with an antidepressant, received antidepressant monotherapy without a concurrent mood stabilizer or an atypical antipsychotic (Table 5). Of the patients receiving

antidepressants, 35 (37%) had a concurrent mood stabilizer, two (2%) had an atypical antipsychotic, and seven (7%) had a mood stabilizer plus an atypical antipsychotic (Table 5). However, most of the 43 clinically diagnosed patients (39/43 [91%]) with an antidepressant had also a mood stabilizer, whereas nearly all of the 51 patients (48/51 [94%]) without a clinical diagnosis of BD and an antidepressant had no mood stabilizer.

Table 5. Proportions of antidepressants, mood stabilizers and atypical antipsychotics in use with the 191 patients in Jorvi Bipolar Study

Variable	AD[1] only		MS[2] only		AAP[3] only		AD+ MS		AD+ AAP		MS+ AAP		AD+ MS+ AAP		No drugs of these groups	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gender																
Men (n=90)	17	18.9	30	33.3	3	3.3	17	18.9	1	1.1	10	11.1	4	4.4	8	8.9
Women (n=101)	33	32.7	16	15.8	0	0.0	18	17.8	1	1.0	9	8.9	3	3.0	21	20.8
p value	0.029		0.005*		0.033		NS		NS		NS		NS		0.020	
Bipolar subtype																
I (n=90)	10	11.1	25	27.8	3	3.3	14	15.6	1	1.1	18	20.0	6	6.7	13	14.4
II (n=101)	40	39.6	21	20.8	0	0.0	21	20.8	1	1.0	1	1.0	1	1.0	16	15.8
p value	<0.001*		NS		0.033		NS		NS		<0.001*		0.030		NS	
Last phase																
Depression (n=106)	34	32.1	14	13.2	1	0.9	30	28.3	2	1.9	5	4.7	7	6.6	13	12.3
Hypomania(n=21)	4	19.0	7	33.3	0	0.0	1	4.8	0	0.	2	9.5	0	0.0	7	33.3
Mania (n=23)	0	0.0	9	39.1	2	8.7	0	0.0	0	0.0	12	52.2	0	0.0	0	0.0
Mixed (n=15)	2	13.3	8	53.3	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0	4	26.7
Depressive mixed (n=26)	10	38.5	8	30.8	0	0.0	3	11.5	0	0.0	0	0.0	0	0.0	5	19.2
p value	0.001*		0.001*		NS		<0.001*		NS		<0.001*		NS		0.007	
Treatment setting																
Outpatient (n=126)	40	31.7	32	25.4	0	0.0	18	14.3	2	1.6	6	4.8	3	2.4	25	19.8
Inpatient (n=65)	10	15.4	14	21.5	3	4.6	17	26.2	0	0.0	13	20.0	4	6.2	4	6.2
p value	0.012		NS		0.010		0.049		NS		0.001*		NS		0.008	
Bipolar diagnosis																
Yes (n=117)	4	3.4	44	37.6	3	2.6	32	27.4	0	0.0	19	16.2	7	6.0	8	6.8
No (n=74)	46	62.2	2	2.7	0	0.0	3	4.1	2	2.7	0	0.0	0	0.0	21	28.4
p value	<0.001*		<0.001*		NS		<0.001*		0.050		<0.001*		0.008		<0.001*	
Rapid cycling																
Yes (n=62)	21	33.9	14	22.6	0	0.0	10	16.1	1	1.6	1	1.6	2	3.2	13	21.0
No (n=129)	29	22.5	32	24.8	3	2.3	25	19.4	1	0.8	18	14.0	5	3.9	16	12.4
p value	NS		NS		NS		NS		NS		0.002*		NS		NS	
Monophasic (n=93)	16	17.2	26	28.0	3	3.2	18	19.4	1	1.1	11	11.8	2	2.2	16	17.2
Polyphasic (n=98)	34	34.7	20	20.4	0	0.0	17	17.3	1	1.0	8	8.2	5	5.1	13	13.3
p value	0.006*		NS		0.037		NS		NS		NS		NS		NS	

[1]AD=antidepressant, [2]MS=mood stabilizer, [3]AAP=atypical antipsychotic,*Significant with Bonferroni correction p<0.05/8=0.006

Table 6. Proportions of the 191 patients in Jorvi Bipolar Study receiving adequate treatment.

| Variable | All patients | | | | A clinical diagnosis of BD | | | | Undiagnosed | | |
| | Total N | Adequate treatment | | | Total N | Adequate treatment | | | Total N | Adequate treatment | |
		n	%	p*		n	%	p*		n	%
Gender											
Men	90	47	52.2		67	45	67.2		23	2	8.7
Women	101	34	33.7	0.009	50	31	62.0	0.563	51	3	5.9
Bipolar subtype											
I	90	50	55.6		67	47	70.1		23	3	13.0
II	101	31	30.7	0.000	50	29	58.0	0.174	51	2	3.9
Last phase											
Depression	106	33	31.1		61	30	49.2		45	3	6.7
Hypomania	21	9	42.9		13	9	69.2		8	0	0.0
Mania	23	23	100.0		23	23	100.0		0	0	0.0
Mixed	15	8	53.3		7	6	85.7		8	2	25.0
Depressive mixed	26	8	30.8	0.000	13	8	61.5	0.000	13	0	0.0
Treatment setting											
Inpatient	65	36	55.4		51	34	66.7		14	2	14.3
Outpatient	126	45	35.7	0.009	66	42	63.6	0.733	60	3	5.0
Rapid cycling											
Yes	62	15	24.2		30	13	43.3		32	2	6.3
No	129	66	51.2	0.000	87	63	72.4	0.005	42	3	7.1
Mono/polyphasic											
Monophasic	93	52	55.9		64	51	79.7		29	1	3.4
Polyphasic	98	29	29.6	0.000	53	25	47.2	0.000	45	4	9.9
Bipolar diagnosis											
Yes	117	76	65.0								
No	74	5	6.8	0.000							

*p-values indicate statistical differences between subgroups in different variables (gender, bipolar subtype etc.).

5.1.3. Overall adequacy of acute-phase treatment

Less than half (81/191, 42.4%) of the patients received adequate acute-phase treatment (Table 6); men more often than women, bipolar I patients more often than bipolar II patients, inpatients more often than outpatients. All manic patients received adequate treatment, whereas less than one-third of depressive or depressive mixed patients. Only one-fourth of patients with rapid cycling and less than one-third of patients with a polyphasic index episode received adequate treatment. Among the patients with rapid cycling or a polyphasic index episode, inadequacy in treatment was mainly due to not having a mood stabilizer or atypical antipsychotic and/or having an antidepressant. The main reasons for inadequate treatment among the patients with a depressive index phase, included

not having a mood stabilizer or an atypical antipsychotic, having an antidepressant during rapid cycling, and/or having valproate monotherapy without an antidepressant.

5.1.4. Impact of diagnosis on adequacy of treatment

Lack of a bipolar diagnosis was by far the most important predictor of inadequate treatment (Table 6). These patients rarely had a mood stabilizer and often had an antidepressant without a mood stabilizer (Table 5). But, even among the patients with a clinical diagnosis of BD, pharmacotherapy was often (in 35% of cases) classified as inadequate. The main reasons for this were lack of a mood stabilizer, having an antidepressant in rapid cycling, and/or treatment of depression with valproate without an antidepressant.

5.1.5. Predictors of adequate acute phase treatment in multivariate models

In the logistic regression model, not having a clinical diagnosis of BD (OR=25.3, p<0.001), rapid cycling (OR=2.5, p=0.041), polyphasic index episode (OR=2.4, p=0.026), and depressive index phase (OR=3.4, p=0.003) predicted not having adequate acute phase treatment.

5.2. Adequacy of maintenance phase pharmacotherapy in BD (Study II)

5.2.1. Pharmacotherapy during the maintenance phase

There were 154 patients with a maintenance phase during the follow-up. The mean duration of the first maintenance phase was 220 days (minimum 14 days, maximum 1180 days). Three-quarters of all the 154 patients, and most of the patients with either BD I or a clinical BD diagnosis (I or II), with a maintenance phase during the follow-up, received mood stabilizers or atypical antipsychotics at some point during the maintenance phase (Table 7). Valproate was prescribed over two times more often than lithium. Of the atypicals olanzapin was the one most often prescribed. Most of the patients who had atypical antipsychotics received also mood stabilizers. Lamotrigine was only prescribed for patients with BD II.

Over a half (55%) of all the patients (Table 7), and most (21/25 [78%]) of the patients without a clinical diagnosis of BD, received antidepressants for some time during the maintenance phase, and most of them had depression preceding that phase. Surprisingly, even a fifth (9/24 [21%]) of the patients with hypomania

preceding the maintenance phase received antidepressants at the beginning of the maintenance phase. There was no difference between the patients having some anxiety disorder during lifetime at 18-month follow-up and those who had not had any anxiety disorders during that time in regard to being prescribed antidepressants some time during the maintenance phase (53% vs. 47%, p=0.957). There was no statistical difference between the proportion of rapid cycling and non-rapid cycling patients being prescribed antidepressants (22/39 [56%] vs. 62/115 [54%], p=0.786), and actually there was a trend towards rapid cycling patients receiving antidepressants more often. Approximately one-third (27-37%) of the patients received the antidepressant without mood stabilizers or atypical antipsychotics. There were some changes in pharmacotherapy among individual patients during the maintenance phase. Nevertheless, most of the changes in pharmacotherapy occured in the acute phase, fewer during the maintenance phase.

Table 7. Proportions of different medications received at different stages of maintenance phase during follow-up by the 154 patients in the JoBS.

