



Outi Mantere

Recognition, Comorbidity, and Outcome of DSM-IV Bipolar I and II Disorders in Psychiatric Care

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Department of Mental Health and Alcohol Research,
National Public Health Institute,
Helsinki, Finland
and
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Finland

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**RECOGNITION, COMORBIDITY, AND OUTCOME OF
DSM-IV BIPOLAR I AND II DISORDERS
IN PSYCHIATRIC CARE**

Outi Mantere

Academic Dissertation

To be publicly discussed, with the permission of the Medical Faculty of the University of Helsinki,
in the auditorium of Jorvi Hospital in Espoo, Turuntie 150, on June 8, 2007, at 12 noon.

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TIIVISTELMÄ

Tämä tutkimus on osa Kansanterveyslaitoksen ja Helsingin ja Uudenmaan sairaanhoitopiirin Jorvin sairaalan psykiatrian tulosyksikön kaksisuuntaisen mielialahäiriön seurantatutkimusta (Jorvi Bipolar Study), jossa seurataan 191 ajankohtaisesta (DSM-IV) mielialajaksosta kärsivää psykiatrisen erikoissairaanhoidon avohoito- ja sairaalapotilasta.

Tutkimusta varten seulottiin Jorvin psykiatrisessa erikoissairaanhoidossa 1630 potilasta, joista 490 haastateltiin puolistrukturoidulla haastattelumenetelmällä [Structured Clinical Interview for DSM-IV disorders, researcher version with psychotic screen (SCID-I/P)]. Tutkimuksessa mukana olevat potilaat (N=191) täyttivät tutkimuksen alussa ajankohtaisen vakavan masennuksen, manian, hypomanian, sekamuotoisen tai depressiivisen sekamuotoisen mielialavaiheen kriteerit. Potilaiden oireita, muut psykiatriset ja somaattiset sairaudet, hoitavan henkilön antama kliininen diagnoosi, hoito ja itsetuhoisuus kartoitettiin sisäänotto-vaiheen lisäksi 6kk ja 18kk haastatteluissa. Tämän lisäksi ajankohtaisen ja uusien sairausjaksojen ajallinen kesto ja laatu kirjattiin koko 18kk:n seuranta-ajalta. Seuranta-aika jaettiin kolmea eri toipumisastetta kuvaavaan jaksoon: 1) täydellinen toipuminen, 2) osittainen toipuminen ja 3) ei toipunut. Toipumista mitattiin myös määrittämällä ajankohtaisen sairausvaiheen ja sairausjakson kesto, aika osittaiseen tai täydelliseen toipumiseen ja aika täydellisestä toipumisesta uusintaan. Verrattaessa kaksisuuntaisen mielialahäiriön tyyppi I ja II komorbiditeettia vakavasta masennuksesta kärsivien komorbiditeettiin vertailuryhmänä käytettiin 269 vakavaa masennusjaksoa sairastavaa potilasta Vantaa Depression Studysta.

Tutkimuksessa todettiin, että kaksisuuntainen mielialahäiriö oli huonosti tunnistettu psykiatrisessa erikoissairaanhoidossa. Niistä kaksisuuntaista mielialahäiriötä sairastavista potilaista, jotka tarvitsivat akuutisti hoitoa, 39% ei ollut koskaan saanut oikeaa kliinistä diagnoosia. Erityisesti tyyppi II häiriötä sairastavat potilaat ja naiset olivat huonommin tunnistettuja. Tunnistaminen näytti tapahtuvan perustuen ajankohtaisesti ilmeneviin ns. klassisiin eli maanisiin tai psykoottisiin oireisiin erityisesti sairaalahoitoa vaativissa jaksoissa.

Kun klassisia oireita ei esiintynyt, kuten tyyppi II sairaudessa mutta myös isossa osassa tyyppi I sairautta, sairaus oli huomattavasti huonommin tunnistettu. Oikea diagnoosi löytyi tyyppi II sairaudessa useimmiten vasta kun potilas oli ollut hoidossa pitkään, eivätkä muut yksittäiset sairauden kuvaan liittyvät tekijät kuin psykoottisuus selittäneet tunnistamista. Näyttää siis, että mielialahäiriö diagnosoitiin perustuen ajankohtaiseen oirekuvaan, unohtaen pitkätaisanamneesin merkitys.

Vaikka tyyppi II mielialahäiriö oli selvästi huonommin tunnistettu kuin tyyppi I, häiriöt erosivat vain muutamassa muussa kliinisessä piirteessä. Komorbiditeetissa eli muussa psykiatrisessa sairastamisessa ei ollut merkitseviä eroja. Sen sijaan ne erosivat ennusteessa. Tyyppi II häiriötä sairastavat potilaat viettivät noin 40% enemmän aikaa masentuneena kuin tyyppi I häiriötä sairastavat. Tämä johtui siitä, että tyyppi II potilailla oli useammin ainakin yksi uusi masennusjakso, suurempi osuus uusista vaiheista oli masennuksia ja masennusjaksojen tiheys oli suurempi. Sen sijaan yksittäinen masennusjakso kesti tyyppi I ja II häiriötä sairastavilla potilailla yhtä kauan.

Komorbiditeetti oli vakavassa masennuksessa ja kaksisuuntaisessa mielialahäiriössä laadullisesti jonkin verran erilaista. Ajankohtaisesti jokin akseli I häiriö oli yleisempi vakavassa masennuksessa kuin kaksisuuntaisessa mielialahäiriössä (69.1% vs. 57.1%) ja ero johtui erityisesti ahdistuneisuushäiriöistä. Jokin persoonallisuushäiriö oli sairauksissa yhtä yleinen, mutta vakavassa masennuksessa oli enemmän klusteri A ja C häiriötä, kaksisuuntaisessa mielialahäiriössä klusteri B:tä.

Viivästyneen tai puuttuvan diagnoosin seuraukset voivat olla vakavia niin yksilölle kuin yhteiskunnalle. Tämän vuoksi tutkimuksen tulosten perusteella on suositeltavaa seuloa kaksisuuntaista mielialahäiriötä erityisesti vakavasti masentuneiden potilaiden joukossa. Kliinisen diagnoosin täytyy kuitenkin aina perustua perusteelliseen kliiniseen haastatteluun ja seurantaan, jossa huomioidaan pitkäaikainen sairauden kulku. Myös muiden psykiatristen sairauksien esiintyminen kaksisuuntaisessa mielialahäiriössä on yleistä ja huonontaa entistään sairauden kulkua. Sen vuoksi se vaatii erillistä arviointia, seuranta ja hoitoa. Masennusoireiden hoito on erityisen keskeinen haaste, jotta kaksisuuntaisen mielialahäiriön ennustetta saataisiin parannettua.

Avainsanat: kaksisuuntainen mielialahäiriö, kaksisuuntainen mielialahäiriö tyyppi II, tunnistaminen, depressiivinen sekamuotoinen jakso, komorbiditeetti, ennuste

ABBREVIATIONS

ADE	Affective Disorder Evaluation
BD	Bipolar disorder
BD I	Bipolar disorder type I
BD II	Bipolar disorder type II
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CDS	Collaborative Depression Study
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
DALY	Disability Adjusted Life-Year
DIG	Diagnostic Interview for Genetic Studies
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
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3 rd edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3 rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition
ECA	Epidemiological Catchment Area Study
GAF	Global Assessment of Functioning Scale
HAM-D	Hamilton Rating Scale for Depression
HUCH	Helsinki University Central Hospital
ICD-10	International Classification of Diseases, 10 th edition
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
MINI	Mini-International Neuropsychiatric Interview
NA	Not applicable
NCS	National Comorbidity Study
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NIMH	National Institute of Mental Health
NOS	Not otherwise specified

NS	Not significant
OR	Odds ratio
PIF	Psychoses in Finland Study
PTSD	Posttraumatic stress disorder
PSSS-R	Perceived Social Support Scale, revised
RDC	Research diagnostic criteria
SADS	Schedule for Affective Disorders and Schizophrenia
SCAN	Schedules for Clinical Assessment of Neuropsychiatry
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
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
VDS	Vantaa Depression Study
WHO	World Health Organization
YMRS	Young Mania Rating Scale

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1. ABSTRACT

This study is part of an ongoing collaborative bipolar research project, the Jorvi Bipolar Study (JoBS). The JoBS is run by the 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. It is a prospective, naturalistic cohort study of secondary level care psychiatric in- and outpatients with a new episode of bipolar disorder (BD). The second report (Study II) also included 269 major depressive disorder (MDD) patients from the Vantaa Depression Study (VDS). The VDS was carried out in collaboration with the Department of Psychiatry of the Peijas Medical Care District.

Using the Mood Disorder Questionnaire (MDQ), all in- and outpatients at the Department of Psychiatry at Jorvi Hospital who currently had a possible new phase of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) BD were sought. Altogether, 1630 psychiatric patients were screened, and 490 were interviewed using a semistructured interview [Structured Clinical Interview for DSM-IV disorders, researcher version with psychotic screen (SCID-I/P)]. The patients included in the cohort (N=191) had at intake a major depressive, manic, hypomanic, mixed, or depressive mixed phase of BD. The demographic characteristics, variables for prior illness history, preceding treatment, current symptoms, psychiatric and somatic comorbidity, clinical diagnosis, and suicidality were evaluated at intake and at 6- and 18-month interviews. All available data were integrated into the form of a graphic life chart based on DSM-IV criteria. Time after the beginning of the index phase was divided into three periods: 1) mood episode, 2) partial remission, or 3) full remission. Five principal outcome measures were used: 1) proportion of time in different symptom states during follow-up, 2) time with full criteria of the index phase, 3) time with full criteria of the index episode, 4) time to full remission, and 5) time to recurrence from the beginning of remission.

Based on this study, BD is poorly recognized even in psychiatric settings. Of the BD patients with acute worsening of illness, 39% had never been correctly diagnosed. The classic presentations of BD with hospitalizations, manic episodes, and psychotic symptoms lead clinicians to correct diagnosis of BD I in psychiatric care. When the classic

presentations were absent, as in BD II patients, but also a large proportion of BD I patients, the disorder was less often recognized. Time of follow-up elapsed in psychiatric care, but none of the clinical features, seemed to explain correct diagnosis of BD II, suggesting reliance on cross-sectional presentation of illness.

Even though BD II was clearly less often correctly diagnosed than BD I, few other differences between the two types of BD were detected, except for some differences in the severity of illness as defined in the diagnostic criteria. BD I and II patients appeared to differ little in terms of clinical picture or comorbidity, and the prevalence of psychiatric comorbidity was strongly related to the current illness phase in both types. At the same time, the difference in outcome was clear. BD II patients spent about 40% more time depressed than BD I patients. The most important factors explaining this difference were higher proportions of BD II than BD I patients having depressive phases, the higher proportion of depressive phases among all phases in BD II, and the higher frequency of these phases during follow-up, whereas duration of depressive phases per se was equal.

Patterns of psychiatric comorbidity of BD and MDD differed somewhat qualitatively. Overall, MDD patients were likely to have more anxiety disorders and cluster A personality disorders, and bipolar patients to have more cluster B personality disorders.

The adverse consequences of missing or delayed diagnosis are potentially serious. Thus, these findings strongly support the value of screening for BD in psychiatric settings, especially among the major depressive patients. Nevertheless, the diagnosis must be based on a clinical interview and follow-up of mood. Comorbidity, present in 59% of bipolar patients in a current phase, needs concomitant evaluation, follow-up, and treatment. To improve outcome in BD, treatment of bipolar depression is a major challenge for clinicians. Patients without clinical diagnosis do not represent the whole bipolar population and screening is warranted to detect BD for purposes of research.

Keywords: Bipolar disorder, Bipolar disorder type II, recognition, depressive mixed episode, comorbidity, outcome

2. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals I-IV:

- I Mantere O, Suominen K, Leppämäki S, Valtonen H, Arvilommi P, Isometsä E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). *Bipolar Disorders* 2004;6:395-405.
- II Mantere O, Melartin TK, Suominen K, Rytsälä HJ, Valtonen HM, Arvilommi P, Leppämäki S, Isometsä ET. Differences in axis I and II comorbidity between bipolar I and II disorders and major depressive disorder. *Journal of Clinical Psychiatry* 2006; 67:584-593.
- III Mantere O, Suominen K, Arvilommi P, Valtonen HM, Leppämäki S, Isometsä E. The clinical predictors of unrecognized bipolar I and II disorders. *Bipolar Disorders*. In press.
- IV Mantere O, Suominen K, Valtonen HM, Arvilommi P, Leppämäki S, Melartin T, Isometsä E. Differences in outcome of DSM-IV bipolar I and II disorders. *Bipolar Disorders*. In press.