	Medication received at some time during the first maintenance phase (≥2 weeks after index episode)											
	All patients						Clinical bipolar diagnosis					
	BD I N=71		BD II N=83		Total N=154		BD I N=66		BD II N=63		Total N=129	
Type of medication	n	%	n	%	n	%	n	%	n	%	n	%
Mood stabilizer	62	87.3	52	62.7	114	74.0	60	90.9	49	77.8	109	84.5
Lithium	24	33.8	10	12.0	34	22.1	24	36.4	10	15.9	34	26.4
Valproate	44	62.0	40	48.2	84	54.5	42	63.6	39	61.9	81	62.8
Oxcarbazepine	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Carbamazepine	4	5.6	3	3.6	7	4.5	4	6.1	2	3.2	6	4.7
Lamotrigine,	0	0.0	11	13.3	11	7.1	0	0.0	10	15.9	10	7.8
Atypical antipsychotic	24	33.8	8	9.6	32	20.8	24	36.4	7	11.1	31	24.0
Olanzapine	18	25.4	3	3.6	21	13.6	18	27.3	3	4.8	21	16.3
Risperidone	14	19.7	3	3.6	17	11.0	14	21.2	2	3.2	16	12.4
Quetiapine	2	2.8	3	3.6	5	3.2	2	3.0	3	4.8	5	3.9
Aripiprazole	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Conventional antipsychotic	11	15.5	6	7.2	17	11.0	11	16.7	6	9.5	17	13.2
Haloperidol	1	1.4	1	1.2	2	1.3	1	1.5	1	1.6	2	1.6
Other neuroleptics	10	14.1	5	6.0	15	9.7	10	15.2	5	7.9	15	11.6
Mood stabilizer or atypical antipsychotic	63	88.7	55	66.3	118	76.6	61	92.4	51	81.0	112	86.8
Mood stabilizer or any antipsychotic	64	90.1	57	68.7	122	79.2	62	93.9	53	84.1	115	89.1
Antidepressant	29	40.8	55	66.3	84	54.5	15	22.7	32	50.8	47	36.4

5.2.2. Adequacy and continuity of maintenance treatment

We found that the proportion of adequate maintenance treatment received of the time needed was 69.3% (783/1129 patient months) for all the 154 patients and 77.9% (766/984 patient months) for patients with a clinical bipolar diagnosis. Less than two-thirds (61%) of the 154 patients received adequate treatment throughout the maintenance phase; 72% of patients with a clinical bipolar diagnosis, but less than half of them with bipolar II or treated as outpatients during the index episode (Table 8). Majority of the patients (94/116, 81.0%) with adequate maintenance treatment at some time during the maintenance phase received it throughout that phase. Only ten patients received new starts of adequate treatment after the beginning of maintenance phase, seven of them within two weeks and the rest within three months. The duration of the maintenance phase did not have an effect on receiving adequate maintenance treatment.

5.2.3. Predictors of adequate maintenance treatment in multivariate models

We made logistic regression models to adjust for confounding factors predicting adequate maintenance treatment received throughout the maintenance phase. The predictors were: having a clinical diagnosis of BD (OR=106.5, p<0.001), having been treated in hospital during the episode before maintenance phase (OR=11.09, p<0.001), rapid cycling (OR=3.4, p=0.030), and comorbid personality disorder (OR=0.373, p=0.038). We also made logistic regression models for the patients with a clinical diagnosis of BD before the maintenance phase. The factors that independently best predicted adequate maintenance treatment received throughout the maintenance phase were the same as in the regression models with all patients, except that clinical diagnosis was not included and having no comorbid personality disorder did not quite reach statistical significance in the model.

Table 8. Proportions of the 154 Jorvi Bipolar Study patients receiving adequate treatment at maintenance phase.

	Adequate maintenance treatment any time during maintenance, n=154			Adequate maintenance treatment throughout maintenance phase, n=154			Adequate maintenance treatment throughout maintenance phase, patients with a clinical bipolar diagnosis, n=129		
	n	%	p	n	%	p	n	%	p
Total	116	75.3		94	61.0		93	72.1	
Female	55	70.5		44	56.4		43	69.4	
Male	61	80.3	0.159	50	65.8	0.233	50	74.6	0.505
Bipolar subtype									
BDI	63	88.7		55	77.5		55	83.3	
BDII	53	63.9	<0.001	39	47.0	<0.001	38	60.3	0.004
Last phase before remission									
Depression	69	71.1		54	55.7		53	67.1	
Hypomania	16	66.7		14	58.3		14	66.7	
Mania	17	100.0		15	88.2		15	88.2	
Mixed	6	100.0		5	83.3		5	100.0	
Depressive-mixed	8	80.0	0.005	6	60.0	0.099	6	85.7	0.194
Rapid cycling									
Yes	29	74.4		24	61.5		24	80.0	
No	87	75.7	0.872	70	60.9	0.941	69	69.7	0.270
Hospital treatment during index episode									
Yes	55	93.2		50	84.7		49	92.5	
No	61	64.2	<0.001	44	46.3	<0.001	44	57.9	<0.001
Clinical BD diagnosis before maintenance phase									
Yes	111	86.0		93	72.1				
No	5	20.0	<0.001	1	4.0	<0.001			
Any personality disorder									
Yes	46	71.9		36	56.3		36	64.3	
No	70	77.8	0.402	58	64.4	0.304	57	78.1	0.083

5.3. Adherence (Study III)

5.3.1. Treatment setting, contents and continuity

Majority of the patients (140/160, 88%) were still in treatment at the 18-month follow-up, most of them being treated in psychiatric settings (135, 84%). Most of the 20 patients who were not in treatment had BD II (16/20, 80%), and majority of them (17/20, 85%) were in remission. Psychiatric hospital treatment during the follow-up had received a third (59/170, 35%) of the patients.

Majority of the patients (87%) were prescribed mood stabilizers or atypical antipsychotics at some point during the follow-up. Nearly all of the patients (91%) also received some kind of psychosocial treatment, mainly supportive psychotherapy (69%) or individual psychotherapy (19%). The mean duration of psychosocial treatment was 17.5 (range 1-120) months.

Although most of the patients received psychopharmacological treatment, the continuity of treatment was often compromised, as nearly half of the mood stabilizer (96/238, 40.3%) and nearly two-thirds of the atypical antipsychotic (80/127, 63.0%) treatment *phases* (one patient could have more than one treatment phase of the same category of medication) were discontinued during the 18-month follow-up. Even though most of the discontinuations occurred in accordance with the treatment plan, nearly half (41/96, 42.7%) of the mood stabilizer and one-third (24/80, 30.0%) of the atypical antipsychotic discontinuations were autonomous (Table 9).

The rates of individual patients who discontinued medications were expectedly somewhat lower. Of the individual patients, one-quarter using mood stabilizers (36/153, 24%) or atypical antipsychotics (19/74, 26%) discontinued at least one treatment phase autonomously. Autonomous discontinuations of these treatments took place mainly in depression (42%) or euthymia (35%), seldom during the other phases. When examined in relation to the follow-up time spent in each phase, and adding the discontinuation of antidepressants, pharmacotherapy was autonomously discontinued more often in depressive (48% observed vs. 36% ecpected, p=0.011) and less often in euthymic (28% observed vs. 37% expected, p=0.040) phases.

5.3.2. Self-reported treatment adherence at 18-month follow-up

At the 18-month follow-up most of the patients were adherent to the treatments they received between the 6- and 18-month follow-ups (Table 10). Nevertheless, some differences emerged in the rates of adherence (from 61% to 85%) between categories and types of treatment (p<0.001), adherence to mood stabilizers being the worst. Specifically, adherence to anxiolytics was better than to psychotherapy/supportive therapy (85% vs. 75%, p=0.004), to mood stabilizers (85%, vs. 61%, p<0.001) or to antidepressants (85% vs. 67%, p=0.007), and adherence to psychotherapy/supportive therapy was better than to mood stabilizers (75% vs. 61%, p=0.019).

The main self-reported reasons for medication nonadherence were side-effects, lack of motivation and/or a negative attitude towards the particular treatment (Table 11). Of the patients who attributed side-effects as a reason for mood stabilizer nonadherence, 65% (11/17) also gave some other reason (negative attitude towards medication 7, not effective 2, not motivated 1, wanted to try without 1), suggesting that side-effects as such may not always be a sufficient

explanation for poor adherence. Respectively, the most often attributed reasons for not coming to psychotherapy sessions regularly were practical barriers to coming to sessions (15/26, 57.7%) and lack of motivation (9/26, 34.6%).

Table 9. History of medication treatment phases and reasons for terminating treatment during 18 months' follow-up in the JoBS

History of treatment phases	Lithium		Valproate		Carba-mazepine[d]		Lamotri-gine		SGA		Antidepres-sant		FGA	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Number of treatment phases	52	100	139	100	14	100	33	100	127	100	214	100	31	100
Discontinued treatment phases	14	26.9	62	44.6	8	57.1	12	36.4	80	63.0	177	82.7	29	93.5
Reasons for discontinuing treatment phases[a]	n	%[b]	n	%[b]	n	%[b]	n	%[b]	n	%[b]	n	%[b]	n	%[b]
Poor/no response	1	6.7	13	16.7	2	25.0	3	21.4	7	7.2	51	26.0	6	23.1
Side-effects	11	73.3	28	35.9	6	75.0	7	50.0	43	44.3	60	30.6	10	38.5
Too expensive medication	0	0.0	1	1.3	0	0.0	1	7.1	7	7.2	0	0.0	0	0.0
No need for treatment because of recovery	0	0.0	2	2.6	0	0.0	0	0.0	16	16.5	33	16.8	7	26.9
Seemed to provoke a new phase[c]											10	5.1		
Patient's autonomous decision	3	20.0	34	43.6	0	0.0	3	21.4	24	24.7	42	21.4	3	11.5

n=number of treatment phases. One patient could have more than one treatment phase of the same medication. SGA=Second generation antipsychotic, FGA=First generation antipsychotic. [a] One treatment phase could include more than one reason for discontinuing; [b] % of the reasons for discontinuing the medication; [c] only 6-18 months' follow-up.

Table 10. Self-reported treatment adherence at the 18-month follow-up in the JoBS.

The patient has come to sessions/been on medication during the last follow-up period	Mood stabilizer		Anti-psychotic		Antidepres-sant		Psychosoci al treatment	
	n	%	n	%	n	%	n	%
Regularly	77	61.1	100	74.6	66	67.3	100	74.6
Somewhat irregularly	15	11.9	20	14.9	12	12.2	20	14.9
Very irregularly	22	17.5	7	5.2	11	11.2	7	5.2
Not at all	12	9.5	7	5.2	9	9.2	7	5.2

5.3.3.   Stability and predictors of treatment adherence

When examining whether adherence to the same category of treatment changes from the 6-month to the 18-month follow-up, we found a change towards lower adherence to mood stabilizers (73% vs. 63%, p=0.015) and antidepressants (83% vs. 72%, p=0.023), but no changes in other groups of medications (antipsychotics, antidepressants) or psychosocial treatment.

There were 134 patients with mood stabilizers at the 6- and 18-month follow-up points and 18 (13%) of them reported nonadherence at both follow-ups.

We made logistic regression models to predict the factors associated with continued nonadherence: we added all the factors significant in the univariate analysis in the model, and adjusted for age, gender and bipolar subtype. Only the level of education, both low basic (not more than elementary school vs. student [p=0.01, OR=5.8 {1.5–22.4}]) and poor professional education (no professional education vs. having professional education [p=0.011, OR=4.2, {1.4–12.8}]) remained a significant predictor of continued nonadherence to mood stabilizers.

5.3.4.   Differences in adherence and attitudes between treatments

We found that adherences to different treatments correlated with each other, except between psychosocial treatment and anxiolytic medication (Table 12). There was a strong correlation between different types of pharmacotherapies for mood disorder. Attitudes towards different forms of treatments were mainly positive and correlated with each other, the only exception being between attitudes towards psychotherapy and somatic medications. In contrast to adherence, these correlations were weak (r=0.10–0.29) or moderate (r=0.30–0.49).

Table 11. Self-reported reasons for medication nonadherence at the18-month follow-up among patients in the JoBS.

Reason(s) for not using medication as prescribed[a]	Mood stabilizer		Anti- psychotic		Anti- depressant	
	n	% of non-adhe-rents N=43	n	% of non-adhe-rents N=16	n	% of non-adhe-rents N=30
Generally a negative attitude towards offered treatment	9	20.9	4	25.0	5	16.7
Lack of motivation	16	37.2	4	25.0	13	43.3
Side-effects	17	39.5	6	37.5	7	23.3
Other reasons	14	32.5	4	25.1	11	36.6

[a]Each patient could have more than one reason for not using the medication classes as prescribed.

Table 12. Spearman's correlations between adherences to treatments at the18-month interview.

Treatment adherence at 18 months	1.	2.	3.	4.	5.
1. Mood stabilizers	1,000	,624[**]	,291[*]	,516[**]	,412[**]
2. Antipsychotics		1,000	,406[*]	,654[**]	,392[**]
3. Anxiolytics			1,000	,391[**]	,068
4. Antidepressants				1,000	,290[**]
5. Psychotherapy					1,000

[**] Correlation is significant at the 0.01 level (2-tailed). Strong = 0.50-1.00, medium = 0.30-0.49, small = 0.10-0.29.

5.3.5. Predictors of treatment nonadherence in multivariate models

The logistic regression models to predict nonadherence with different forms of treatments included all the variables significant in the univariate analyses as explaining variables, adjusted for age, gender and bipolar subtype. In the model for nonadherence to *mood stabilizers* at the 18-month follow-up significant predictors were negative attitudes towards mood stabilizers (negative vs. positive OR=4.3, p=0.023, [1.2–14.8]) and having some current anxiety disorder at the 6-month interview (OR=2.6, p=0.029, [1.1–6.0]). Predictors of nonadherence to *antipsychotics* at the 18-month follow-up were borderline personality disorder (OR=7.4, p=0.027, [1.2–43.7]), having current substance dependence at

the 6-month follow-up (OR=12.1, p=0.45, [1.1–139.4]) and having negative attitudes towards antipsychotics (negative vs. positive OR=7.6, p=0.041, [1.1–53.3]). Predictors of nonadherence to *psychotherapy/supportive psychotherapy* at the 18-month follow-up were having a current anxiety disorder at the 6-month follow-up (OR=3.53, p=0.011, [1.3–9.3]) or during lifetime (OR=2.9, *p*=0.043, [1.0–8.1]) and having negative attitudes towards psychotherapy (negative vs. positive OR=23.3, p<0.001, [4.1–133.5]).

5.4. Disability in BD (Study IV)

5.4.1. Patients on disability pension at baseline

Altogether, a fifth (40, 21%) of the 191 patients were already on disability pension before enrollment in the study. These patients were expectedly older, but did not differ with regard to gender, bipolar subtype, marital status, or education. Patients who had been granted a disability pension before baseline were excluded from the prospective analysis.

5.4.2. Patients granted a pension during the 18-month follow-up

Of the 151 remaining patients 38 (25%) were granted a disability pension during the 18-month follow-up. Most of the patients had BD (32/38, 84%) as the primary clinical diagnosis (ICD-10) for being granted a disability pension; however, in four cases the clinical diagnosis was unipolar depression, in one case schizoaffective disorder and in one case unknown.

5.4.3. Sociodemographic and clinical differences

5.4.3.1. Baseline

There were many differences already at baseline between the patients who were granted a disability pension during the follow-up and the non-pensioned patients (see study IV, table 1). The patients who had been granted a disability pension during follow-up were significantly older, more often male, had more often BD type I, had longer duration of BD and had been more often treated in psychiatric hospitals than those not pensioned, but they did not differ with regard to marital status, living arrangement or education. They also had lower levels of overall social and occupational functioning (SOFAS), were more depressed (BDI, HAM-D), perceived less social support (PSSS-R), were on sick leave and perceived themselves unable to work markedly more often than their non-pensioned counterparts, and had more often alcohol and other substance use disorders.

There were no differences in the proportion of pensioned and non-pensioned patients with anxiety disorders overall. However, of specific anxiety disorders, pensioned patients had more often GAD (generalized anxiety disorder) (11/38 [29%] vs. 13/113 [12%], p=0.011). Proportions of patients with any personality disorder did not differ between these two groups, neither proportions of manic or depressive predominant polarity.

5.4.3.2. During the 18-month follow-up

The course of the disease differed somewhat between the patients pensioned/not pensioned during the 18-month follow-up. The patients who were granted a disability pension reached full remission less often (43% vs. 73%, p=0.001) than non-pensioned patients, but the proportion of partial remission was similar in the two groups (51% vs. 60%, p=0.383). The patients who were granted a disability pension spent less time in in euthymia (mean 28% vs. 45%, p=0.005) and more time in major depressive phases (mean 54% vs. 29%, p<0.001) than non-pensioned patients, but there were no differences in the proportion of time spent in manic, hypomanic, mixed or depressive mixed phases, or with hypomanic or depressive symptoms.

As the pensioned patients had overall a more severe and chronic course of illness than non-pensioned patients, they expectedly received somewhat more treatments and clinical appointments. The median number of visits to doctors was equal (3.0) during the first 6 months, but higher between the 6- and 18-month follow-up (p=0.001) among the pensioned (4.0) than non-pensioned (2.0) patients. The median number of visits to any personnel was 10.0 vs. 8.0 respectively during the first 6 months (p=0.599) and 12.0 vs. 7.0 between the 6- and 18-month interviews (p=0.012). The adequacy of pharmacological acute phase treatment did not differ significantly (47% pensioned vs. 37% non-pensioned, p=0.266), but the pensioned patients had more adequate treatment during the first maintenance phase (89% vs. 70%, respectively, p=0.048). Adherences to medications, or attitudes towards mood stabilizers, antipsychotics or psychotherapy did not differ significantly during follow-up, the pensioned ones being at least as adherent as the non-pensioned ones.

The patients with *permanent* disability pension *at* 18-month follow-up were older (mean 47.2 vs. 33.1 years, p<0.001), more often BD type I (60.3% vs. 40.8%, p=0.013), had more often had alcohol dependence (53.4%, vs. 33.1%, p=0.008) and post-traumatic stress disorder (25.9% vs. 11.5%, p=0.013) during their lifetime, had better basic education (p=0.005) but less vocational education (p=0.034). They were also more depressed (according to HAM scores p=0.018, but there was no difference in BDI scores), anxious (BAI scores, p= 0.039), had less social support (PSSR scores p=0.022) and they were more disabeled (SOFAS scores, p<0.001).

5.4.4. Predictors for time to disability pension during the 18-month follow-up

5.4.4.1. Univariate analyses

We made univariate analyses with Cox model to investigate the effect of each predictor on the interval time from intake to the date the pension was granted (Table 13). In these analyses, the significant predictors of granted disability pension were older age, male gender, bipolar type I, depressive index phase, number of manic phases, longer duration of BD, comorbid substance abuse, GAD and avoidant personality disorder, greater number of psychiatric hospital treatments, and perceived poor economic situation. Granted disability pension was associated also with more time spent in major depressive episodes, greater proportion of time spent in depressive states overall, and smaller proportion of time spent in euthymia during the follow-up. Moreover, granted disability

Figure 2. Kaplan–Meier survival curves for subgroups divided by age (< or ≥40 years), gender, bipolar subtype, and perceived ability to work, predicting time to being granted a disability pension during the 18-month follow-up in the Jorvi Bipolar Study.
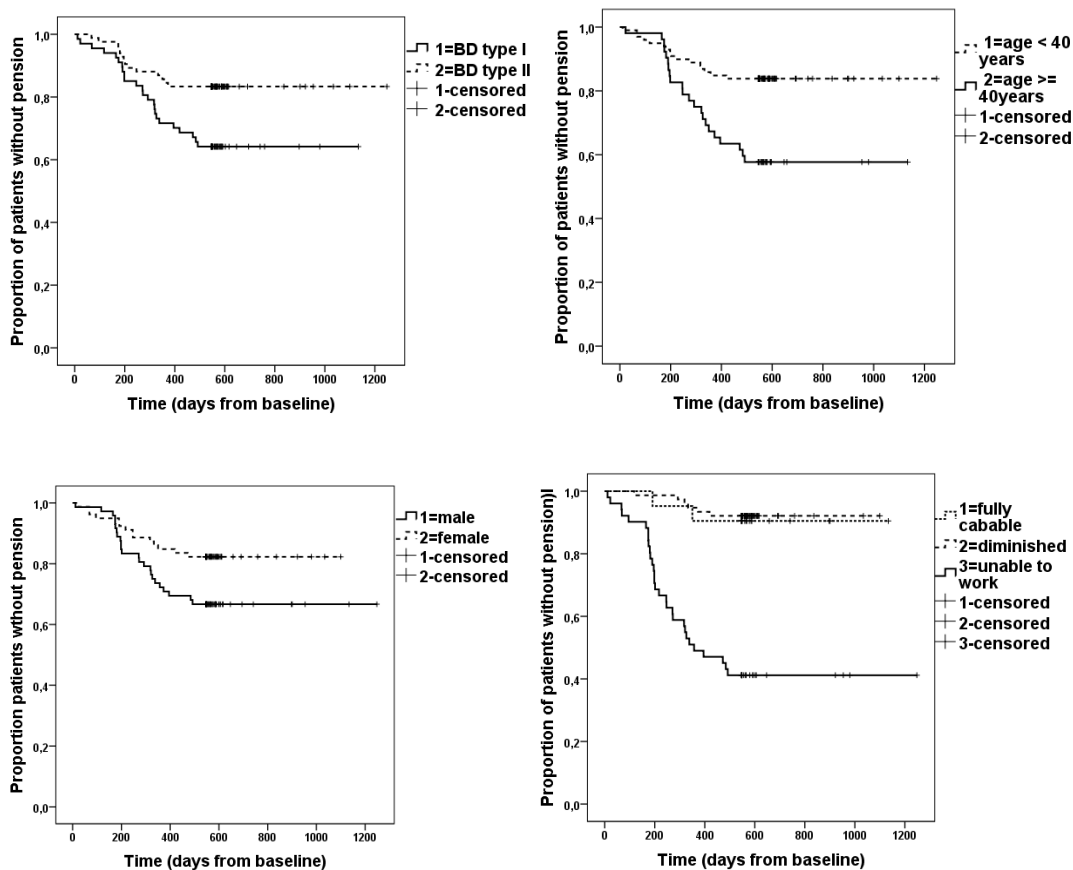
pension was associated with lower perceived working ability, higher BDI (Beck Depression Inventory), HAM-D (Hamilton Rating Scale for Depression) and BAI (Beck Anxiety Inventory) scores, and lower SOFAS (Social and Occupational Functioning Assessment Scale) and PSSS-R (Perceived Social Support Scale-Revised) scores (Table 13, Figure 2).