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3. INTRODUCTION

Bipolar disorder (BD) is a recurrent and chronic illness. Even though the natural course of some patients includes full recovery after distinct phases, according to the latest clinical studies, patients spend half of their time in a symptomatic state (Judd et al., 2003c; Post et al., 2003; Joffe et al., 2004). Even after syndromal recovery, patients all too often do not reach symptomatic or functional recovery, and practically all patients encounter affective recurrences. The disorder has a profound influence on functional outcome, psychosocial factors, and quality of life. The standardized mortality ratio of BD patients is about 20 (Harris and Barraclough, 1997), and an estimated 25-50% attempt suicide at least once (Goodwin, 1990; Jamison, 2000; Slama et al., 2004), and 30-75% have suicidal ideation (Suppes et al., 2001; MacKinnon et al., 2005). Because of the burden of the illness on the individual, family, and society, BD is among one of the most disabling disorders in the world (Morselli and Elgie, 2003). In the Global Burden of the Disease Study (Murray and Lopez, 1997), neuropsychiatric disorders explained 22% of disability-adjusted life-years (DALYs) in developed countries, and MDD was the 4th and BD I the 22nd leading course of DALYs worldwide; obviously, the significance of BD would be far greater if BD II were included together with BD I instead of MDD. The course is further complicated by an exceptionally high degree of other comorbid psychiatric disorders, up to 80% during the lifetime according to several studies (McElroy et al., 2001; Suppes et al., 2001; Dittmann et al., 2002; Henry et al., 2003; Judd et al., 2003b; Simon et al., 2004a; Bauer et al., 2005a). At the same time, while the effect of treatment in BD I is well documented, good-quality evidence in BD II is lacking (Hadjipavlou et al., 2004).

Despite the severity of the illness, BD is poorly recognized. It has been estimated that systematic evaluation of depressive patients would find twice as many bipolar patients as found based on clinical diagnosis (Hantouche et al., 1998; Ghaemi et al., 2000; Kiejna et al., 2006). It appears that the diagnosis of BD is made either during the first year of treatment or after a delay of 8-10 years (Ghaemi et al., 2000). The delays in diagnosis are alarmingly long considering the serious burden caused by delayed diagnosis and the adverse consequences of inappropriate treatment.

To improve the treatment and recognition of BD, more information on the clinical picture of the disorder, especially BD type II, is needed. Diagnosis is the basis for all treatment, but reasons for unrecognized BD have not been investigated. Only a few studies have reported current and lifetime comorbidity or outcome in a cohort with BD I and II patients, and the results are conflicting and not generalizable. The Jorvi Bipolar Study (JoBS) is a prospective, naturalistic cohort study of 191 secondary level care psychiatric out- and inpatients with a new phase of DSM-IV BD. In the JoBS, the predictors of chronicity, recurrences, and suicidal behavior as well as work and functional disability are investigated and the adequacy of treatment evaluated. This thesis focuses on the recognition, clinical picture, comorbidity, and outcome of bipolar patients followed up for 18 months.

4. REVIEW OF THE LITERATURE

4.1 Diagnostic boundaries of bipolar disorder I, bipolar disorder II, and major depressive disorder

In the current diagnostic manual for psychiatric research, DSM-IV (APA, 1994), as well as ICD-10 (WHO, 1993), which is the only official diagnostic system for clinical use in Europe, mood disorders include major depressive disorder (MDD), bipolar disorders (BD) type I and II, dysthymia, and cyclothymic disorder. BD is further divided into BD type I, BD type II, and BD not otherwise specified (NOS). The diagnostic boundary between MDD and BD seems clearer than that between BD I and BD II. This thesis will focus on BD and MDD as defined in the DSM classification used in psychiatric research worldwide.

4.1.1 Classification and validity of psychiatric disorders

Classification and subtyping of diseases, that is, diagnoses, serve three purposes: prediction of treatment response, prognosis, and etiologic research. In psychiatry, some characteristic features of diagnostics set important challenges for defining diagnostic criteria. Explicit diagnostic criteria since *the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III)* (APA, 1980) have structured clinical practice, become a norm in research, provided a universal language in teaching, and improved communication between the users of psychiatric services, caregivers, and society at large (Kendell and Jablensky, 2003).

In psychiatry, *criteria of validity* of a diagnosis can be described as follows: 1) *antecedent validators* (familiar aggregation, premorbid personality, demographic factors, precipitating factors), 2) *concurrent validators* (symptom profiles, psychological tests, biological markers), 3) *predictive validators* (diagnostic stability over time, outcome, response to treatment), and 4) delimitation from other disorders (*exclusion criteria*) (Kendler, 1980; Kendell and Jablensky, 2003). The biological phenotypes (molecular genetics, molecular biology, neuroanatomy, neurochemistry, neurophysiology, cognitive neuroscience) included in the concurrent validators of the previous model are increasingly the focus of etiological research.

Clearly, the current diagnostic system should be challenged from the viewpoint of research. If the validity of a categorical disorder is defined as a zone of rarity (zones where individuals with certain combinations of features are rare), one could argue that no psychiatric diagnosis is currently valid (Kendell and Jablensky, 2003). Etiological studies on psychiatric disorders have shown that many different genes contribute to the etiology of most of psychiatry's major syndromes and some genes are risk factors for what

have until now been regarded as unrelated syndromes (Kendell and Jablensky, 2003). Also, the same environmental factors contribute to the genesis of several different syndromes. A fundamental element of research is that the subjects of research can be explicitly defined. It may be appropriate for most epidemiological research, studies of clinical course, and clinical trials to be based on syndromes in clinical use without proven validity; etiologic research, however, needs valid criteria (Kendell and Jablensky, 2003). In attempting to solve this problem, some researchers suggest new, narrower or broader borders for mood disorders. Others suggest dimensional measuring of narrow symptoms instead of syndromes. In personality disorders, a means of considering diagnoses based on prototype theory from philosophy of mind has been introduced (Westen et al., 2006). This might prove valuable when describing the way clinicians understand diagnoses; according to Westen, the clinicians preferred the prototype view to complex comorbidity according to DSM categories when evaluating individual patients (Westen et al., 2006). The ICD-10 diagnostic system is in most countries used in a prototype way, without the lists of research criteria applied in Finland.

One feature of a diagnosis is that it is a reduction of a more complex entity to a simpler one, something apprehensible and manageable. The aim is to characterize the illness experience as an example of a more general phenomenon, something shared by others, and a rewarding subject for research (Sadler, 2005). If validity and *utility* of a diagnosis are differentiated, it can be said that most current psychiatric diagnoses have great utility for clinicians (Kendell and Jablensky, 2003). At the same time, diagnostic characterization involves a movement away from viewing an individual's illness as a singular, unique phenomenon. A suffering and needful patient presents a unique failure or inadequacy of his own personal resources to aid himself (Sadler, 2005). For the patient, the value and validity of the diagnosis may differ strongly from those for clinicians or researchers.

4.1.2 Distinction between bipolar disorder I and II

Mania and melancholia are two of the earliest human diseases described, having been recognized as illnesses since ancient times (Goodwin, 1990; Angst and Marneros, 2001). Hippocrates (460-337 BC) was the first to systematically describe the two illnesses, and Aretaeus of Cappadocia in the 1st century thought of them as different images of a single disease (Angst and Marneros, 2001). In the 18th century, several independent scientists in Germany, England, and Italy had described melancholia and mania to be longitudinally associated (Angst and Marneros, 2001), and in the mid-19th century, French researchers suggested a one illness theory of mania and depression: *la folie circulaire* by Falret, and *folie à double forme* by his student Baillarger (Goodwin, 1990; Angst and Marneros, 2001). "The father of modern psychiatry", Emil Kraepelin in 1893 distinguished psychotic illnesses from each other (Angst and Marneros, 2001); his model of mood disorders can be said to be a *one-disease model*, including also the foundation for the later development of spectrum concepts (Goodwin, 1990). Thus, manic-depressive illness had become the first fully developed disease model in psychiatry, even encompassing psychological and social

factors (Goodwin, 1990). The German Kleist and Leonhard further distinguished manic-depressive and recurrent depressive patients (called *bipolar and monopolar or unipolar patients*) (Angst and Marneros, 2001), which has been the basis for classificatory systems in psychiatry since DSM-III (APA, 1980) and ICD-10 (WHO, 1993). However, at least five mood disorder models still have their supporters (see Section 4.1.8). Schizoaffective disorder has not been included in these theoretical models.

In the 1970s, a subgroup of BD patients with hypomanic instead of manic phases was identified (Goodwin et al., 1972; Dunner et al., 1976; Fieve et al., 1984). BD types I and II have subsequently become separated based on the presence of manic and mixed phases in BD I and hypomanic phases in BD II (see Sections 4.1.3 and 4.1.4). The distinction has been largely supported by studies describing increased risk for BD II among relatives of BD II, while the relatives of patients with BD I have both BD I and II (Gershon et al., 1982; Coryell et al., 1984; Fieve et al., 1984; Endicott et al., 1985; Andreasen et al., 1987; Rice et al., 1987; Heun and Maier, 1993; Sadovnick et al., 1994; Kelsoe, 2003).

Otherwise, surprisingly modest differences have been found in studies comparing BD I and II. The studies are presented in Table 1, and for recent reviews of the differences see (Berk and Dodd, 2005; Skeppar and Adolfsson, 2006). The differences in sociodemographic and clinical features are presented in Table 2, differences in comorbidity in Sections 4.2.2 and 4.2.3 and Table 5., and differences in outcome in Section 4.3.4 and Table 6. Biological studies seem to prefer BD I patients and comparisons between BD and MDD, and thus, the biological validation of BD I and II remains a subject for future research. The few studies comparing neurobiological differences between BD I and II thus far seem not to support distinguishing between these disorders (McGrath et al., 2004). In addition, while many differences in personality and temperament have been suggested (Berk and Dodd, 2005; Savitz and Ramesar, 2006; Skeppar and Adolfsson, 2006), the results remain controversial.

Several but contradictory reports of other differences exist. Age at onset has been described to be either earlier in BD I (Coryell et al., 1989; Tondo et al., 1998; Suppes et al., 2001; Serretti et al., 2002a; Post et al., 2003) or equal (Judd et al., 2003b). BD I patients may have a higher proportion of males (Tondo et al., 1998) or gender distribution may be similar (Suppes et al., 2001; Judd et al., 2003b; Post et al., 2003). BD I patients have had a higher severity of depressive phases (Serretti et al., 2002a; Judd et al., 2003b), more hospitalizations (Coryell et al., 1989; Serretti et al., 2002a), and more psychotic features at intake (Benazzi and Akiskal, 2001; Serretti et al., 2002a; Akiskal and Benazzi, 2003; Judd et al., 2003b) or during the lifetime (Suppes et al., 2001). BD II patients have been more (Tondo et al., 1998) or less (Post et al., 2003) likely to be married, more likely to be divorced (Tondo et al., 1998), more likely to be employed (Coryell et al., 1987), and more likely to have a higher income (Post et al., 2003). No difference was detected in other studies in education (Tondo et al., 1998; Judd et al., 2003b; Post et al., 2003) or marital status (Judd et al., 2003b). BD II patients were more likely to have a depressive first phase in one study (Tondo et al., 1998), while another study found no difference (Judd et al., 2003b) and a third study reported

manic/hypomanic onset more often in BD I and slightly more depressive onsets in BD II (Suppes et al., 2001). Suicidality has been more prevalent in BD II (Tondo et al., 1998; Serretti et al., 2002a; Balazs et al., 2003), in BD I (Angst and Marneros, 2001), or equally prevalent (Coryell et al., 1989; Dalton et al., 2003; Leverich et al., 2003; Post et al., 2003).

The significance of these differences remains uncertain because of several limitations in previous studies. First, the cohorts are mostly highly selected, and thus, the results are hardly generalizable to the majority of patients found in secondary care treatment. Second, possible confounding factors (age, comorbidity, acute state) have not been reported or controlled in the analyses. It is not surprising that BD I has more psychotic features and hospitalizations excluded by definition in hypomanic phases. In addition, cross-sectional severity of the symptoms is likely to correlate with hospitalization and psychotic features, and longitudinal severity with many sociodemographic features. Thus, differences in the severity of the illness cannot be used as strong evidence for the existence of two separate disorders.