5.4.4.2. Multivariate analyses

To adjust for confounding factors, we created Cox regression models predicting the time to being granted a disability pension during the 18-month follow-up (Table 14).

In the first phase, we created models for all 151 patients who were not on pension at baseline, controlling for age, gender, and bipolar subtype in all models. We added other factors one by one if they were either significant or almost significant (p<0.10) in univariate analysis or considered clinically or theoretically important. As we were specifically interested in determining the possible effect of comorbidities on being granted a disability pension we included all anxiety disorders and personality disorders in the multivariate analysis irrespective of their significance in the univariate analyses. We found that the time to being granted a disability pension was independently predicted by higher age, male sex, depressive index episode, GAD, avoidant personality disorder and higher number of psychiatric hospital treatments (Table 14). Age was not significant if perceived working ability was added in the model, as age and perceived working ability are correlated (Spearman's rho 0.306, p<0.001), but perceived working ability was highly significant (HR=9.09, 95%CI=3.85-21.49, p<0.001). When we included times and proportions of time spent in different phases during the 18-month follow-up, we found that the proportion of time that was spent in depression predicted being granted a pension during the follow-up (after removing the highly intercorrelated depressive index episode variable), but having avoidant personality disorder was no longer significant.

In the second phase, to evaluate whether the results were dependent on specific subgroups, we made stratified analyses by splitting the data with 151 patients by bipolar subtype (BD I vs. BD II), age (<40 vs. ≥ 40 years at baseline), and gender (Table 14). We created Cox regression models for each of these six groups using the same predictors as in the first analysis, and found differences in predictors between the subgroups.

We also made logistic regression models predicting being on permanent disability pension at the 18-month follow-up, controlling for age, bipolar subtype and sex in all models. The significant predictors for being on permanent disability pension at 18-month follow-up were higher age, BD type I, borderline personality disorder, PTSD and level of basic education (elementary school at highest vs. student).

Table 13. Cox model univariate analyses of predictors for time to being granted a disability pension for employed patients with BD in the Jorvi Bipolar Study during an 18-month follow-up.

Predictor at entry	Being granted a disability pension during the follow-up		
	HR	95% CI	p
Age	1.047	1.02-1.08	0.001
Gender, male	2.036	1.05-3.99	0.035
BD I	2.354	1.22-4.55	0.011
Married or cohabiting	1.368	0.70-2.67	0.369
Basic education	0.751	0.54-1.06	0.106
Vocational education	0.976	0.74-1.29	0.862
Duration of disease	1.042	1.02-1.07	0.002
Index episode depression	2.239	1.11-4.52	0.024
Number of episodes before baseline			
Depressive	1.004	0.98-1.03	0.711
Manic	1.141	1.07-1.22	<0.001
Psychotic symptoms lifetime	1.242	0.90-1.72	0.187
Rapid cycling	0.937	0.67-1.32	0.708
Alcohol dependence, lifetime	2.274	1.20-4.13	0.012
Some anxiety disorder, lifetime	1.103	0.58-2.09	0.764
Some personality disorder	1.340	0.71-2.53	0.368
Borderline personality disorder	1.458	0.74-2.89	0.280
Avoidant personality disorder	2.582	1.14-5.87	0.024
PTSD, lifetime	1.748	0.80-3.82	0.160
GAD, lifetime	2.824	1.40-5.70	0.004
Number of psychiatric hospital treatments	1.301	1.18-1.43	<0.001
Economic situation	10.588	1.42-79.14	0.012
Perceived work ability	10.463	4.78-22.90	<0.001
SOFAS score	0.948	0.92-0.98	0.001
BDI score	1.046	1.02-1.08	0.004
HAM-D score	1.073	1.03-1.12	0.003
YMRS score	0.964	0.92-1.01	0.157
BAI score	1.027	1.00-1.05	0.046
PSSS-R score	0.959	0.94-0.99	0.002
Extroversion	0.963	0.89-1.04	0.323
Neuroticism	1.042	0.97-1.13	0.288
Life-chart-based predictors			
Duration of depression during follow-up	1.002	1.00-1.00	0.018
Proportion of time spent in depression during follow-up	1.020	1.01-1.03	<0.001
Proportion of time spent in euthymia during follow-up	0.986	0.98-1.00	0.014

Abbreviations: PTSD=Post Traumatic Stress Disorder, GAD=Generalized Anxiety Disorder, SOFAS=Social and Occupational Functioning Assessment Scale, BDI=Beck Depression Inventory, HAMD=Hamilton Depression Rating Scale, YMRS=Young Mania Rating Scale, BAI=Beck Anxiety Inventory, PSSS-R=Perceived Social Support Scale-Revised, EXT= Extroversion, NEU=Neuroticism

Table 14. Multivariate analyses using Cox regression model of predictors for time to work disability pension during an 18-month follow-up for all 151 patients with bipolar disorder belonging to the labor force in the Jorvi Bipolar Study and for these same patients stratified by age, bipolar subtype, and gender.

	All 151 patients belonging to labor force			Patients stratified by age, bipolar subtype, and sex											
				Age				Gender				Bipolar subtype			
				<40 years, n=99		≥40 years, n=52		Male, n=72		Female, n=79		Type I, n=67		Type II, n=84	
Predictor	p	HR	95% CI	p	HR	p	HR	p	HR	p	HR	p	HR	p	HR
Age	0.005	1,04	1.01-1.08					0.041	1.05	0.053	1.04	0.001	1.10	0.963	1.00
Gender, male	0.025	2.35	1.11-4.95	0.033	3.55	0.061	2.96					0.215	1.94	0.070	3.12
BD I	0.095	1.86	0.90-3.39	0.431	0.62	0.004	6.95	0.081	2.44	0.468	1.55				
Index episode depression	0.036	2.15	1.05-4.41	0.863	1.10	0.096	2.46	0.041	2.62	0.860	1.13	0.123	2.12	0.325	1.80
GAD	<0.001	4.86	2.21-10.67	0.010	5.59	<0.001	11.22	0.192	2.40	0.001	7.75	0.005	6.88	0.005	5.26
Avoidant personality disorder	0.005	3.70	1.48-9.25	0.153	3.09	0.070	3.41	0.004	8.65	0.182	2.53	0.014	6.41	0.505	1.57
Borderline personality disorder	0.091	1.93	0.90-4.14	0.011	4.88	0.458	1.64	0.683	1.29	0.095	2.75	0.260	2.07	0.162	2.35
No. of psychiatric hospitalizat.	<0.001	1.33	1.18-1.50	<0.001	1.48	0.145	1.16	0.011	1.25	<0.001	1.41	<0.001	1.47	0.500	0.77

GAD=Generalized Anxiety Disorder; HR= hazard ratio.

6.   DISCUSSION

6.1.   Main findings

The most important finding in the first study was that less than half (42%) of the patients with an acute phase of BD received adequate treatment. Clinical diagnosis was by far the most important predictor of adequate treatment, and our study strengthens the value of correctly diagnosing bipolar disorder. However, having a diagnosis does not guarantee proper treatment, as only two-thirds (65%) of the patients with a clinical diagnosis of BD were given adequate treatment. Lack of attention to the longitudinal course is another major problem area, as only a minority of patients with rapid cycling or a polyphasic episode received appropriate treatment. Undertreatment is also related to the depressive phases as less than a third of depressed patients received adequate treatment.

Maintenance phase treatment was not more appropriate, as less than two-thirds (61%) of BD patients received adequate maintenance treatment. As in the acute phase, having a clinical diagnosis was by far the most important predictor of receiving adequate maintenance treatment. However, maintenance treatment was compromised in more than a quarter (27%) of the patients even with a clinical diagnosis of BD. In addition to being undiagnosed, patients most at risk for receiving inadequate or intermittent maintenance treatment are those treated in outpatient settings and those with vaguer or less prominent forms of symptoms such as BD II or comorbid personality disorders. Maintenance treatment seems mainly to follow the treatment given in the acute phase, and the problems in the adequacy of maintenance treatment follow the shortcomings in the acute phase.

Even though treatments were offered, they were often not used as prescribed. A quarter of the patients discontinued pharmacological treatments by their own decision, and of the medications continued, a third was not used regularly enough to be effective. The highest risk for autonomous discontinuation was when patients were depressed. The main reasons for medication nonadherence were side-effects, lack of motivation, and negative attitudes toward offered treatment. For individual or supportive psychotherapy, the reasons were practical barriers to coming to sessions and lack of motivation. Although rates of nonadherence do not necessarily differ between mood-stabilizing medications, the predictors for nonadherence do. Furthermore, adherence to one medication does not guarantee adherence to another, nor does a patient's adherence at one timepoint ensure adherence at another, as the patient's adherence may change over time. Patients' attitudes toward treatments affect adherence to medications as well as to psychosocial treatments and should be monitored repeatedly. Nonadherence to psychotherapy is as common as medication nonadherence and should be given more attention.

The main finding of the last study is that BD I and II are associated with a major risk of long-term work disability, as 25% of the patients belonging to the

labor force were granted a disability pension after an acute episode during medium-term follow-up. The main predictors of being granted a disability pension are a more severe course of the disease, higher age, male gender, depression-related cumulative burden, and comorbidities. However, the predictors may vary depending on bipolar subtype, age, and gender. We also found that patients' subjective estimations of their vocational ability were surprisingly correct in predicting the need for future disability pension.

6.2. Methods

6.2.1. Representativeness of the cohort sample

The JoBS is the first clinical cohort study based on systematic screening for BD among psychiatric in- and outpatients within a geographically defined catchment area. Due to the screening, the cohort includes both clinically diagnosed and undiagnosed patients with BD, which is thus uniquely representative. Screening also enabled us to make comparisons of BD I and BD II unbiased by sampling. The sampling of patients at the beginning of an acute new phase enabled investigation of the patients from the time they usually come to psychiatric care.

   The present naturalistic study was based on a relatively large (N=191) cohort of both in- and outpatients of BD, including both BD I and BD II, independent of clinical diagnosis, and representing secondary care psychiatric BD patients with an acute phase. Finland has no private psychiatric hospitals, and public psychiatric care is free of charge. Most BD I patients are likely to seek treatment or contact a psychiatrist in an acute phase. By using the MDQ screen, most BD patients in psychiatric care in the area with an incident illness episode were likely found.

6.2.2. Screening

We screened a large number of psychiatric patients (N=1630) with the MDQ, the cutoff modified by including as positive patients without problems due to episodes to increase sensitivity for BD II. This modification of the cutoff in the screen was based on the pilot study of the JoBS (Isometsä et al., 2003). The higher sensitivity but lower specificity of the modified MDQ resulted in a higher number of false positives to be excluded in the SCID interview.

6.2.3. Diagnostic measures and life chart methodology

The diagnoses of BD and comorbid disorders were carefully assigned by psychiatrists with a minimum of five years of clinical experience using SCID-I interview (First et al., 2002), having information from all patient records available and completed with several informants in any case of uncertainty. The interrater reliability was excellent (kappa 1.0 for both BD I and II). The SCID is the most

commonly used and best validated diagnostic instrument in psychiatric research, and it was used here in the way shown to be the most valid. However, the reliability of comorbid diagnoses were not evaluated. Axis II diagnoses were assessed using the semi-structured SCID-II interview for DSM-IV. Because we included the patients in an acute phase, this may have had some impact on the results. However, patients were met three times and comorbid disorders were assessed in a later subacute phase; the diagnoses of personality disorder were based on multiple sources of information and a longitudinal view of patients' functioning during euthymic phases, not on current behavior. Still, despite our best efforts, we cannot fully exclude the possibility that the current state might have biased the assessment of personality. The design of our study was constructed to be as close as possible to the situation in which a clinician meets mood disorder patients during the acute phase.

One of the most influential methods in this study was the use of a life chart. The life chart methodology is generally accepted as part of follow-up studies of BD. The graphic life chart we used in this study is similar but not identical to the Longitudinal Interval Follow-Up Evaluation (LIFE) or NIMH life chart methodology used in other prospective studies reporting separately on both BD I and II (Dittmann et al., 2002; Joffe et al., 2004; Judd et al., 2002; Judd et al., 2003; Post et al., 2003; Tondo et al., 1998). As we aimed to assess the life chart phases compatible with DSM-IV criteria, which are part of everyday clinical practice and known to all clinicians, we used the graphic life chart that was planned and used in the Vantaa Depression Study (Melartin et al., 2004). As with LIFE, probes related to important events were used to investigate change points in the psychopathologic state. However, unlike with LIFE, the life chart was made directly comparable with DSM-IV criteria, and the patients' follow-up time was classified into periods of four DSM-IV phases of BD (major depression, mania, hypomania, mixed episode), including also depressive mixed states, full remission phases with no symptoms, and partial remission when criteria for neither mood episode nor full symptomatic remission were fulfilled. Even though the life chart was constructed in the two follow-up interviews based on patient reports, all available patient records, and other informants when needed, the underreporting of some milder illness phases, such as short hypomanic or depressive mixed episodes, cannot be excluded. However, bias in the comparison of BD I and II is unlikely in this respect.

In addition, we used many structured and semi-structured measures, both objective and subjective, to investigate a broad range of factors from several domains: socio-demographic factors, work disability factors, clinical variables, and temperamental and psychosocial factors (perceived social support, size of social network, and negative life events).

We also used register-based data on the granted disability pensions, when and on the basis of which diagnoses they were granted, and on hospital treatments, their dates and diagnoses, enabling us to get precise information for the whole cohort. To our knowledge, no previous prospective studies have been

conducted on the predictors of long-term working disability or being granted a disability pension among patients with BD I or BD II.

6.2.4. Study limitations

Although we took patients into the cohort during the early acute phase, thus minimizing treatment effect at baseline of the study (Mantere et al., 2004), we cannot exclude the possibility that in some cases the study itself may have affected somewhat the number of patients receiving a clinical bipolar diagnosis, as well as the treatment they received in the acute phase (study I) or during the follow-up (study II). As the study was naturalistic, serum levels of lithium or valproate could be related to the self-reported adherence only when measured based on clinical indication. Also, to avoid undue complexity in the data, dosages of the numerous pharmacological agents were not evaluated. Thus, our results represent the upper limit of the proportion of patients classified as having received adequate treatment in the acute (study I) or maintenance phase (study II). Also the rates of adherence relied on the patients' self-report, which is likely to underestimate nonadherence (study III).

Since we included depressive mixed states as a distinct phase, which would be diagnosed as major depressive episodes in the DSM-IV, we had 26 fewer cases of depression in the index phase, and 9 more cases with rapid cycling and 4 more cases with polyphasic episodes during the follow-up, as compared with the use of strict DSM-IV diagnoses. However, classifying the depressive mixed states as depressions would have had no impact on the rate of adequate treatment of depression (31.1% vs. 31.1%).

The timing of study between 2002 and 2004 may have influenced the medications chosen, specifically affecting lamotrigine treatment since lamotrigine became reimbursed for bipolar disorder in Finland during the study (studies I and II). There are no studies of the Finnish prescribing patterns of medications from 2002 to date, but register studies have been conducted in other Nordic and European countries (Bjorklund et al., 2015; Carlborg et al., 2015; Haeberle et al., 2012; Hayes et al., 2011; Kessing et al., 2016), likely representing the same kind of trends as in Finland during the last 15-20 years. According to these studies, there has been a general increase in the proportion of patients with BD who have been prescribed psychotropic medication. The proportion of patients treated with antidepressants has been steady or increased, but the proportion of patients with antidepressant monotherapy has decreased. The proportion of patients treated with atypical antipsychotics and anticonvulsants (valproate, lamotrigine) has significantly increased. Simultaneously there has been a significant decrease in the proportion of patients treated with typical antipsychotics. The proportion of patients treated with lithium has remained constant or decreased. According to these rates, the adequacy of treatment today may be somewhat better than during our study, but the use of antidepressants that has risen in most of the studies deserves attention and might affect the adequacy of treatment in a negative way.

However, even though a change has occurred in the proportions of different medications prescribed after 2004, according to the aforementioned studies, the main change took place before 2002-2004.

Some changes in the definitions of adequate pharmacotherapy have been made since 2002-2004, but as no universally accepted definition of adequate treatment for all types and phases of BD exists, any definition of adequate pharmacological treatment is somewhat arbitrary. Hence, estimates of the frequency of adequate treatment depends on such definition (studies I and II).

In the second study, we focused on the first maintenance phase after the index episode, and the picture might have been somewhat different had we also studied maintenance phases over a longer period. A methodological limitation is also the timing of the maintenance phase, as no consensus has been reached on how the longitudinal treatment phases should be defined. In particular, whether a distinct continuation phase should be included and when precisely it should end and, consequently, the maintenance phase begin. In this study, we did not separate a continuation phase, and the maintenance phase was defined to start on the day when full criteria for an acute phase ended. However, we did not find that the duration of the maintenance phase had any effect on the adequacy of treatment.

When measuring adherence, we used a self-developed interview questionnaire, the same as used in the Vantaa Depression Study, making it possible to compare these two studies but likely affecting the comparison of our results with other studies. Also, as in other studies of adherence, attrition is a critical question, and we do not know whether the patients who came to follow-up visits were more adherent than the dropped-out patients.

In the fourth study, although we were able to investigate a wide range of predictors for disability, an important limitation was that we did not measure cognitive functioning, which has been shown to influence functional ability, even in euthymic patients with BD (Andreou & Bozikas, 2013; Wingo et al., 2009).

Even though the study data were collected over 10 years ago, the conditions for which a disability pension can be granted have not changed significantly in Finland over this period. Likely the only significant epidemiological change has been an increase in the number of bipolar diagnoses, probably due to improved recognition, so the limitation of the timing of data collection is theoretical and unlikely to markedly influence the predictors for a disability pension.

6.3.   Adequacy of acute phase pharmacotherapy in BD (study I)

Pharmacotherapy is the foundation of treatment for BD, so the finding that even in the acute phase less than half (42%) of the patients with BD received adequate

treatment is alarming. This result was mostly due to lack of a clinical diagnosis of BD, as only a small minority (7%) of the undiagnosed patients received adequate treatment. That only a minority of misdiagnosed patients receive guideline-concordant treatment was reported also in a recent Chinese study (Xiang et al., 2012). Thus, the value of correctly diagnosing BD cannot be overemphasized, but a clinical diagnosis of BD does not guarantee proper treatment, as only two thirds (65%) of patients received adequate treatment. In addition to diagnosis, we found that rapid cycling and a polyphasic episode were associated with inadequate treatment. Also, the rate of adequate treatment varied markedly by illness phase; treatment received was adequate for mania (100%), but far from adequate for bipolar depression (31% among all patients, 49% among patients with a clinical diagnosis).

This study was the first to evaluate the difference in quality of treatment provided to in- and outpatients. Outpatients received clearly (36% vs. 55%) less adequate treatment, reflecting mainly the significantly greater proportion of patients with a diagnosis of BD in hospital settings, as well as differences in the proportion of BD I and BD II patients and differences in the types of mood phases in different settings. Most BD depressions are treated in outpatient settings, and we found that only a fraction of these cases received adequate treatment. Treatment of depressive phases may be problematic even among inpatients, as Lim et al. (Lim et al., 2001) reported in their study of 1,471 hospitalized BD I patients; they found that 31% of depressive patients with psychotic features and 17% of those without these features were discharged without the recommended pharmacotherapy. These findings are of major importance because the course of bipolar disorder is dominated by depressive phases (Judd et al., 2002; Judd et al., 2003; Post et al., 2003), and these phases carry a high risk for suicide (Tondo et al., 2003) and functional disability (Judd et al., 2005).

Undertreatment also appears to be related to the longitudinal course of the disorder, as only a minority of patients with rapid cycling or a polyphasic episode received appropriate treatment. The main reasons for inadequate treatment in rapid cycling were absence of a mood stabilizer and having a concurrent antidepressant. Even though avoiding antidepressants in rapid cycling is recommended in most practice guidelines, we found that the proportion of patients receiving antidepressants was not lower for rapid cyclers than for non–rapid cyclers and, in fact, the trend was the opposite; this was also evident among the clinically diagnosed patients with rapid cycling. Also previous studies (Lloyd et al., 2003; Simon et al., 2004) have found that a rapid cycling course of illness may not reduce the proportion of patients receiving antidepressants. So, it seems that having a rapid cycling course of disease does not influence whether antidepressants are prescribed. Reasons for this prescribing of antidepressants for patients with rapid cycling may be that the attending psychiatrists do not pay sufficient attention to the longitudinal course of the illness or the pharmacotherapy of the former phase or episode remains poorly monitored, with the result that the treatment does not follow transitions of rapid cycling and

polyphasic episodes. More systematic use of life charts and regular mood ratings would likely be beneficial in helping clinicians grasp the longitudinal course of their patients' illness and thus improve the quality of care.