Table 1. Previous clinical cohorts including BD I and BD II patients

Name/ or place of the cohort	Inpatients/ outpatients at intake	Place of sampling	Current mood	Size of the cohort, BD I/BD II n (%)	Follow-up, years	Diagnostic method	Comparison of BD I and BD II	Key references
National Institute of Mental Health Collaborative Depression Study (CDS)	79.1%/20.9%	Five academic centers in the USA	Acute manic, hypomanic, mixed, or major depressive episode	135 (65.5%)/ 71 (34.5%), total 206	20	Schedule for Affective Disorders and Schizophrenia (SADS), Research Diagnostic Criteria (RDC)	Yes	(Coryell et al., 1989; Judd et al., 2003b; Judd et al., 2005; Judd et al., 2003c)
Stanley Foundation Bipolar Network	0%/100%	Four academic sites in the USA and one in Netherlands; added also self-referral patients	Not reported	Varies from 239 (83.0%)/ 49 (17.0%), total 288 to 681 (78.5%)/ 187 (21.5%) total 868	1	Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-P) Axis II self-rated; DSM-IV	Yes	(Kupka et al., 2005; Leverich et al., 2003; McElroy et al., 2001; Nolen et al., 2004; Post et al., 2003; Suppes et al., 2005)
Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)	0%/100%	Multicenter study in the USA	Acute manic, hypomanic, mixed or major depressive episode 59.6% of patients	Varies from 360 (75.8%)/ 115 (24.2%), total 475, up to total 812	2	Affective Disorder Evaluation (ADE), Mini-International Neuropsychiatric Interview (MINI), DSM-IV	Yes	(Perlis et al., 2006b; Simon et al., 2004b)
Stanley Foundation, German cohort	0%/100%	Hospitalization or self-referral	Not reported	108 (74.0%)/ 38 (26.0%), total 146	2.5	SCID-P, SCID-II, DSM-IV	Yes	(Dittmann et al., 2002)
Henry	100%/0%	Two university hospitals in France	Acute hospitalization, not specified	237 (74.5%)/ 81 (25.5%), total 318	No	Diagnostic Interview for Genetic Studies (DIG), DSM-IV	No	(Henry et al., 2003)
Sardinia	Not reported	Several clinical trials from mood disorder unit in Sardinia	Not reported	293 (65.1%)/ 157 (34.9%), total 450	1	Various criteria, no structured interview	Yes	(Baldessarini et al., 2003; Tondo et al., 1998; Tondo et al., 2001)
McMaster Regional Mood Disorder Program	0%/100%	Mood disorder program in Canada	Not reported	97 (70.3%)/ 41 (29.7%), total 138	3	SCID, DSM-IV	Yes	(Joffe et al., 2004)
Milan, Italy	87.1%/12.1%	Subjects combined from clinical and genetic samples from tertiary care in Italy	Major depressive phase	863 (86.0%)/ 141 (14.0%), total 1004	No	SADS, DSM-III-R and DSM-IV	Yes	(Serretti et al., 2002a)

Table 2. Review of the main differences between BD I and BD II in patient characteristics and clinical history

Reported differences	
Sociodemographic variables	
Gender	BD II more female (Tondo et al., 1998) Equal (Judd et al., 2003b; Post et al., 2003; Suppes et al., 2001)
Marital status	Married BD II>BD I (Tondo et al., 1998), BD I>BD II (Post et al., 2003) Divorced BD II>BD I (Tondo et al., 1998) No difference (Judd et al., 2003b)
Family history of BD	More BD II in families of BD II patients (Andreasen et al., 1987; Coryell et al., 1984; Endicott et al., 1985; Fieve et al., 1984; Gershon et al., 1982; Heun and Maier, 1993; Kelsoe, 2003; Rice et al., 1987; Sadovnick et al., 1994)
Clinical history	
Age at onset, treatment or hospitalization	BD II>BD I (Coryell et al., 1989; Post et al., 2003; Serretti et al., 2002a; Suppes et al., 2001; Tondo et al., 1998; Baldessarini et al., 2003) No difference (Judd et al., 2003b)
Total episodes	No difference (Serretti et al., 2002a; Judd et al., 2003b)
Depressive phases	BD II>BD I (Serretti et al., 2002a)
Suicidality	BD I>BD II (Angst and Marneros, 2001) BD II>BD I (Balazs et al., 2003; Serretti et al., 2002a; Tondo et al., 1998) No difference (Coryell et al., 1989; Dalton et al., 2003; Leverich et al., 2003; Post et al., 2003)
Hospitalizations	BD I>BD II (Coryell et al., 1989)
Cross-sectional severity	
Psychotic symptoms	BD I>BD II (Akiskal and Benazzi, 2003; Benazzi and Akiskal, 2001; Judd et al., 2003b; Serretti et al., 2002a)
Symptoms scores/ severity in depression	BD I>BD II (Judd et al., 2003b)

4.1.3 Mania and hypomania

The mania-specific DSM-IV criteria of a manic phase (APA, 1994) include A) a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary) and B) during the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is irritable) and have been present to a significant degree: 1) inflated self-esteem or grandiosity, 2) decreased need for sleep, 3) more talkative than usual or pressure to keep talking, 4) flight of ideas or subjective experience that thoughts are racing, 5) distractibility, 6) increase in goal-directed activity or psychomotor agitation, or 7) excessive involvement in pleasurable activities that have a high potential for painful consequences (Table 3).

Table 3. DSM-IV criteria for Manic Episode

- A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).
 - B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
 1. inflated self-esteem or grandiosity
 2. decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
 3. more talkative than usual or pressure to keep talking
 4. flight of ideas or subjective experience that thoughts are racing
 5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
 6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
 7. excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
 - C. The symptoms do not meet the criteria for a Mixed Episode.
 - D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
 - E. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication or other treatment) or a general medical condition (e.g., hyperthyroidism).
- Note:** Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.
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Diagnosis of bipolar disorder according to the Diagnostic and statistical manual of mental disorders, Fourth Edition (DSM-IV), Text Revision (American Psychiatric Association, 2000)

The DSM-IV hypomania-specific criteria for a hypomanic phase (APA, 1994) differ from the criteria of a manic phase in that the expression "abnormally changed" is omitted from criterion A, and duration of only 4 days is required (Table 4). Also, hypomania is differentiated from mania in that the phase must not be severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and no psychotic features are present. By contrast, the criteria for hypomania also specify that C) the episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic and D) the disturbance in mood and the change in functioning are observable by others. The requirement of three (in euphoric mood) or four (in irritable mood) B criteria is the same as in mania.

Table 4. DSM-IV criteria for Hypomanic Episode

- A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.
- B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
1. inflated self-esteem or grandiosity
 2. decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
 3. more talkative than usual or pressure to keep talking
 4. flight of ideas or subjective experience that thoughts are racing
 5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
 6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
 7. excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.
- D. The disturbance in mood and the change in functioning are observable by others.
- E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.
- F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

NOTE: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder.

Diagnosis of bipolar disorder according to the Diagnostic and statistical manual of mental disorders, Fourth Edition (DSM-IV), Text Revision (American Psychiatric Association, 2000)

Some criteria of mania and hypomania require further consideration based on the literature available. First, the definition of a hypomanic phase lasting at least 4 days in the DSM-IV is arbitrary. *Brief hypomania* with 2 or more days is as widely accepted as valid as the current definition of 4 or more days in the DSM-IV based on family history of BD, symptom profile, and outcome (Coryell et al., 1995; Akiskal et al., 2000; Benazzi, 2001a; Angst et al., 2003; Judd et al., 2003a). Second, the weakest point in the differential diagnosis of hypomania and mania arises from the ill-defined qualifying words "without marked social or occupational dysfunction", which must be interpreted by the classifier without any further instructions. Given that currently manic patients tend not to have insight into this aspect of the illness (Dell'Osso et al., 2002), and insight seems to be poorer in BD II when the mood is stabilized (Pallanti et al., 1999), other informants are often needed. Third, the distinction between normally and "abnormally" elevated mood is often not clear.

Not all bipolar patients experience depressive phases. The prevalence of *unipolar mania* is reported in only two studies. Angst et al. (Angst et al., 2004) describe that in a sample of hospitalized patients, followed-up prospectively for a mean of 17.6 years (0-33 years), 14/160 BD I patients (8.8%) had only manic episodes. However, the diagnosis was not confirmed in a structured interview, the follow-up time varied markedly, and only 43% of patients were interviewed personally. Yazici et al. (Yazici et al., 2002) note that 48/272 patients (17.6%) with manic episodes from a mood disorder unit in Istanbul had no major depressions in at least 4 years of retrospective follow-up. No study has reported the prevalence in a representative sample of patients, but most likely in outpatient samples with prospective follow-up, the prevalences would be considerably lower. The true existence of unipolar mania is often questioned (Goodwin, 1990). However, two prospective studies suggest at least some patients have a stable form of unipolar mania (Shulman and Tohen, 1994; Solomon et al., 2003). In one study of 50 BD patients who at baseline had had at least 3 manic phases without depression, 6/50 (12%) stayed unipolar manic in a 5-year follow-up (Shulman and Tohen, 1994). In another study, 7/27 unipolar manic patients (26%) had no major depressions during 15-20 years of follow-up, and 5/27 patients (19%) did not even have minor depressions (Solomon et al., 2003).

4.1.4 Mixed phase

The term *mixed states* was introduced and described by Kraepelin in 1896 (Angst and Marneros, 2001). He distinguished two general classes of mixed states: a *transition form*, where depression changes into mania or vice versa, and an *autonomic form*, a disorder of its own (Angst and Marneros, 2001; Marneros, 2001b). He also distinguished six subtypes of mixed states: three were based on manic mood (basic elements of euphoria, flight of ideas, and hyperactivity), and three on depressive mood (basic elements of depressive mood, depressive thoughts, and weakness of volition) (Marneros, 2001b). For instance, a depressive or anxious mania is evident if euphoria is replaced by depressive mood, but two

of the three basic elements of mania are present (Marneros, 2001b). Also, manic stupor is present when mood is euphoric, but two other major components of depression are evident (Marneros, 2001b). Basically, three modern definitions of mixed states can be presented: 1) *broad definitions*, where the presence of single depressive symptoms within a manic phase is considered sufficient for a mixed phase, 2) *narrow or strict definitions*, where only the co-existence of full symptomatology of a manic and depressive phase allows the diagnosis of a mixed phase, and 3) *moderate definitions*, where prominent depressive symptoms within a manic or hypomanic phase are sufficient (Marneros, 2001b).

In the DSM-IV, strict criteria are used: the criteria must be met for both a manic episode and a major depressive episode (except for duration) nearly every day over at least a 1-week period (APA, 1994). Thus, the DSM-IV describes a mixed episode to be present only in BD I, with no equivalent in BD II. In addition, either alternating or concurrent symptoms of mania and depression are present (APA, 1994). A mixed episode thus defined has been prevalent currently in 7-24% of hospitalized manic patients (Sato et al., 2002; Gonzalez-Pinto et al., 2003; Berk et al., 2005) and in 3% of BD patients from a treatment system (Bauer et al., 2005b). The nature of pure manic and mixed phases differs in terms of phenomenological presentations (Dilsaver et al., 1999; Cassidy et al., 2000), natural course (Cassidy and Carroll, 2001), and specific treatment responses (Swann et al., 1997). Much more confusion in the literature exists in differentiating manic and mixed states than manic and hypomanic states.

The differences in the severity of manic and depressive symptoms in a mixed phase or mixed vs. manic phase remain controversial. In most studies, the manic symptoms seem qualitatively and quantitatively similar in manic and mixed states, and the difference stems from the number of depressive symptoms (McElroy et al., 1995). Some report manic and depressive symptoms to have a strong positive relationship (Bauer et al., 2005b).

Only a few studies have longitudinally analyzed the individual constancy of specific features of manic and mixed phases such as psychotic symptoms in mania or presence of mixed features. Existence of psychotic features in mania does not seem a stable feature: in a 15-year follow-up, patients who had psychotic features at intake mania were only twice as likely to have psychotic features in follow-up compared with patients with nonpsychotic mania at intake (Coryell et al., 2001). Patients with a current mixed phase are more likely to have had a mixed phase as a first episode than manic patients (McElroy et al., 1995), and to longitudinally have a greater number of mixed phases (McElroy et al., 1995). In an individual, mixed and manic states can alternate longitudinally without full stability of the pattern (McElroy et al., 1995; Perugi et al., 1997; Sato et al., 2003). The constancy of mixed or manic episodes during hospitalizations appeared more constant than by chance alone in one register study, the number of constant cases still being only 20% (Woods et al., 2001). The constancy was greater in a clinical study in hospitalized manic (57/62, 92% of manic patients) than mixed (13/68, 69.2%) patients from

the first to second phase (Cassidy et al., 2001a). Adolescents may have more mixed manias and rapid or ultrarapid cycling than adults, but long-term studies are needed to confirm whether this model is to be changed in adulthood for these patients or whether it is a feature of early onset BD (Kyte et al., 2006).

The DSM-IV definition of a mixed state is problematic for four reasons: 1) the mixed features are evident in a dimensional rather than a strictly categorical manner, 2) a mixed state for BD II is not included, 3) simultaneous occurrence of manic and depressive symptoms and *ultrarapid cycling mood* (change of depressive and manic mood faster than the time periods required for a major depressive or manic phase) are not differentiated, and 4) some symptoms of mania and depression overlap (McElroy et al., 1995).

4.1.5 Depressive mixed phase

No official diagnostic system includes a mixed state for BD II. However, it seems that sub-threshold admixtures of depression with hypomania are common (Angst and Marneros, 2001; Bauer et al., 2005b) as a milder form of mixed states, corresponding to the differences between manic and hypomanic states. In Europe, the term *depressive mixed state*, and in the US, *mixed hypomania* have been used. However, increasing evidence supports the existence and significance of the prevalence of manic symptoms in depression (in 70%) and depressive symptoms in hypomania/mania (Bauer et al., 2005b; Suppes et al., 2005). In the Stanley Foundation Bipolar Treatment Network cohort, at 57% of visits with hypomanic patients, the criteria of mixed hypomania were met (Suppes et al., 2005); mixed hypomania was defined as a state when the Young Mania Rating Scale score was ≥ 12 and the Inventory of Depressive Symptomatology – Clinician-Rated Version (IDS-C) ≥ 15 (Suppes et al., 2005). Benazzi and Akiskal (Benazzi and Akiskal, 2001) have studied the prevalence of depressive mixed states when defined to fulfill the criteria of a major depressive phase with two or more (DMX2) or three or more (DMX3) simultaneous hypomanic symptoms. Thus defined, the prevalence of DMX3 has been 46.3% in BD II patients and 7.8% in MDD patients, and that of DMX2 73.1% in BD II patients and 42.1% in MDD patients (Benazzi and Akiskal, 2001; Berk et al., 2005). Furthermore, the prevalence of DMX2 in depressed bipolar patients was 81.8% (Akiskal and Benazzi, 2003).

The stability of depressive mixed states needs to be validated longitudinally. In a retrospective follow-up study (Sato et al., 2003), the presence of categorical depressive mixed states was constant in 71% of bipolar patients, and the dimensional score of the number of intra-episode manic symptoms was moderately significant; the authors interpreted the results as indicating that the inter-episode stability of DMX was not sufficiently high to establish a distinct clinical entity.

The broader the definition of mixed states, the more evident the need for phenomenological exactness in differentiating between state and trait of patients. Obviously, the various definitions and clinical picture of bipolar mixed states together form a spectrum that extends from the occurrence of depressive features within mania to the occurrence of manic

features within depression, with admixtures in between (McElroy et al., 1995; Berk et al., 2005). Thus, a dimensional view of mood becomes necessary: depressive and manic symptoms are dimensionally present to a varying extent even in the same individual. Some authors hypothesize that a mixed state, rather than an independent state of mood, is evident when an episode arises from a temperament of opposite polarity (Marneros, 2001b). Akiskal et al. (Marneros, 2001b) have speculated that depressive temperament with manic psychosis, cyclothymic temperament with depression, or hyperthymic temperament with depression underlie a mixed symptomatology. While this has not been validated, the opposite was true (Perugi et al., 1997). Furthermore, the authors do not use the term "temperament" as a normal variant of healthy persons, but have constructed the criteria based on samples of mood disorder patients; thus, the borders of subsyndromal states of mood are not clear-cut. Thus far, the definition provided by Benazzi and Akiskal (Benazzi and Akiskal, 2001) DMX3 seems most suitable as a categorical state comparable to mixed states in BD I, but the term needs to be validated and the results replicated by independent authors. Careful evaluation of the demarcation between depressive mixed state and borderline personality disorder is also needed (Magill, 2004).

4.1.6 Differences between depressive patients with bipolar or major depressive disorder

Several clinical studies have tried to differentiate patients with unipolar and bipolar depression [recently reviewed in (Bowden, 2001; Skeppar and Adolfsson, 2006)]. The strongest evidence distinguishing BD patients from MDD patients comes from family risk studies. BD patients have more often had a family history of BD (Angst, 1986; Cassano et al., 1992; Winokur et al., 1993a; Winokur et al., 1993b; Ghaemi et al., 2004; Perlis et al., 2006a). In addition, BD patients typically have an earlier age at illness onset (Cassano et al., 1992; Winokur et al., 1993a; Hantouche et al., 1998; Benazzi, 2001b; Kupfer et al., 2002; Serretti et al., 2002a; Akiskal and Benazzi, 2005; Perlis et al., 2006a). BD I patients have the earliest age at illness onset (Cassano et al., 1989; Serretti et al., 2002a; Berk and Dodd, 2005), at first treatment (Serretti et al., 2002a), and at first hospitalization (Cassano et al., 1989).

In prospective studies, BD patients have had a higher total number of episodes (Winokur et al., 1993a; Winokur et al., 1993b), depressive phases (Cassano et al., 1992; Ghaemi et al., 2004; Akiskal and Benazzi, 2005; Perlis et al., 2006a), and hospitalizations (Winokur et al., 1993b). BD I patients have had the greatest number of illness episodes (Serretti et al., 2002a) and hospitalizations (Serretti et al., 2002a). In one study, BD I patients had the most depressive phases (Cassano et al., 1989), but no statistically significant difference was evident in another study (Serretti et al., 2002a). Postpartum depression is common in BD (Goodwin, 1990; Ghaemi et al., 2004). BD patients are also more affected by seasonality (Shin et al., 2005).

Cross-sectional differences in depression of BD and MDD patients remain controversial. BD patients have had more psychotic features in depression (Mitchell et al., 2001), with BD I patients having the most (Serretti et al., 2002a). No differences in symptom scores between BD I and MDD were detected in some studies (Hantouche et al., 1998; Benazzi, 1999; Mitchell et al., 2001), while in a study with patients mixed from clinical and genetic studies, MDD had more serious depressive symptoms than BD I (Serretti et al., 2002a), and in a sample from three depression treatment studies, BD I had more serious depressive symptoms than MDD (Perlis et al., 2006a).

Several studies [reviewed in (Berk and Dodd, 2005; Skeppar and Adolfsson, 2006)] suggest that depression in BD (especially BD II) is characterized by such *atypical features* as hypersomnia, hyperphagia, marked fatigue, and rejection sensitivity (APA, 1994). In recent studies with BD and MDD patients, BD patients have had more atypical features of depression (Benazzi and Rihmer, 2000; Benazzi and Akiskal, 2001; Mitchell et al., 2001; Serretti et al., 2002a; Ghaemi et al., 2004). The DSM-IV criteria for *melancholic depression* are loss of pleasure or mood nonreactivity, plus at least three of the following criteria: distinct quality of mood from sadness, worse symptoms in the morning, early morning awakening, marked psychomotor change, significantly decreased eating or weight, and marked guilt (APA, 1994). The results from studies reporting differences in the prevalence of melancholia in MDD vs. BD have been more controversial than from studies on atypical depression; however, the prevalence of melancholia seems similar in different mood disorders when overall severity of depression is controlled (Berk and Dodd, 2005), although higher prevalence of melancholic features in BD I has also been suggested (Skeppar and Adolfsson, 2006).

Temperamental features might form one etiologic factor underlying mood disorders (Akiskal et al., 2000; Perugi and Akiskal, 2002; Skeppar and Adolfsson, 2006). The common coexistence of personality disorders and mood disorders seems to support this theory. Several studies have compared temperament behind mood disorders in BD and MDD patients, as reviewed in (Mendlowicz et al., 2005), and BD I and BD II patients, as reviewed in (Savitz and Ramesar, 2006), but thus far the results have been contradictory and it remains unclear which features are true etiological differences and which result from the longitudinal course of the disorder. In other studies, some aspects of mood lability, impulsivity, and aggression (excited depression, agitated depression, anger attacks, irritation) have been found to be different between MDD and BD (Hantouche et al., 1998; Serretti et al., 2002a; Maj et al., 2003; Benazzi et al., 2004; Deckersbach et al., 2004; Perlis et al., 2004; Akiskal and Benazzi, 2005; Nowakowska et al., 2005; Serretti and Olgiati, 2005). Recently, a dimensional spectrum of mood lability was suggested with specific features differentiating BD, especially rapid and ultrarapid cycling, and borderline personality disorder (MacKinnon, 2006). In a review of studies with BD I and II patients, Savitz and Ramesar (Savitz and Ramesar, 2006) conclude that the results thus far suggest that certain personality traits are associated with BD in a state-independent manner, that personality is at least partly heritable, and that various temperaments aggregate in the nonaffected relatives of bipolar probands. According to them, however, it

remains unclear whether specific personality traits co-segregate with affectively ill individuals (Savitz and Ramesar, 2006). In many studies reporting temperamental features in BD patients or comparing BD and MDD patients, the use of terminology is confusing, and especially in studies describing features like agitation, limits of symptoms of mood states, residual symptoms, and true temperamental (variants of normal) features are not well defined.

Overall, clinical studies comparing depression in unipolar and bipolar patients have several methodological limitations, most importantly that they seldom describe representative patient samples of MDD, BD I, and BD II, but include only two of the groups, and that they mostly comprise hospitalized patients. No study has been able to describe a large set of characteristics in the same cohort, controlling for important confounding factors like differences in symptom status. In addition, the magnitude of differences mostly does not seem clinically relevant, and the results are largely conflicting. Thus, the true differences in clinical characteristics and symptom profile between unipolar and bipolar depression remain open and warrant further research.

4.1.7 Stability of diagnosis in mood disorders

Stability of diagnosis serves as one validator of MDD, BD I, and BD II, and thus, incidences of conversion to another mood disorder, or switching, have been a subject of research. Generally, a conversion is thought to only occur from MDD to BD I or BD II and from BD II to BD I, while a later absence of manic or hypomanic phases is a sign of recovery, not leading to a change in diagnosis. In the Iowa 500 study, patients that had been hospitalized for a major depressive episode were followed for a mean of 4.3 years, and 22/225 (9.8%) had a manic episode during this time (Winokur and Wesner, 1987). In a mixed cohort of MDD patients (172 patients from an imipramine study, 53 hospitalized patients, and 181 patients retrospectively assessed at intake), 50/209 (23.9%) were bipolar after a median follow-up of 25 years (Angst and Preisig, 1995). In the NIMH Collaborative Program on the Psychobiology of Depression – Clinical Studies, a study with inpatients as well as outpatients, 19/381 (5.0%) had hypomania and 20/381 (5.2%) mania during the 10-year follow-up (Coryell et al., 1995). Furthermore, 12/94 BD II patients (12.8%) developed mania (Coryell et al., 1995). In a study of outpatients with an initial diagnosis of MDD (mean age at intake 44.4 years), 41/206 (19.9%) developed mania during a mean prospective follow-up of 3 years; the high proportion might be explained by 90% of patients being in their first or second mood episode (Akiskal et al., 1983). In a sample of 74 young patients (mean age at intake 23.0 years) hospitalized for depression, 30/74 (41%) had hypomania or mania during the 15-year follow-up (Goldberg et al., 2001). The conversion from MDD to BD II might be as common (5.0% vs. 5.2%) (Coryell et al., 1995) or slightly more common (27% vs. 19%) (Goldberg et al., 2001) than that from MDD to BD I. The conversion from MDD to BD seems highest during the first 5 years of follow-up (Coryell et al., 1995) or equally distributed (Goldberg et al., 2001). In studies of depressed adolescents, 20-49% became bipolar in 7-15 years of follow-up (Geller et al., 2001). In summary, then, polarity conversion from MDD to BD is estimated to be 1-2% per year

(Winokur and Wesner, 1987; Angst and Preisig, 1995; Coryell et al., 1995), and conversion from BD II to I from less than 1% to 2% per year in a longer follow-up (Coryell et al., 1995; Angst et al., 2005). The switch rate from BD to schizoaffective disorder or schizophrenia in a follow-up study of patients hospitalized for first mania was 7/173 (4.0%) (Tohen et al., 2003).

Reported predictors of switching from MDD to BD [reviewed in (Goldberg et al., 2001)] include younger age at intake (Akiskal et al., 1983; Winokur and Wesner, 1987), earlier age at onset (Akiskal et al., 1983; Angst and Preisig, 1995), bipolar family history (Akiskal et al., 1983; Angst and Preisig, 1995; Goldberg et al., 2001), higher number of episodes (Angst and Preisig, 1995), atypical, hypersomnic, or retarded features of depression (Akiskal et al., 1983), pharmacological hypomania (Akiskal et al., 1983), postpartum episodes (Akiskal et al., 1983), psychotic depression (Akiskal et al., 1983; Goldberg et al., 2001), more hospitalizations (Winokur and Wesner, 1987), and hypomanic symptoms (Regeer et al., 2006). In a 15-year follow-up study, a switch from MDD to BD was prevalent in 9% of patients without psychotic features, but in 20% of patients who met DSM-IV criteria for depressive disorders with psychotic features (Jager et al., 2005). In the NEMESIS study, the lifetime prevalence of hypomanic symptoms as measured by items of CIDI in people without a diagnosis of BD was 1.2%, and in the 2-year follow-up the positive predictive value of hypomanic symptoms for post-baseline depression was 17.9%, and for post-baseline BD 7.1% (Regeer et al., 2006). Thus, the cross-prediction across mood symptoms was high. In addition, the predictive value increased in a dose-response fashion with increasing number of mood symptoms (Regeer et al., 2006).