6.4. Adequacy of maintenance phase pharmacotherapy in BD (study II)

As BD is a long-term disease with nearly all patients having one or more recurrences, practice guidelines recommend maintenance treatment after an acute episode. We found that three-quarters (75%) of patients received adequate maintenance treatment at some point during the maintenance phase but only two-thirds (68%) of the time they should have received it. However, less than two-thirds (61%) of patients received adequate maintenance treatment throughout the maintenance phase and, thus, the benefit of pharmacological protection against relapses. Even among the clinically diagnosed patients, less than three-fourths (73%) received adequate maintenance treatment continuously. As BD is a life-threatening (Tondo et al., 2003) and often chronic mental disorder with marked psychosocial impairment (Goldberg & Harrow, 2004; Judd et al., 2002; Judd et al., 2003; Judd et al., 2005; MacQueen et al., 2001; Post et al., 2003; Strakowski et al., 1998) and considerable health costs (Hirschfeld & Vornik, 2005; Kleinman et al., 2003), providing adequate maintenance treatment is an important aim.

Clinical bipolar diagnosis was by far the most important predictor of adequate treatment, but it did not guarantee proper treatment. Another important predictor of adequate treatment was having been treated as an inpatient during the last episode, highlighting the problems present in outpatient contexts. Also, the presence of a comorbid personality disorder predicted a lower likelihood of receiving uninterrupted adequate maintenance treatment. This may be one reason for the finding in several studies that an additional diagnosis of a personality disorder in patients with BD leads to poorer outcomes (Bieling et al., 2003), including poorer medication compliance, more days in the hospital, lower rates of recovery, more severe mood symptoms, lower levels of functioning, and increased incidence of substance use disorders (Magill, 2004). Furthermore, patients with comorbid personality disorder may have an increased risk of suicide attempts (Garno et al., 2005; H. Valtonen et al., 2005). Another course-related independent predictor was rapid cycling, which seemed to have resulted in more pharmacotherapy efforts to control repeated illness cycles.

The efficacy of antidepressants in the maintenance treatment of bipolar disorder is not supported by controlled evidence, and most of the treatment guidelines recommend discontinuing them after a few months of remission. There is striking incongruity between the wide use of and the weak evidence base for the efficacy and safety of antidepressant drugs in bipolar disorder. Few well-designed, long-term trials of prophylactic benefits have been conducted, and there is

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insufficient evidence for treatment benefits with antidepressants combined with mood stabilizers. A major concern is the risk for mood switch to hypomania, mania, and mixed states (Pacchiarotti et al., 2013). Still, in this study, we found that more than half of the patients prescribed antidepressants at the beginning of a maintenance phase lasting longer than six months still had them after six months in remission. Half of these patients had residual or prodromal depressive symptoms at the maintenance phase, so in these cases antidepressants may have been prescribed for these symptoms. Contrary to the disagreement over the role of antidepressants in treating BD in general (Pacchiarotti et al., 2013), antidepressants are usually not recommended for patients with rapid cycling. Still, we found no significant difference between the proportions of rapid cycling and non-rapid cycling patients receiving antidepressants, as in our previous study of the treatment in the acute phase (Arvilommi et al., 2007); in fact, we observed a trend in patients with rapid cycling being prescribed antidepressants more often. Our results are in line with the findings from SFBN (Dittmann et al., 2002), STEP-BD (Simon et al., 2004), and EMBLEM (Cruz et al., 2008) studies, although in these the separation between treatment phases (acute or maintenance) remained unclear. Thus, although the patients with rapid cycling more often received adequate maintenance treatment, they also often were prescribed antidepressants. This may in part be because rapid cycling patients more often experienced depression preceding the first maintenance phase and more depressive phases in all before the first maintenance phase than non-rapid cycling patients. However, even when we included only the patients who had depression preceding the maintenance phase in the analyses, we found no significant difference between the rapid and non-rapid cycling patients receiving antidepressants either in the beginning or any time during the first maintenance phase. That antidepressants may be a risk for patients with rapid cycling (even in depression) was supported by the STEP-BD study by Schneck et al. (Schneck et al., 2008), in which episodes of mood disorder in 1,742 patients with BD I and II were evaluated for up to one year of treatment and antidepressant exposure was associated with worse cycling. In an a priori analysis in the STEP-BD study, despite preselection for good antidepressant response and concurrent mood stabilizer treatment, antidepressant continuation in rapid cycling was associated with worsened maintenance outcomes, especially for depressive morbidity opposite to antidepressant discontinuation (El-Mallakh et al., 2015).

This study is one of the first to investigate maintenance treatment received using the life chart methodology, with the possibility of reporting longitudinal patterns of maintenance treatment. In a previous cross-sectional study, Ghaemi et al. (Ghaemi et al., 2006) found that most agents used in the acute phases of BD were used in similar proportions in the maintenance phase. Our longitudinal follow-up confirmed their cross-sectional observation, as treatments were seldom changed during the maintenance phase, independent of its duration. Thus, it seems that in usual clinical practice, treatment prescribed in the maintenance phase typically follows the treatment prescribed in the acute phase. This practice

of continuing the agents used in the acute phase was criticized by Goodwin and Jamison (Goodwin & Jamison, 2007), who stated that while this is appropriate for managing the period immediately after resolution of the acute episode (the continuation phase of treatment), it certainly is not the best approach to true prophylaxis. Simply because a drug has antimanic properties, one cannot assume that it will be effective in the prevention of new episodes in the future, particularly depressive episodes (Goodwin & Jamison, 2007). Further longitudinal effectiveness studies are needed to assess strategies to enhance the adequacy of interventions during the continuation and treatment phases in patients with bipolar disorders.

6.5.   Adherence to treatments in BD (study III)

Treatment of BD depends on the illness phase and is complex, usually involving numerous medications to be started and discontinued. However, poor adherence in BD is a major obstacle to effective treatment. The aim was to investigate adherence to pharmacological and psychosocial treatments during an 18-month follow-up among patients with BD I and BD II. Even though nearly all patients had received mood stabilizers or atypical antipsychotics and psychosocial treatment, the effect of pharmacological treatment was often compromised by nonadherence. The pharmacological treatments were autonomously discontinued by a quarter of the patients, and of the medication continued, a third was not used regularly enough to provide a benefit. The main reasons the patients gave for nonadherence were side-effects, lack of motivation, and a negative attitude toward the offered treatment; for individual/supportive psychotherapy, reasons included practical barriers to coming to sessions and lack of motivation. The highest risk for discontinuing pharmacotherapy autonomously was present when patients were depressed. Negative attitude was the only predictor common to all; otherwise, the predictors of nonadherence differed among mood stabilizers, antipsychotics, and individual/supportive psychotherapy. Patients' adherence also often changed during the follow-up.

Lack of treatment provision does not seem to be a central problem among patients with BD, as most patients with BD continued to receive psychiatric care 18 months after entering the study in an acute phase. Also, nearly all patients had received mood stabilizers or atypical antipsychotics and psychosocial treatment. However, even though some pharmacotherapies were appropriately discontinued by the physician, every fourth patient discontinued at least one medication treatment phase autonomously.   There were some differences between medications in the reasons for discontinuing them. Lithium was discontinued nearly always in agreement with the treating physician because of its side-effects, whereas valproate was most often discontinued autonomously. The autonomous discontinuation occurred most often during depression, even after accounting for the high proportion of time spent in depressive phases.   The reason for

autonomous discontinuation in depression may be that patients consider their depression to be due to their medication or deem the medication to be ineffective, although Jamison et al. (Jamison et al., 1979) found no significant relationship between perceived effectiveness and reported compliance.

However, continuing medications does not mean using the medications appropriately, as about a third of patients admitted not having taken them regularly. Even though it is somewhat difficult to compare studies because of methodological differences, our results are broadly in line with other studies (Colom et al., 2000; Copeland et al., 2008; Gonzalez-Pinto et al., 2010; Keck Jr et al., 1997; Manwani et al., 2007; Perlis et al., 2010; Sajatovic, Bauer et al., 2006; Sajatovic et al., 2008; Sajatovic et al., 2009), confirming nonadherence to be a major problem in the treatment of BD. The adherence of individual patients often changed in the follow-up, so adherence at one timepoint does not guarantee adherence at another. The adherence rates between different mood stabilizers were very similar, consistent with many previous studies (Baldessarini et al., 2008; Colom et al., 2000; Gianfrancesco et al., 2006; Sajatovic, Valenstein et al., 2006; Sajatovic et al., 2007), suggesting that nonadherence is more a question of patient factors. Even though we found that the correlations between categories of drugs are strong, adherence to one drug does not guarantee adherence to another.

In our study, the main reasons patients gave for nonadherence were side-effects, lack of motivation, and negative attitudes. There were no major differences between mood stabilizers, antipsychotics, and antidepressants in the reasons patients gave for discontinuance, despite marked pharmacological differences between the medications. There are different views of the importance of side-effects as a reason for nonadherence in BD. Experts perceive side-effects to be a prominent reason for adherence problems (Velligan et al., 2009), but data suggest that clinicians are less likely than patients to attribute nonadherence to side-effects (Vieta et al., 2012). Even though several studies have linked side-effects to nonadherence (Baldessarini et al., 2008; Gitlin et al., 1989; Keck Jr et al., 1997; Manwani et al., 2007), others have not (Kleindienst & Greil, 2004; Sajatovic et al., 2006; Scott & Pope, 2002). In the STEP-BD study, (Perlis et al., 2010) found only a weak association. Some have argued that it is the fear of side-effects rather than actual side-effects that predicts nonadherence (Scott & Pope, 2002). It may also be that, although side-effects influence nonadherence, their role is most important when other negative factors are also present. Schumann et al. (Schumann et al., 1999) noted that while side-effects were often reported as a reason for discontinuing medications, no differences were seen between adherent and nonadherent patients with respect to frequency and type of side-effects. Also, Rosa et al. (Rosa, Marco et al., 2007) reported that every patient, adherent or not, had side-effects from lithium. In this study, we found that most (65%) of the patients who attributed side-effects to explain mood stabilizer nonadherence also gave some other reason for it.