Predictors of a switch from MDD to BD I include psychotic features (Akiskal et al., 1995; Coryell et al., 1995; Jager et al., 2005), greater severity of intake episode (Akiskal et al., 1995), and a family history of mania or schizoaffective mania (Coryell et al., 1995). Predictors of switching from MDD to BD II include younger age at intake (Akiskal et al., 1995; Coryell et al., 1995), mood instability (Akiskal et al., 1995), and duration of depression of more than 2 years (Coryell et al., 1995). Predictors of a switch from BD II to I remain open; one study found no differences between the 12 switchers and 59 nonswitchers (Coryell et al., 1995), but the power of the study was poor.

Most bipolar patients could be said to be "switchers" given that several studies uniformly report that 60% of BD begins with a depressive phase (Lish et al., 1994; Tondo et al., 1998; Judd et al., 2003b; Morselli and Elgie, 2003). Delay from the first depression to the first mania was in one study a mean of 6.4 years (median 4 years) (Akiskal et al., 1983). However, this means that the younger the cohort of mood disorder patients, the more likely they are to convert in follow-up. Thus, a study reporting the relation of patients' age at intake, age at onset, age at conversion, and time in follow-up is needed. Some of the patients might not be true converters, but false switchers arising from diagnostic problems. The diagnostic criteria have changed since the beginning of the follow-up, and none of the studies was initiated using the current DSM-IV criteria of BD II; thus, some BD II might have been diagnosed as MDD at intake. Several factors may therefore explain a

portion of the converters. In any case, the proportions can be said to be moderate, and diagnostic stability is commonly used as a validator of the three mood disorders (MDD, BD I, and BD II). Since switching is relatively uncommon, it is difficult to have cohorts with the power to detect predictors of conversion after a long follow-up.

4.1.8 Alternative views of mood disorders

Whereas abundant evidence exists on the differences between MDD and BD to support their categorical division into two disorders, the division of BD into types I and II has been the subject of more controversy. At least five models of mood disorders have their supporters: 1) the *three-disorder model of MDD, BD I, and BD II* as introduced in previous sections, 2) a *two-disorder model with MDD and BD*, 3) the *dimensional model of mood disorders*, 4) a *four-disorder model with separate MDD, BD I, BD II, and bipolar spectrum disorders*, and 5) a *two-disorder model with concurrent or alternating major depression and mania*, where the two are coexisting in some (currently bipolar) individuals like comorbid disorders. The diagnostic boundaries of these categories do not necessarily follow the boundaries of BD and MDD diagnoses as defined in the DSM-IV.

Criticism of the categorical distinction of MDD and BD as reviewed in (Cassano et al., 2004) is based on: 1) clinical studies showing that BD is frequently misdiagnosed as unipolar MDD and consequently mistreated (Manning et al., 1997; Hantouche et al., 1998; Ghaemi et al., 1999; Ghaemi et al., 2001; ten Have et al., 2002; Kessing, 2005a; Kiejna et al., 2006), and patients with recurrent unipolar major depression have a significant number of manic or hypomanic symptoms (Cassano et al., 2004; Serretti and Olgiati, 2005); thus, no clear-cut limit between the two disorders is found; 2) theoretical studies warning about the limitations of the categorical diagnoses of BD and unipolar depression (Kendler and Gardner, 1998; Benazzi and Akiskal, 2001; Akiskal and Benazzi, 2003; Kelsoe, 2003; Alda, 2004; Berk et al., 2005; MacQueen et al., 2005); 3) epidemiological studies supporting a widening of the boundaries of the bipolar spectrum to include hypomania, cyclothymia, and BD NOS (Angst, 1998); 4) familial and genetic studies indicating that the familial aggregation of BD and severe unipolar depression is at least partly due to common genetic factors and that the etiology of such broad syndromes as MDD and BD is multifactorial (McGuffin and Katz, 1989; Duffy et al., 2000); and 5) lack of validity of these diagnostic categories in terms of zones of rarity (Kendell and Jablensky, 2003).

The dimensional view of mood disorders above lies at the foundation of the so-called *spectrum models*. The term "spectrum" was first used in psychiatry by Kety et al. (Angst and Cassano, 2005) in a description of *schizophrenia spectrum disorders* and refers to the broad range of disorder manifestations, from core symptoms to temperamental traits (Cassano et al., 2002). The manifestations of the spectrum may represent during, between, or in the absence of a full-syndrome level of the disorder. It has been proposed that all forms of BD and perhaps all primary mood disorders are best conceptualized as a spectrum of related illnesses that overlap clinically and are genetically heterogeneous (Judd et al., 1997; Kendler and Gardner, 1998; Judd and Akiskal, 2000; Judd et al., 2003b; Kelsoe, 2003; Alda, 2004; MacQueen et al., 2005).

The bipolar spectrum (Angst and Cassano, 2005) describes a continuum of symptoms comprising a complex range of bipolar subtypes (Perugi and Akiskal, 2002; Angst and Cassano, 2005). However, use of the term is extremely confusing. A framework for dimensions used in the definition of bipolar spectrum as suggested by Goodwin (Goodwin, 1990) includes 1) severity of depressive, manic, and mixed states, 2) polarity, 3) cyclicality, 4) duration of episodes, 5) instability or rapidity of state changes, and 6) responsiveness to treatment. Some speak of bipolar spectrum comprising only BD I and II, while others expand it to include up to half of mood disorder patients (Angst and Cassano, 2005). Klerman in 1981 suggested a continuum of manic conditions to include 1) mania, 2) hypomania, 3) hypomania or mania induced by drugs, 4) cyclothymic personality, 5) depression with family history of mania, and 6) mania without history of depression (Angst and Marneros, 2001). Based on the severity of symptoms, Angst has distinguished between hypomania (m), cyclothymia (md), mania (M), mania with mild depression (Md), mania and major depression (MD), and major depression with hypomania (Dm) (Angst and Cassano, 2005). *Soft bipolar spectrum* is a term coined by Akiskal (Perugi and Akiskal, 2002; Akiskal et al., 2006) This spectrum is characterized by a recurrent tendency to hypomanic excursions which, when coupled with depressive periods of varying duration and severity, give rise to the various subtypes of the spectrum (Akiskal et al., 2006). The soft bipolar spectrum disorders are characterized by personality-like features, are built on several temperament types, are constant, and rarely lead to hospitalization or other serious outbursts (Perugi and Akiskal, 2002). Recently, in genetic studies, the bipolar spectrum has been used to refer to psychopathological states or endophenotypes that may share a common genetic basis (Kelsoe, 2003; Alda, 2004; MacQueen et al., 2005). To conclude, no consensus has yet been reached on the term bipolar spectrum, and this is reflected in the results of spectrum research not being comparable.

Some researchers suggest a comorbidity of *depression and mania as distinct disorders* rather than as a single bipolar disorder (Joffe et al., 1999; Schweitzer et al., 2005). The authors state that if mania and depression are opposite poles of a unitary disease entity, both should respond to the same treatment, which according to them is not the case. However, several authors have argued against the comorbidity theory using the same study results against the model as Joffe et al. used to support the model and state that at least lithium is a drug of choice for both mania and depression (Dunner, 1999; Swann, 1999).

The dimensional view of mood disorders is mainly criticized for the poor clinical utility of the concept (Patten, 2006). Dimensions are more difficult to integrate, for example, with clinical practice guidelines. Dimensional symptom ratings can hardly guide treatment; for instance, a high depressive score can be due to normal bereavement (Patten, 2006). A spectrum that does not clearly differentiate temperament and personality, or overt psychopathology, may not be useful in clinical practice (Patten, 2006). One important measure of clinical utility would be any evidence that spectrum disorders benefit from

treatment (Patten, 2006). For the purposes of research, defining a spectrum disorder too broadly and unspecificly may dilute results in studies searching for underlying etiology (Patten, 2006).

Although this argumentation between categorical and dimensional view only a few years ago seemed to be "either-or" directed, a consensus is now being formulated similar to that of comorbidities, that is, both views are needed for different clinical and research purposes. Discrete, categorical disease entities and dimensions of continuous variation are not mutually exclusive means of conceptualizing psychiatric disorders; both are compatible with a threshold model of disease and may account for different or even overlapping psychiatric morbidity (Kendell and Jablensky, 2003). The difference between categorical and dimensional views is diluted because dimensionally measured features can be divided categorically, categories can be used as dimensions, and many categorical disorders include dimensionally defined criteria. In clinical practice and for purposes of research of treatment, categorical diagnoses might be the only practical way to classify the disorders, but in etiological and epidemiological studies, dimensional views can add important information. The reliable characterization and validation of sub-syndromal states similar to BD would enhance research on genetic markers and modes of genetic transmission, provide an approach for identifying individuals at increased risk for development of BD, and permit the evaluation of early intervention treatments (Goodwin, 1990). After conducting long follow-up studies on both MDD and BD, Judd et al. (Judd et al., 2003b) recently recommended a combination of categorical and dimensional views of BD, stating:

The number of significant differences between BP (bipolar disorder) I and BP II presents an argument to support the conceptualization of these two disorders as being different illnesses. At the same time, there are a sufficient number of qualitative similarities between BP I and BP II to suggest that they exist in a clinical spectrum... BP I and BP II may thereby represent, respectively, manic and depressive extremes in an affective liability threshold model.

4.2 Comorbidity of bipolar disorder and major depressive disorder

Unipolar and bipolar mood disorders are highly comorbid (Szadoczky et al., 1998; de Graaf et al., 2003). This co-occurrence of mental syndromes is important for both theoretical and clinical reasons. In investigating possible etiological and phenomenological continuities and differences between MDD and BD, information on patterns of comorbid disorders and the possible dependence of these patterns on illness episodes, phases, subtypes, or other factors, such as gender, is required. From a clinical perspective, presence of comorbidity has a profound impact on course, prognosis, outcome, and quality of episodes of mood disorders (Kessler et al., 1999; Pini et al., 1999; Dunayevich et al., 2000; McElroy et al., 2001; Dittmann et al., 2002; Boylan et al., 2004; Simon et al., 2004b; Gaudiano and Miller, 2005; Strakowski et al., 2005), increasing healthcare utilization (Cassidy et al., 2001b) and complicating treatment (Colom et al., 2000;

McIntyre et al., 2004; Simon et al., 2004a; Gaudiano and Miller, 2005; Singh and Zarate Jr, 2006). To date, the psychiatric comorbidity of unipolar MDD has been more extensively investigated, whereas the picture of differences in the overall pattern of comorbidity between bipolar I and II disorders and unipolar and bipolar disorders appears more fragmentary.

4.2.1 Definition of the concept

Comorbidity refers to the co-occurrence of two or more distinct disorders in one person over a defined period of time. The concept has been used in general medicine and applied to psychiatry initially for research purposes, especially since the construction of DSM-III (APA, 1980). The *categorical approach* to diagnosis used in the DSM assumes that one disorder is present or absent according to the presence or absence of specified criteria, thus allowing for several distinct disorders to be present at the same time. A *dimensional view* of comorbidities is widely used, particularly in describing personality. Three main alternative theoretical models of psychiatric comorbidity have been presented: 1) the co-occurrence of multiple disorders is better reformulated as complexity of many psychiatric conditions, and co-occurrence of discrete diseases as an artifact of the existing diagnostic systems, 2) although psychopathology consists of discrete entities, current diagnostic categories do not fully reflect these entities and require simplification, further elucidation, or both in various areas of comorbidity; and 3) the nature of heterogeneity is intrinsic, consisting partly of true disease entities and partly of maladaptive response patterns such as anxiety (Maj, 2005).

4.2.2 Current comorbidity of bipolar disorder

In clinical studies reporting current comorbidity of BD I and II (Table 5), total axis I comorbidity has been estimated to be 40% (McElroy et al., 2001), anxiety disorders 30% (McElroy et al., 2001; Simon et al., 2004a), and substance use disorders 4-13% (McElroy et al., 2001; Simon et al., 2004a) or as high as 42% (Strakowski and DelBello, 2000). Only some areas of comorbidity have been investigated in BD [recently reviewed in (McIntyre et al., 2004; Bauer et al., 2005a; Krishnan, 2005)], because no study has reported all structurally assessed axis I and II disorders, most studies have been conducted using DSM-III-R criteria, bipolar II has almost always been underrepresented, and estimates of prevalence of comorbid disorders in psychiatric settings may be skewed due to poor recognition of BD.