Even though only a few differences existed between mood stabilizers and antipsychotics in the reasons the patients gave for nonadherence, their predictors

differed. Anxiety disorders predicted nonadherence to mood stabilizers but not to antipsychotics, whereas borderline personality disorder and current substance dependence predicted nonadherence to antipsychotics, but not to mood stabilizers. Negative attitudes predicted nonadherence to both mood stabilizers and antipsychotics. One possible explanation for these differences is differences in the patients for whom the medications were prescribed. However, there were no differences in the proportions of patients with substance use problems, anxiety disorders, personality disorders, including borderline personality disorder, or a low level of education. The reason for the differing adherence rates between medications may be related to the more sedative, anxiety-relieving, and weight-gaining properties of atypical antipsychotics.

In this study, the effect of comorbidity on adherence varied between medications. The findings regarding the role of comorbidity on adherence in previous studies are partly conflicting (Busby & Sajatovic, 2010). Comorbid substance abuse has been significantly correlated with poor treatment adherence in many (Baldessarini et al., 2008; Gonzalez-Pinto et al., 2006; Keck Jr et al., 1997; Manwani et al., 2007; Perlis et al., 2010; Sajatovic et al., 2006; Sajatovic et al., 2007; Sajatovic et al., 2009; Teter et al., 2011) but not all studies (Colom et al., 2000; Sajatovic et al., 2008). Anxiety disorder has seldom been reported as an important predictor of nonadherence. However, Perlis et al. (Perlis et al., 2010) found that current anxiety disorder at study entry was associated with poor adherence. Feske et al. (Feske et al., 2000) reported that a history of panic attacks, but not current or past anxiety, predicted poor adherence. There was no difference in the presence of anxiety between adherent and non-adherent patients in the studies by Sajatovic et al. (Sajatovic et al., 2006; Sajatovic et al., 2008). Comorbidity with personality disorder was the strongest factor in predicting poor compliance in the study of euthymic bipolar patients by Colom et al. (Colom et al., 2000), but not by Schumann et al. (Schumann et al., 1999).

In our study, negative attitude was an important predictor of nonadherence, the only predictor common to all treatments. Also, in previous studies, attitudes and beliefs have been related to medication adherence (Jamison et al., 1979; Pope & Scott, 2003; Sajatovic et al., 2009; Schumann et al., 1999; Scott & Pope, 2002). Schumann et al. (Schumann et al., 1999) even observed that a negative attitude toward prophylaxis was the only factor that correlated significantly with nonadherence. Scott and Pope (Scott & Pope, 2002) reported that attitudes and behavior were better predictors of nonadherence in BD than medication side-effects. Also, Adams and Scott (Adams & Scott, 2000) found that highly adherent patients showed a greater perception of illness severity and had stronger beliefs about the benefits of treatment and that these variables were better predictors of adherence than side-effects. In addition, Dharmendra and Eagles (Dharmendra & Eagles, 2003) noted that adherence was associated with more positive attitudes toward lithium, but not with better lithium knowledge. However, knowledge and attitude were positively correlated. On the other hand, Rosa et al. (Rosa et al., 2007) reported that knowledge level was directly related to treatment adherence.

Although we found that attitudes are quite stable, it may be possible to modify them (Strauss & Johnson, 2006). Attitudes can be modified with, for example, psychoeducation and cognitive therapy (Berk et al., 2010). Levin et al. (Levin et al., 2015) reported the results of a secondary analysis of pooled data from two uncontrolled prospective trials of customized adherence enhancement (CAE), a psychosocial intervention delivered over four to six weeks. CAE is a module-based intervention flexibly administered to address the specific reasons a person with BD might be non-adherent with prescribed medications. Over two-thirds of the 86 poorly adherent patients with BD who received CAE converted to good adherence. Converters had better medication attitudes than non-converters following treatment, even after controlling for baseline adherence. The authors concluded that their results support the notion that improved attitudes are a driver of behavioral change that translates into better adherence.

Although psychosocial treatments are effective components of managing BD (Miklowitz, 2008; Miklowitz & Scott, 2009), adherence to psychosocial treatments among patients with BD has rarely been studied. The only reported results are drop-out rates from psychotherapy studies, which have been similar to rates for pharmacotherapy nonadherence in BD (Busby & Sajatovic, 2010), consistent with our rates of psychosocial nonadherence. In our study, the main reasons patients with BD gave for poor psychosocial adherence were practical barriers to coming to sessions and lack of motivation. The independent predictors for nonadherence were negative attitudes toward psychotherapy and, somewhat unexpectedly, having an anxiety disorder. In previous studies, comorbid anxiety disorder has been associated with a more complicated course of BD (Lee & Dunner, 2008). Accordingly, non-adherent patients with anxiety disorder may form a subgroup with a more difficult course of BD.

6.6. Predictors of long-term disability in BD (study IV)

Work is an important part of functioning and long-term working disability has many negative consequences. However, long-term work disability and disability pension among patients with BD has been very little studied. Only a few previous cross-sectional studies have reported on long-term working disability and disability pensions for patients with BD (Grande et al., 2013; Gutierrez-Rojas et al., 2011; Schoeyen et al., 2013). Consequently, the factors predicting long-term working disability and disability pensions among patients with BD are not well known. This study is the first prospective study of predictors for being granted a disability pension among patients with BD I and BD II.

This study confirms the view of patients with BD having a poor prognosis, as after an acute episode, a quarter of the patients belonging to the labor force were granted a disability pension. Being granted a disability pension was predicted by

higher age, male gender, depressive index episode, comorbidity with GAD or avoidant personality disorder, and a higher number of psychiatric hospital treatments. In addition, patients' subjective estimations of their vocational ability were surprisingly accurate in predicting the granting of a future disability pension. Moreover, the depression-related cumulative burden and proportion of time spent in depression during the follow-up were important predictors. On the other hand, the predictors seemed to be, in part, dependent on bipolar subtype, age, and gender.

Twenty-one percent of the 191 patients were already on a pension before entering the study. During the 18-month follow-up, an additional quarter (25%) of the remaining 151 patients were granted a disability pension, which is more than twice the proportion of patients with unipolar MDD (11.3%) being granted a disability pension during a similar 18-month follow-up in the neighboring city of Vantaa, Finland (Rytsala et al., 2007). By the end of the 18-month follow-up, nearly half (41%) of the JoBS cohort patients had been granted a disability pension. The proportion of patients in the few previous studies that reported the proportions of patients unable to work has ranged from 15% to 22% (Kogan et al., 2004; Reed et al., 2010; Suppes et al., 2001). Also, very few previous studies have reported the proportions of patients with BD receiving a disability pension (Grande et al., 2013; Gutierrez-Rojas et al., 2011; Schoeyen et al., 2011a; Schoeyen et al., 2011b; Schoeyen et al., 2013), the proportion ranging from 17% among euthymic patients with BD (Grande et al., 2013) to 52.5% (also including patients who were in the process of receiving a disability pension) among patients selected from district computerized records as suffering from BD (Gutierrez-Rojas et al., 2011). The proportions of bipolar patients with a long-term disability found in the present study are broadly similar to those in previous cross-sectional studies. However, regardless of the apparent similarity in percentages, they are only partially comparable, owing to differences in measures.

Older age was strongly associated with being granted a disability pension, with an unadjusted risk among patients over 40 years of age more than double that of younger patients. Of the other sociodemographic factors, only male gender was also associated with risk. Grande et al. (Grande et al., 2013) and Schoeyen et al. (Schoeyen et al., 2013) also found higher age to be associated with receiving a disability pension.

Of the illness-related factors, we found that the total number of psychiatric hospitalizations predicted being granted a disability pension during the follow-up. The number of hospitalizations has also been found to predict work functioning in many (Burdick et al., 2010; Dickerson et al., 2004; Elinson et al., 2007; Rosa et al., 2009), but not all (Hammen et al., 2000) previous studies (Tse et al., 2014). However, the studies using the granting of a disability pension as an outcome measure differ somewhat regarding the significance of the number of hospitalizations. For example, Schoeyen et al. (Schoeyen et al., 2013) reported that the number of hospitalizations for depressive episodes predicted the granting of disability pension, Gutierrez-Rojas et al. (Gutierrez-Rojas et al., 2011) found that

repeated hospitalizations (three or more) were associated with being occupationally disabled, but Grande et al. (Grande et al., 2013) reported no association between the number of admissions and receiving a disability pension. In all, the number of previous hospitalizations likely represents a proxy for the long-term course of the illness, thus serving as a crude indicator of a recurrent and chronic course.

Another important factor that predicted being granted a disability pension was depression. A depressive index episode and the proportion of time in depression during the follow-up predicted being granted a disability pension. Current depression, either syndromal or subsyndromal, is also one of the most consistent predictors of work functioning in previous studies (Huxley & Baldessarini, 2007; Sanchez-Moreno et al., 2009). It appears that even modest changes in the severity of depression are associated with changes in functional impairment and disability, whereas changes in mania or hypomania are not as consistently associated with differences in functioning (Altshuler et al., 2006; Judd et al., 2005; Simon et al., 2007). Even though the number of previous episodes has been reported to predict functional disability there has been no agreement about whether it is the previous manic or the previous depressive phases that have a more deleterious effect (Grande et al., 2013). In a long-term follow-up, Goldberg and Harrow (Goldberg & Harrow, 2011) found that depressive syndromes, but not manic syndromes, in the year preceding follow-up were significantly associated with poorer global, work, and social functioning. Also, the studies using the granting of a disability pension as an outcome measure have reported somewhat discrepant findings on the impact of current and previous episodes on disability. For example, Gutierrez-Rojas et al. (Gutierrez-Rojas et al., 2011) found current depressive symptoms and a higher number of previous manic episodes to be associated with being granted a disability pension. Also, Grande et al. (Grande et al., 2013) found an association between the number of manic episodes and being granted a disability pension in their euthymic patients but no association between the number of other phases and being granted a disability pension. In contrast, Schoeyen et al. (Schoeyen et al., 2013) found no difference in pensioned and non-pensioned patients with more than four episodes of depression or mania/hypomania. In our study, the number of previous manic episodes, but not previous depressive phases, predicted being granted a disability pension, but the effect of manic phases disappeared when controlled for age and bipolar subtype. On the other hand, the granting of a disability pension was associated with more time spent in major depressive episodes and a greater proportion of time spent in depressive states overall during the follow-up. In general, it seems that depression has a more current effect on vocational disability, whereas the effect of mania accumulates with a progressing number of episodes.