Few studies (McElroy et al., 2001; Bauer et al., 2005a) describe the overall pattern of current axis I comorbidity, although current prevalences correspond to the clinical situation better than lifetime prevalences. This is probably because psychiatric comorbidity should be evaluated only in euthymic patients. However, it is theoretically relevant to determine the extent to which the current phase affects prevalences of comorbidity and how constant comorbid disorders remain in follow-up. Only fragmentary information from highly selected populations with BD is available. One study that

evaluated cross-sectionally the presence of two current axis I disorders in manic and mixed patients (Dilsaver and Chen, 2003) reported lower prevalences in manic patients, which is supported by lower lifetime axis I prevalences in manic patients in another study (Dell'Osso et al., 2000). Lifetime prevalences of comorbidity in psychotic patients were highest in depressive BD I patients and lowest in manic patients in one study (McElroy et al., 1995); in another study, no differences in lifetime comorbidity of distinct anxiety disorders were found (Dell'Osso et al., 2000). Thus, it remains controversial whether and, if so, by how much current illness phase affects prevalences of axis I disorders in BD. Axis II diagnoses may also be inflated by the presence of a current mood episode (Peselow et al., 1995).

4.2.3 Comorbidity of bipolar disorder during lifetime

Several clinical studies have reported lifetime prevalences of comorbid DSM-IV axis I disorders in BD (McElroy et al., 2001; Suppes et al., 2001; Dittmann et al., 2002; Henry et al., 2003; Judd et al., 2003b; Simon et al., 2004a; Bauer et al., 2005a), but information is more conflicting than on current prevalences. Total axis I lifetime comorbidity in bipolar patients has been estimated at about 60-80% (Pini et al., 1999; McElroy et al., 2001; Suppes et al., 2001; Simon et al., 2004a; Bauer et al., 2005a) or as low as 35% (Vieta et al., 2000; Vieta et al., 2001; Dittmann et al., 2002). More specifically, estimates of lifetime prevalence of comorbid anxiety disorders vary between 42% and 56% (McElroy et al., 2001; Henry et al., 2003; Boylan et al., 2004; Simon et al., 2004a; Bauer et al., 2005a). The reported lifetime prevalences of substance use disorders in BD are higher in recent American studies (33-72%) (Kay et al., 1999; Cassidy et al., 2001b; McElroy et al., 2001; Suppes et al., 2001; Judd et al., 2003b; Simon et al., 2004a; Bauer et al., 2005a) than in European studies (15-26%) (Pini et al., 1999; Vieta et al., 2000; Vieta et al., 2001; Dittmann et al., 2002) [for review including older studies, see (Cassidy et al., 2001b; Bauer et al., 2005a)].

The prevalence of personality disorders appears higher in studies focusing only on axis II disorders (30-50%) (Peselow et al., 1995; Ucock et al., 1998; Kay et al., 1999; Brieger et al., 2003; George et al., 2003) than in studies also including axis I disorders (25-33%) (Colom et al., 2000; Vieta et al., 2000; Vieta et al., 2001). The prevalence of axis II diagnoses may also be inflated by the presence of a current mood episode (Peselow et al., 1995); a more accurate view would likely be achieved by using additional informants (Peselow et al., 1995). However, the presence of a personality disorder may also influence the likelihood of a mood episode.

No differences between bipolar I and II have been found in total axis I (McElroy et al., 2001; Suppes et al., 2001; Dittmann et al., 2002) and substance use disorders (McElroy et al., 2001; Suppes et al., 2001; Dittmann et al., 2002; Judd et al., 2003b), but anxiety disorders are reported to be either equally distributed (McElroy et al., 2001; Suppes et al., 2001; Dittmann et al., 2002) or up to twofold in BD II (Henry et al., 2003; Judd et al., 2003b) (Table 5).

Table 5. Differences in comorbidity of BD I and II patients

Comorbidity during lifetime	BD I>BD II	BD II>BD I	No statistical difference BD I vs. BD II
Axis I disorders			67% vs. 57% (McElroy et al., 2001) 35.9% of 108 vs. 37.8% of 38 (Dittmann et al., 2002) 146/214 (68%) vs. 30/47 (64%) (Suppes et al., 2001)
Any anxiety disorders		27/71 (38%) vs. 32/135 (23.7%) (Judd et al., 2003b)	100/239 (42%) vs. 22/49 (45%) (McElroy et al., 2001) 92/214 (43%) vs. 23/47 (49%) (Suppes et al., 2001) 10.4% of 108 vs. 18.4% of 38 (Dittmann et al., 2002) 190/360 (5.8%) vs. 53/115 (46.1%) (Simon et al., 2004b)
Any substance use disorders			107/239 (45%) vs. 15/49 (31%) (McElroy et al., 2001) 90/214 (42%) vs. 16/47 (34%) (Suppes et al., 2001) 25.5% of 108 vs. 28.9% of 38 (Dittmann et al., 2002) 67/135 (49.6%) vs. 28/71 (39.4%) (Judd et al., 2003b)
Any eating disorders			11/239 (5%) vs. 6/49 (12%) (McElroy et al., 2001) 9.4% of 108 vs. 0% of 38 (Dittmann et al., 2002) 30/214 (14%) vs. 10/47 (21%) (Suppes et al., 2001)
Comorbidity at intake			
Axis I disorders			84/239 (35%) vs. 28/49 (24%) (McElroy et al., 2001)
Any anxiety disorders	123/360 (34.2%) vs. 22/115 (19.1%) (Simon et al., 2004b)		76/239 (32%) vs. 10/49 (20%) (McElroy et al., 2001)
Any substance use disorders			9/239 (4%) vs. 3/49 (6%) (McElroy et al., 2001)
Any eating disorders			3/239 (1%) vs. 1/49 (2%) (McElroy et al., 2001)

4.2.4 Comorbidity of bipolar disorder compared with major depressive disorder

Some epidemiological studies have assessed differences in comorbidity between MDD and BD. The study with the largest number of bipolar subjects (Szadoczky et al., 1998) reported those with MDD to have more comorbid axis I and total anxiety disorders than those with BD, in contrast to other epidemiological findings (Kessler et al., 1997; Angst, 1998; de Graaf et al., 2003). In these studies, substance use disorders were more prevalent, up to 60%, in BD (Angst, 1998; de Graaf et al., 2003). In the epidemiological studies where differences in only a single comorbid disorder were reported, BD patients had twice as much panic disorder (Chen and Dilsaver, 1995b), obsessive-compulsive disorder (OCD) (Chen and Dilsaver, 1995a), social phobia (Kessler et al., 1999), and substance use disorders (Regier et al., 1990; Winokur et al., 1998) as MDD patients. However, no clinical study has compared the overall comorbidity profile of unipolar and bipolar mood disorders. Only two clinical studies on anxiety disorders were available (Pini et al., 1997; Yerevanian et al., 2001). Both studies described anxiety during lifetime to be more prevalent in MDD, one reporting (comparing psychotic patients) 92% in MDD and 79% in BD (Pini et al., 1997), the other (conducted retrospectively and based on patient charts) 48% in MDD, 48% in BD II, and 12.5% in BD I (Yerevanian et al., 2001). One clinical cohort reported similar prevalence of substance abuse disorders in BD and MDD (12% vs. 15%, ns) (Winokur et al., 1998). One genetic study with a mixed sample of acute and euthymic patients reported several distinct anxiety disorders to be more prevalent in BD (Simon et al., 2003).

On axis II, overall prevalence of personality disorders seems similar, but MDD patients may have more cluster C and BD patients more cluster B personality disorders (Brieger et al., 2003; Schiavone et al., 2004). The overall picture of MDD-BD differences is conflicting and fragmentary due to variation in diagnostic, inclusion, and exclusion criteria, treatment settings, and time periods investigated, and because focusing on single comorbid disorders may result in inflated estimates of prevalence (Melartin et al., 2002). Thus, the existence and quality of differences in the overall comorbidity of mood disorders remain uncertain.

4.3 Course and outcome of bipolar disorder

BD is a recurrent and chronic illness. Even though the natural course of some patients includes full recovery after distinct phases, according to the latest clinical studies, patients spend half of their time in a symptomatic state (Judd et al., 2003b; Judd et al., 2003c; Post et al., 2003; Joffe et al., 2004), interepisode symptoms are extremely common (Judd et al., 2003c), and practically all patients encounter affective recurrences (Dittmann et al., 2002; Judd et al., 2003c; Perlis et al., 2006b). The disorder has a profound influence on functional outcome, psychosocial factors, and quality of life, and because of the burden of the illness on the individual, family, and society, it is among one of the most disabling disorders worldwide (Morselli and Elgie, 2003).

4.3.1 Methods used to assess outcome in bipolar disorder

Several specific features of BD compared with MDD restrict the direct use of scores developed for MDD when assessing BD outcome. Mixed episodes with concomitant depressive and manic symptoms, rapidly changing mood and polyphasic episodes, and even improved functionality in hypomanic phases are among these features. The need for uniform measures of outcome in mood disorders is clear, and future research should aim to develop better instruments for recognizing problems in the current terminology and methodology reported in studies with MDD as well as with BD patients (Keller, 2003; Melartin, 2004). However, in studies with both BD I and BD II, the diversity of methods is not as striking as in studies on MDD.

The life chart methodology (LCM) is a generally accepted instrument of follow-up studies of BD. In this method, the changes of mood are graphically presented, and other factors, such as medication, hospitalizations, or life events, can be added in order to better evaluate the causes and consequences of mood variation. The first life chart methodology, the *Longitudinal Interval Follow-Up Evaluation* (LIFE), was developed for use in the *National Institute of Mental Health* (NIMH) Collaborative Depression Study (CDS) longitudinal reports (Judd et al., 2003b; Judd et al., 2003c) and has been slightly modified with experience (Post et al., 1988). LIFE (or the NIMH life chart methodology, NIMH-LCM) is used in all prospective clinical studies including BD types I and II separately (Tondo et al., 1998; Dittmann et al., 2002; Judd et al., 2003b; Judd et al., 2003c; Post et al., 2003; Joffe et al., 2004). However, despite seemingly using the same life chart, rating has been done based on NIMH criteria of severity ratings (Tondo et al., 1998; Dittmann et al., 2002; Judd et al., 2003b; Judd et al., 2003c; Post et al., 2003) or cut-off scores in Young Mania Rating Scale (YMRS) and Hamilton Depression Scale (HAM-D) in one cohort (Joffe et al., 2004). Moreover, the mood was classified in time periods of whole weeks (Tondo et al., 1998; Judd et al., 2003b; Judd et al., 2003c), while in one cohort (Post et al., 2003) exact durations in days was reported, and in other studies, time units remain unclear (Tondo et al., 1998; Joffe et al., 2004); this presumably affects the prevalence of phases, especially of shorter phases like hypomanias.

4.3.2 Course specifiers

Some special course specifiers for BD are used. A *chronically ill patient* is defined as a person who has been ill (in a monophasic or polyphasic episode) for the preceding two years. In DSM-IV, *rapid cycling* has been defined as four or more distinct episodes (phases) in one year (APA, 1994). *Seasonal type* means that during the previous two years at least two major depressive phases and full remissions or shifts of mood were present at the same time of year, no other depressions were evident, and seasonal depressions dominate over nonseasonal depressions over the lifetime.

The most commonly used course specifier is rapid cycling [for review, see (Kupka et al., 2003)]. In prospective follow-up studies, the prevalence of rapid cycling has been 15-38.2% (Maj et al., 1994; Baldessarini et al., 2000; Tondo et al., 2001; Coryell et al., 2003; Schneck et al., 2004; Kupka et al., 2005). Of patients with rapid cycling at intake, 79.3% had a rapid cycling course during the next year, in contrast to 44.9% of nonrapid cyclers (Post et al., 2003). Rapid cycling is more prevalent in women (Bauer et al., 1994; Maj, 1999; Coryell et al., 2003; Schneck et al., 2004; Yildiz and Sachs, 2004; Kupka et al., 2005). Patients prone to rapid cycling have younger age at onset in most (Coryell et al., 2003; Schneck et al., 2004; Yildiz and Sachs, 2004), but not all (Bauer et al., 1994), studies. Views of the constancy of rapid cycling vary: some see it as a transient, nonfamilial manifestation of BD (Coryell et al., 2003), others suggest a familial form (MacKinnon et al., 2002). A dimensional rather than a categorical definition of rapid cycling has been supported because the number of phases is linearly distributed in all available studies (Bauer et al., 1994; Kramlinger and Post, 1996; Maj, 1999; Kupka et al., 2005).

A *polyphasic episode*, also known as *switching* of mood or "*continuous cycling*" in older literature, is defined as a sequence of changing mood without remission in between (Maj et al., 2002). This specifier is not included in the DSM-IV. Approximately half of patients (47%) are estimated cross-sectionally to have a polyphasic episode (Coryell et al., 1987; Winokur and Kadrmas, 1989; Maj et al., 2002). Correlates of a polyphasic episode include family history of BD in one study (Winokur and Kadrmas, 1989) but not in another (Maj et al., 2002), younger age at illness onset (Winokur and Kadrmas, 1989), and a depressive index phase (Winokur and Kadrmas, 1989); no differences between polyphasic and monophasic patients were found in gender (Maj et al., 2002) or age at first psychiatric contact (Maj et al., 2002). Having polyphasic episodes is not a very constant feature: in a prospective study of 165 BD I patients followed up for 7 years, 13% of the sample had only polyphasic episodes, 33% only monophasic episodes, and 54% both types of episodes (Turvey et al., 1999). In another study with a 10-year follow-up, patients who were monophasic at intake retained the monophasic type in 62/73 cases (84.9%), while a polyphasic course was less constant, in 56% of cases with initially polyphasic episodes (Maj et al., 2002).

4.3.3 Course and outcome of bipolar patients

Several long-term outcome studies (Coryell et al., 1998; Maj et al., 1998; Judd et al., 2002; Tohen et al., 2003; Goldberg and Harrow, 2004) show that BD I is a recurrent and chronic disorder. BD has had a worse naturalistic course than MDD (Angst and Preisig, 1995; Goldberg and Harrow, 2004); one older study reported more episodes and hospitalizations for BD, but a more chronic course for MDD (Winokur et al., 1993b). Syndromal recovery is much more common than symptomatic and functional recovery in both MDD (Keller, 2003) and BD I (Keck et al., 1998; Tohen et al., 2003; Goldberg and Harrow, 2004). Of 134 BD I patients hospitalized for a manic or mixed phase, syndromic recovery occurred in 48%, symptoms continued in 26%, and functional recovery occurred in 24% over a 12-month period (Keck et al., 1998). Median time to full remission in 123 first-admission psychotic BD I patients was 16 weeks, most relapses occurred within the first year after remission, and the median time to recurrence was 22 months (Bromet et al., 2005). A large multicenter study, STEP-BD, that included aggressively treated BD I and II patients but reported the outcome for the whole cohort, stated that 858/1469 patients (58.4%) reached full remission, and 416/858 patients (48.5%) subsequently experienced recurrences during the two years of prospective follow-up (Perlis et al., 2006b). In a cohort of hospitalized manic patients, 10/34 BD I patients (32%) had no full remission during the 10-year follow-up (Goldberg and Harrow, 2004).

Several studies describe recent-onset BD I. In the Cincinnati study with 109 first-episode patients, 50% of patients achieved syndromal recovery, and 35% syndromic recovery within one year (Strakowski et al., 1998). In the McLean-Harvard first-episode study, a cohort of 166 BD I inpatients was followed up for 2-4 years after the first lifetime hospitalization for mania. Practically all patients (162/166; 97.6%) experienced syndromal recovery, but 28% remained symptomatic, only 43% achieved functional recovery, and 57% had new illness episodes (Tohen et al., 2003). Syndromal recovery did not mean functional recovery; subsyndromal symptoms had an impact on functional capacity (Tohen et al., 2003). However, these numbers might only reflect the good recovery found in manic and monophasic episodes since no comparison group in a later phase of illness was used. In the Suffolk County Mental Health Project, a 24-month follow-up of a subgroup of 155 first-admission psychotic BD patients revealed that 74% achieved at least one 2-month period of full remission, but only 41% reached functional remission (Global Assessment of Functioning (GAF) Scale score >70) (Craig et al., 2004). In the NIMH study, 20 patients with a first episode or multiple episodes of BD matched for gender and age showed no differences in the number of episodes per year during the first 2 years (Winokur et al., 1993b). Thus, even in first-episode patients, BD is a severe illness.

BD II patients seem to have a high number of depressive phases and spend half of their time in depressive states in the few prospective studies describing BD II outcome (Coryell et al., 1989; Judd et al., 2003a; Joyce et al., 2004).

4.3.4 Differences between bipolar disorder types I and II in outcome

Only five prospective cohorts report information on outcome of BD I and II patients separately (Coryell et al., 2003; Judd et al., 2003b; Judd et al., 2003c; Post et al., 2003; Joffe et al., 2004; Kupka et al., 2005) (Table 6). The *National Institute of Mental Health* (NIMH) Collaborative Depression Study (CDS) included 146 RDC BD I (Judd et al., 2002) and 86 BD II (Judd et al., 2003a) patients followed up for a median of 16 (2-12) years. The patients spent half of the time syndromatically ill (Judd et al., 2003b). Statistically significant differences in outcome between BD I and II were 1) the duration of the index episode after intake of BD II being two times that of BD I, 2) BD II patients more often having at least one new depressive phase and a higher number of depressive phases, 3) BD II patients spending three times longer in phases of major depression and depressive symptoms, and 4) BD I patients having more hospitalizations, mixed phases, and time in hypomanic symptoms (Judd et al., 2002; Judd et al., 2003a; Judd et al., 2003c). The percentage of weeks with subsyndromal affective symptoms, number of affective episodes, and duration of episodes were similar in both groups (Judd et al., 2002; Judd et al., 2003a; Judd et al., 2003b; Judd et al., 2003c). Thus, these recent findings from the CDS suggest that BD II is an even more chronic disorder than BD I and is characterized by a depressive course (Coryell et al., 1989; Judd et al., 2003b; Judd et al., 2003c; Judd et al., 2005). However, the more depressive course of BD II was not evident in two other studies describing differences between BD I and II, the Stanley Foundation Study (Post et al., 2003) and a clinical study by Joffe et al. (Joffe et al., 2004).

The difference in the prevalence of rapid cycling course according to type of BD remains unclear. Rapid cycling has been more prevalent in BD II than in BD I in some studies (Bauer et al., 1994; Tondo et al., 1998; Maj, 1999; Maj et al., 1999; Coryell et al., 2003; Koukopoulos et al., 2003), but more prevalent in BD I than in BD II in others (Serretti et al., 2002b; Kupka et al., 2005), while still others report equal distribution (Suppes et al., 2001; Dittmann et al., 2002; Schneck et al., 2004). The controversial results might arise from differences in cohort sampling and definitions of phases. BD I and II seem to have similar proportions of polyphasic index episodes (Coryell et al., 1987; Maj et al., 2002).

Table 6. Differences in outcome of BD I and BD II patients in prospective follow-up studies¹

	BD I>BD II	BD II>BD I	No statistical difference BD I vs. BD II
Number of phases, mean±SD (median)			3.3±2.5 (2.5) vs. 4.2±2.6 (4) (Judd et al., 2003b)
Number of depressive phases, mean±SD (median)		2.5±2.4 (0) vs. 0.8±1.1 (2) (Judd et al., 2003b)	
Number of manic phases, mean±SD (median)	0.6±1.0 (0) (Judd et al., 2003b)		
Number of hypomanic phases, mean±SD (median)	0.5±0.8 (0) vs. 0.2±0.5 (0) (Judd et al., 2003b)		
Duration of depression			median 12 weeks vs. 13 weeks (Judd et al., 2003b) mean 5.12±4.62 months vs. 4.51±3.36 months (Tondo et al., 1998)
Duration of mania			median 6 weeks (Judd et al., 2003b)
Duration of hypomania			median 2 weeks vs. 6 weeks (Judd et al., 2003b)
Duration of hypomania or mania			mean 3.31±2.01 months vs. 2.86±2.50 months (Tondo et al., 1998)
Duration of all episodes			median 10 weeks vs. 13 weeks (Judd et al., 2003b) mean 4.06±2.68 months vs. 3.79±2.10 months (Tondo et al., 1998)
At least one new depressive phase		34/46 (73.9%) vs. 41/82 (50.0%) (Judd et al., 2003b)	
Recurrence	Not specified (Dittmann et al., 2002)		0.74±0.86% vs. 0.72±1.34% (Tondo et al., 1998)
Proportion of time in any mood episode mean±SD (median[range])			26.5±27.6 (16.2[0.0-100.0])% vs. 32.7±27.9 (24.0[0.0-100.0])% (Judd et al., 2003b) 19.56±18.44% vs. 16.09±21.47% (Tondo et al., 1998)
Proportion of time in major depressive phase mean±SD (median[range])		5.8±13.2 (0.1[0.0-66.3])% vs. 17.4±22.0 (9.4[0.0-84.6])% (Judd et al., 2003b)	32.8% vs. 33.5% (Post et al., 2003) Not specified (Joffe et al., 2004)
Proportion of time in manic plus hypomanic phases, mean	7.2% vs. 1.0% (Judd et al., 2003c) 2.0% vs. 0.4% (Joffe et al., 2004)		11.8% vs. 7.6% (Post et al., 2003)
Proportion of time in depressive symptoms, mean±SD (median[range])		8.8±14.2 (3[0-82])% vs. 14.2±16.4 (8[0-77])% (Judd et al., 2003c)	
Proportion of time asymptomatic (no depression or mania/hypomania), mean±SD (median[range])			53.4±34.1 (62[0-99])% vs. 44.2±33.1(43[0-100])% (Judd et al., 2003c) Not specified (Joffe et al., 2004; Post et al., 2003)

¹ Judd et al. report findings after the end of intake episode, others during the entire time in follow-up

4.4 Epidemiology of bipolar disorder

4.4.1 Prevalence of bipolar disorder and bipolar spectrum

The lifetime prevalence of BD I is commonly estimated to be about 1%, but in recent epidemiological studies it has varied from 0.2% to 3.3% (Weissman et al., 1988; Kessler et al., 1994; Bebbington and Ramana, 1995; Angst, 1998; Bijl et al., 1998; ten Have et al., 2002; Grant et al., 2005; Kessler et al., 2005; Pini et al., 2005; Schaffer et al., 2006; Perälä, 2007). The 12-month prevalence of BD is reported to be 0.1-2.0% (ten Have et al., 2002; Mitchell et al., 2004; Kessler et al., 2005; Pini et al., 2005). In European studies, a median of 0.9% was calculated (Pini et al., 2005). A rare disorder like BD is difficult to find reliably in population studies, and the results have been highly dependent on the diagnostic instrument (Kessler et al., 1997; Regeer et al., 2004; Angst, 2006; Perälä, 2007). Use of systematic diagnostic tools, such as the *Diagnostic Interview Schedule* (DIS) and the *Composite International Diagnostic Interview* (CIDI), has increased reliability (Bebbington and Ramana, 1995; Kessler et al., 2006), but in a study comparing different screens to detect BD I, many cases still went undetected in population studies (Perälä, 2007). No epidemiologic study has been able to use clinicians as primary diagnosticians; at best, psychologists (Angst, 1998) (prevalence rate of bipolar spectrum over a maximum period of 35 years 5.5%) or professional interviewers (lifetime prevalence of BD I 3.3%) (Grant et al., 2005) were used; thus, prevalences appear to be lower with lay interviewers.

BD I is only infrequently detected in epidemiological studies, but BD II is even more difficult to establish with certainty (Bebbington and Ramana, 1995). With structured interviews conducted by experienced psychiatrists, the diagnostic reliability of BD II can be equal to BD I (Simpson et al., 2002); as noted above, this is not the case in epidemiological studies. Only two studies on adults have given lifetime prevalences separating BD I and II (Szadoczky et al., 1998; Scully et al., 2004), the former found the lifetime prevalence of BD II to be higher (2.0%) than of BD I (1.5%) (Szadoczky et al., 1998), the latter reported the opposite finding (BD II 0.1%, BD I 0.3%) (Scully et al., 2004). The prevalence of hypomania in the *Epidemiological Catchment Area Study* (ECA) database was 0.5%, lower than the 0.8% for mania (Weissman et al., 1988). Even when the proportion of BD II in psychiatric care is known to be at least equal to that of BD I, epidemiological studies seem to find only a small proportion of BD II.