Although, consistent with Grande et al. (Grande et al., 2013), we did not find anxiety disorders overall to be predictive of receiving a disability pension in our subjects, we found that one of the specific lifetime comorbid anxiety disorders, GAD, predicted being granted a disability pension. Comorbidity with anxiety

disorders has been associated in previous studies with a younger age at onset, greater overall morbidity reflected in more hospitalizations and worse overall prognosis, slower or inferior treatment responses, more substance abuse, and greater economic costs (Vazquez et al., 2014). Some anxiety disorders may be characterized as persistent rather than episodic and have trait-like aspects. In a study by Boylan et al. (Boylan et al., 2004) they found that of the anxiety disorders, GAD and social anxiety disorder had the most negative impact on outcome. They speculated that the adverse impact of GAD and social anxiety disorders may be explained by the clinical course of these anxiety disorders because for patients with either of these disorders, symptoms of negative emotionality, worry, and tension are likely to persist in euthymic periods. Although in our study social anxiety disorder did not predict the granting of a disability pension, avoidant personality disorder and, possibly, borderline personality disorder among the younger patients were predictors. Personality disorder comorbidity also predicted the granting of a disability pension in the study by Grande et al. (Grande et al., 2013), but the authors did not report the significance of specific personality disorders. Previous studies have revealed that co-occurring personality disorder features in patients with BD predict a worse outcome (Fan & Hassell, 2008). On the other hand, although Wenze et al. (Wenze et al., 2014) found that the degree of personality disorder pathology predicted depressive symptoms, they did not find an association with functional impairment. Loftus et al. (Loftus & Jaeger, 2006) also observed that comorbid personality disorder was associated with impaired functioning but this relationship was not independent of mood symptoms in multivariate analysis. The adverse effects of personality disorder comorbidity are likely to persist also during the euthymic period. Some patients may have coping capabilities that permit them to work effectively despite episodes or subsyndromal symptoms, whereas patients with comorbid personality disorder or GAD may function poorly even when their symptoms of BD do not attain the level of diagnosis.

Many factors affect working ability, some of which may be conceived as subjective. Accordingly, one of our most striking findings was that patients' subjectively perceived ability to work at the time of the baseline interview was the most powerful predictor of being granted a disability pension during the follow-up, if included as a predictor. This finding was in line with the results of the five-year follow-up of the analogous study among patients with MDD in Vantaa, Finland (the Vantaa Depression Study) (Holma et al., 2012). We found that a poor or lacking perceived ability to work was related to a more difficult course of BD and correlated with age, duration of disease, number of hospital treatments, and SOFAS score. Thus, the subjective perception appears firmly rooted in individual patients' true illness experience, as well as the clinician-assessed current level of functioning. Still, perceived ability likely also captures other subjective aspects of vocational ability, such as feelings regarding ability to work and motivation to work.

7. CONCLUSIONS AND FUTURE IMPLICATIONS

7.1 Conclusions

Treatment of BD depends on the illness phase and is complex, usually involving numerous medications to be started and discontinued. To receive adequate treatment for this disorder, a clinical diagnosis is by far the most important prerequisite. In addition, besides the correct diagnosis being crucial, rapid cycling and polyphasic episodes make receiving adequate treatment in secondary care less probable. Thus, a lack of attention to the longitudinal course of bipolar disorder appears to pose an obstacle to providing adequate treatment. Problems in treatment are associated mostly with outpatient settings, where adequacy of treatment of bipolar depression is a major concern. Thus, improving the quality of treatment of bipolar depression in psychiatric outpatient settings is a central public health issue.

Provision of continuity in maintenance treatment is compromised in more than a third of patients with BD. As expected, clinical diagnosis plays a decisive role in determining adequacy of maintenance treatment. It seems that maintenance treatment mainly follows the treatment given in the acute phase, and the problems in the adequacy of maintenance treatment follow the shortcomings in the acute phase. In addition to the central role of clinical diagnosis, patients most at risk for receiving inadequate or intermittent maintenance treatment are those treated in outpatient settings and those with more vague or less prominent forms of symptoms such as BD II or comorbid personality disorders.

However, even if patients receive adequate treatment, they often are nonadherent to the medications received. During a period of 18 months, more than half of the patients had either autonomously discontinued a medication or admitted to using it too irregularly to derive a benefit. The highest risk for discontinuing pharmacotherapy autonomously is present when patients are depressed. Even though rates of nonadherence appear not to differ between treatments, their predictors do. Moreover, adherence to one medication does not guarantee adherence to another, nor does a patient's adherence at one timepoint ensure adherence at another. Nonadherence to psychosocial treatment is an important problem and should be given more attention. Patients' attitudes toward treatments influence adherence to all treatments and should therefore be given more attention and monitored. Because attitudes can be modified with psychosocial interventions (e.g., with psychoeducation), such interventions should be offered to all patients with BD.

Our study contributes to the findings that BD places a major burden on patients and society. BD I and BD II are associated with a major risk of long-term work disability, with the proportion of patients with a disability pension rising to

41% in the 18-month follow-up. Severe clinical course, depressive burden, comorbid disorders, higher age, and male gender are likely to be the main predictors of being granted a disability pension for BD. In addition, patients' subjective perceptions of their ability to work are a surprisingly correct in predicting their future work status. However, the predictors may vary depending on the subtype of illness, gender, and age group of the patient.

7.2. Clinical and research implications

BD is a complex disease, with many different phases appearing in different sequences in time and requiring different treatments, so the clinician is faced with many more options than in the treatment of MDD. The first, and often difficult, task is to recognize and diagnose BD. As the disease often begins with, and often involves years of, depression, it is not possible to make a diagnosis before the first manic, mixed or hypomanic phase. Also, even when the patient has experienced manic, mixed or hypomanic phases, the patient most often comes into contact with health services in a depressive phase and in that mood often does not remember or express having also had other kinds of phases. However, fortunately, the proportion of bipolar patients receiving a clinical diagnosis of BD has markedly increased in the last 10 to 20 years. Even so, the importance of making the right diagnosis cannot be overemphasized.

Unfortunately, once the right diagnosis is finally made the difficulty does not end. To make the right treatment decision, it is not enough to recognize the nature of the acute phase; the clinician also has to work out how the disease developed earlier, the longitudinal course of BD. So, even if the clinician makes the right treatment choice considering the phase the patient is suffering at that moment, the decision may be inadequate when considering the phases before the current one. Also, even if the decision is right at that moment, the phase and the longitudinal course may change, demanding new decisions and changes to the treatment. In particular, this is the case with rapid cycling or polyphasic episodes.

Our studies show that the adequacy of treatment of BD is compromised in both the acute and the maintenance phases of the disorder. Besides clinical diagnosis, one of the most difficult aspects in considering the adequacy of treatment, in both the acute and maintenance phases, is taking the longitudinal course into account. Thus, antidepressants are often used in patients with a rapid cycling course even if practice guidelines and evidence show that antidepressants should not be used if there is a rapid cycling course, not even when the present phase is depression. Also, treatments are not easily discontinued or changed, even if the phase changes. This is also reflected in the maintenance phase where problems seem to follow the shortcomings of the treatment in the acute phase. The problems are especially seen in the outpatient context where most bipolar

depressions are treated. Because of these difficulties, a life chart should always be created for patients with BD and available when treatments are considered.

A lot has happened since our study was conducted; people with BD are being diagnosed much more often, sometimes even too often, and the prescription of mood stabilizing agents has increased. However, the use of antidepressants deserves attention because the rate has been stable or possibly increased since the time of study, although evidence for the efficacy of antidepressants in BD is poor; antidepressants are only recommended in acute depression in addition to mood stabilizing agents in some guidelines, but are not recommended as maintenance treatment. However, despite the stable or increased use of antidepressants, the proportion of patients receiving antidepressant monotherapy has fortunately decreased. The high use of antidepressants may partly reflect that treatment of bipolar depression is still problematic as only a few effective choices exist, and they help only a proportion of patients. So, the prescription of antidepressants may be an effort to help people with bipolar depression in some way, as learned from the treatment of MDD. However, when prescribed, the antidepressants are often not discontinued after the depression has remitted and are continued in the maintenance phase. There is a need for studies investigating the factors affecting the prescribing patterns in BD with the increasing knowledge of BD among clinicians and the changes that have occurred in the trends of prescribing medications to patients with BD. What medications, in which situation, and why the clinician prescribes are important to understand when educating clinicians.

However, even if adequate treatment is prescribed, it is left to the patient to take the medicine. More than half of patients with BD either discontinue the treatments or do not take them regularly enough to get benefits of them. The first clinical problem is how to recognize nonadherence. As clinicians are reported to be poor at recognizing adherence problems, the use of other methods, like scales, electronic monitoring, and serum concentrations (see, e.g., Sajatovic et al. (Sajatovic et al., 2010)) to monitor adherence would be important. As problems exist with every method, it is advisable to use more than one method. The second problem is how to help patients be more adherent. Psychosocial interventions (e.g., psychoeducation) have been shown to be efficient in fostering adherence among patients with BD and should be offered to patients with BD. The reasons and thus treatment for nonadherence differ for each individual and so must be customized for each patient. As the problem is especially high during depressive phases, attention should be given to evaluate and help patients with depression adhere to their treatments.

Long-term work disability has been researched surprisingly seldom, especially when taking into account the tremendous burden of the disease on the patient and society as a whole. The factors affecting working disability are still poorly understood. Our study is the first prospective longitudinal study of the predictors of long-term working disability. As expected, a more severe course of the disease predicted long term working disability, as well as current depressive states. Care should be taken that these patients get individually tailored treatment

with adequate acute and maintenance treatment, including psychosocial treatment, monitored for adherence and the course of the disease followed with a life chart, and have an easy access to care in case of worsening symptoms. We found that comorbidity with GAD or avoidant personality disorder predicted being granted a disability pension. The effect of treating these comorbidities on long-term disability should be studied, especially if our findings can be replicated in other studies. We found that patients' subjectively perceived disability at the acute phase was a surprisingly correct forecast of being granted a disability pension in the near future. So this simple question could be of help for the clinician to be used when assessing the patients' risk of future long-term disability.

BD has been proposed to be a neuroprogressive disease, but there is still not enough evidence for that claim. Many patients with BD experience a progressive decline of functioning, which may be the result of a slowly accumulating load of different elements (allostatic load) that in the end results in long-term disability. Also, some patients may be less capable of carrying this load, like those who have been abused in childhood, those who are less educated, and patients with comorbidities. It may also be that there are (genetically) different populations of BD, with different prognosis from the start. Accordingly, there may be a (genetic) subpopulation of patients with BD who have many of the factors associated with chronicity, like poor response to medications, increasing frequency of episodes, and cognitive deficits.

As cognition has often been associated with functional disability, it would be important to investigate the role of cognition compared to other (clinical) factors affecting disability in different phases and especially longitudinally. Treatments like functional remediation may offer a better functional prognosis in cognitively disabled patients.

More studies on the reasons for long-term disability are needed to help us find better ways to prevent functional decline. It has been reported that the functional prognosis of BD has not improved in the last decades despite the modern treatments, indicating that our treatments are not effective in preventing functional disability.

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8. Acknowledgements

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