The lifetime prevalence of bipolar spectrum (including mania, hypomania, and soft bipolar spectrum) is estimated to exceed 6% (Angst, 1998; Szadoczky et al., 1998; Judd and Akiskal, 2003; Moreno and Andrade, 2005; Pini et al., 2005; Kessler et al., 2006). In the Zurich study, the DSM-IV criteria of hypomania were modified to be less strict in terms of duration and severity (Angst and Cassano, 2005), and two alternative models were created. The MDD to BD ratio with DSM-IV criteria was 9.4. While the more strict modified criteria yielded a mood disorder prevalence of 49.5% and an MDD to BD ratio of 2.9, the less strict

criteria gave the same prevalence of mood disorders, but a ratio of 1.0 for MDD to BD (Angst and Cassano, 2005). However, the Zurich study cannot be seen as an epidemiological study, and the prevalences seem highly overestimated. The same is true in the EPIDEP study, where the rate of soft bipolar spectrum and MDD was reported to be 3:2 in patients with a major depressive episode in psychiatric care (Akiskal et al., 2006). When the limits are expanded, the prevalences clearly increase, but the broad definitions and the high prevalences of bipolarity can be strongly criticized and their meaningfulness questioned (Patten, 2006).

In Finnish studies, the prevalence of BD has been estimated to be lower than international prevalences (Lehtinen et al., 1990; Veijola et al., 1996; Räsänen et al., 1998; Kieseppä et al., 2004; Perälä, 2007). The most recent Finnish general population study, Psychoses in Finland (PIF) (Perälä, 2007), used several screening methods and structured interviews by psychiatrists to confirm the diagnosis of patients screening positive for psychotic symptoms. The study reported a lifetime prevalence of 0.24% for BD I; with the inclusion of register diagnoses of BD I the prevalence reached 0.42% (Perälä, 2007). The Tampere Depression Project used the Present State Examination as a diagnostic instrument to evaluate the prevalence of BD and MDD in primary care (N=437) and secondary care (N=435). In community health centers, the 12 month prevalence of BD was 2.1%, and in community mental health centers, 7.6% (Sorvaniemi and Salokangas, 2005). In Finland, the Hospital Discharge Register includes the primary and secondary diagnoses of all psychiatric patients who are hospitalized. Previously, the annual rate of BD in all hospitalized patients was estimated at 0.03% (Räsänen et al., 1998). In another study, the annual incidence of BD I was 5.8% (95% CI=5.4 to 6.3) (Kieseppä et al., 2004). The accuracy of register diagnoses of BD I as compared with the SCID interview has been evaluated to be good in a double-blinded study (Kieseppä et al., 2000); however, the accuracy was not evaluated in patients given another diagnosis. Furthermore, comorbid diagnoses are seldom indicated in the Hospital Discharge Register: in only 18% of hospital stays was any comorbidity reported (Sorvaniemi and Hintikka, 2005). Moreover, the register study design is highly vulnerable to undiagnosed BD. Rather than being due to late onset age (Räsänen et al., 1998), the low prevalence and incidence of BD in Finland might indicate severe underreporting of BD: first, not all BD I patients are hospitalized, and second, not all are recognized as bipolar.

4.5 Recognition of bipolar disorder

The majority of BD patients are treated in psychiatric care (Kessler et al., 1997; Morselli and Elgie, 2003), although 26% have never sought help for emotional problems (ten Have et al., 2002). Even in psychiatric settings, BD is all too often incorrectly diagnosed. Given the importance of understanding what leads to missing a diagnosis of BD, surprisingly little information is available on this topic. Clinically, missing (hypo)manic symptoms in anamnesis, lack of systematic evaluation, and some forms of disorder can be suspected to lead to missed diagnosis. Misdiagnosed patients are thought to usually be treated as unipolar depressive, borderline personality disorder, or schizophrenic patients.

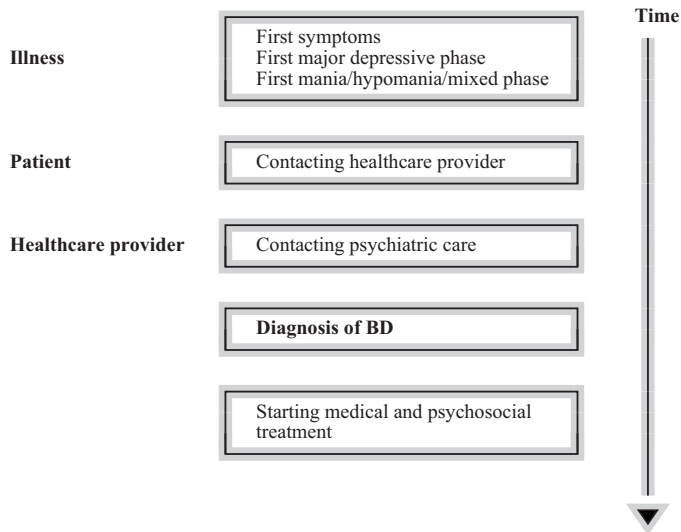


Figure 1. Time to adequate treatment of BD

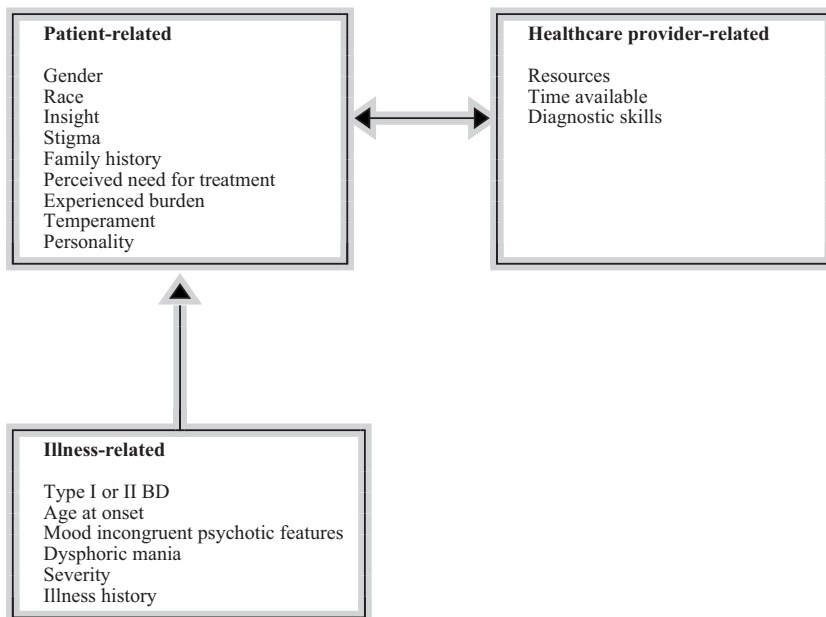


Figure 2. Factors behind unrecognized bipolar disorder

4.5.1 Delay in diagnosis

Correct diagnosis is the basis for all successful treatment. However, in BD, correct diagnosis and treatment (Figure 1) are especially complicated due to several features of the disorder and patients (Figure 2). The most common misdiagnosis of bipolar patients is thought to be unipolar depression, and several reasons for this can be suggested: the first episode in BD is most often depression (Lish et al., 1994; Tondo et al., 1998; Judd et al., 2003b; Morselli and Elgie, 2003), and especially BD II patients spend most of their time in depression (Judd et al., 2002) and have several depressive episodes before the first hypomania (Tondo et al., 1998). Thus, the patient may initially seek help for depression and the switch or preceding bipolar picture may go unnoticed.

Delay from illness onset to the first contact with healthcare, from primary care to psychiatric services, and from initial symptoms to treatment initiation (Kessler et al., 1998; Goldberg and Ernst, 2002), might be several years in psychiatric disorders. The diagnosis of BD appears to be made either during the first year of treatment or after a long delay (Ghaemi et al., 1999; Ghaemi et al., 2000). In a multicenter European study, the bipolar diagnosis in 71% of patients was set by a psychiatrist (Morselli and Elgie, 2003). Thus, for correct diagnosis to be made, the time to psychiatric treatment appears crucial. In patients receiving a bipolar diagnosis with delay, the delay from onset of illness to correct diagnosis was a mean of 5.7 years (Morselli and Elgie, 2003) or 8-10 years (Lish et al., 1994; Hantouche et al., 1998; Tondo et al., 1998; Ghaemi et al., 1999; Ghaemi et al., 2000; Goldberg and Ernst, 2002; Baethge et al., 2003; Baldessarini et al., 2003; Hirschfeld et al., 2003b). In a survey of bipolar members of the US National Depressive and Manic-Depressive Association (Lish et al., 1994; Hirschfeld et al., 2003b), one-third (34%) of respondents had had more than 10 years of treatment before receiving a bipolar diagnosis. The delay from illness onset to treatment is 1-2.7 years longer for BD II (Tondo et al., 1998; Baldessarini et al., 2003) and 1.3 years longer for women (Baldessarini et al., 2003). The delay from first symptoms to mood-stabilizing treatment is 8-10 years (Suppes et al., 2001; Goldberg and Ernst, 2002), being slightly longer for BD II (Suppes et al., 2001). However, correct diagnosis does not equal correct treatment; the factors correlating with unrecognized BD may also result in poor compliance to treatment (Colom et al., 2005; Fleck et al., 2005; Vieta, 2005).

4.5.2 Undiagnosed bipolar disorder

The proportion of BD patients who remain undiagnosed is alarmingly high in various types of cohorts. In two cohort studies (Ghaemi et al., 1999; Ghaemi et al., 2000) of bipolar patients in inpatient or outpatient settings, the proportion of patients diagnosed primarily at intake as unipolar was about 40%. In the French EPIDEP multicenter study (Hantouche et al., 1998), the proportion of BD II patients increased from 22% to 40% when a systematic evaluation of hypomania was conducted. In family practice, of the patients screened for depression, 28/108 (26%) were diagnosed as bipolar with a semistructured

instrument (DSM-III-R) (Spitzer et al., 1990b), and of these, 20/28 (71%) were previously undiagnosed (Manning et al., 1997). In the Netherlands Mental Health Survey and Incidence Study (NEMESIS), 73/136 patients (54%) went unrecognized because they had not contacted healthcare or had failed to disclose their manic symptoms (ten Have et al., 2002). In the Polish DEP-BI sample of 246 outpatients with recurrent major depression, 48/246 (19.5%) were found to have previously unrecognized BD I and 86/246 (35.0%) BD II in a structured interview (Kiejna et al., 2006). In a post-detoxification inpatient substance abuse program for men, 85/295 patients (28.8%) had BD I or II, and of these, 42/85 (49%) had not been previously diagnosed with BD (Albanese et al., 2006). MDD was the most commonly assigned misdiagnosis (Albanese et al., 2006). In a Danish register study, 2315/4116 patients (56.2%) who at any time between the years 1994 and 2002 received a diagnosis of BD got the diagnosis at the first treatment period, and 38.6% of patients who initially had another diagnosis were diagnosed first as MDD patients (Kessing, 2005b); however, the diagnoses were only made based on the register. In summary, bipolar patients with the diagnosis may represent only a fraction of the subjects with the disorder, and the true epidemiological extent of this problem awaits reliable estimation.

4.5.3 Differences between recognized and unrecognized bipolar disorder patients

No clinical studies have been published in which the characteristics of clinically unrecognized bipolar patients in psychiatric care are reported. The factors affecting use of health services in general are well analyzed (Andersen, 1995). In studies reporting reasons for delayed diagnosis or treatment of BD (Figure 3), delay was dependent on illness characteristics [age at onset (Goldberg and Ernst, 2002), type I or II (Akiskal et al., 2003; Baethge et al., 2003; Baldessarini et al., 2003), mood incongruent psychotic features (Azorin et al., 2006), dysphoric mania (Akiskal et al., 1998; Dilsaver and Akiskal, 2005), illness severity (Goldberg and Ernst, 2002; ten Have et al., 2002) or course (Baldessarini et al., 2003)], patient characteristics like gender (Lish et al., 1994; Baethge et al., 2003; Baldessarini et al., 2003; Hirschfeld et al., 2003b), race (Bhugra and Flick, 2005), or cyclothymic temperament (Akiskal et al., 2003), communication by the patient [insight, stigma, family history (Hambrecht, 1995), perceived need (Mojtabai et al., 2002; ten Have et al., 2002), the burden experienced (ten Have et al., 2002; Hirschfeld et al., 2003b)], and care provider [resources (Bhugra and Flick, 2005), available time, diagnostic skills (Lish et al., 1994; Hirschfeld et al., 2003b)].

4.5.4 Consequences of missed diagnosis

The delays in diagnosis are alarmingly long considering the serious burden caused by the delay and the adverse consequences of inappropriate treatment (Hantouche et al., 1998; Baldessarini et al., 2003; Hirschfeld et al., 2003b). Undiagnosed bipolar patients may be four times more likely to attempt suicide and 1.5 times more likely to be hospitalized than diagnosed patients, generating considerable extra costs to society (Li et al., 2002; Birnbaum et al., 2003; Shi et al., 2004). In a register study, 78% of unrecognized bipolar

patients had serotonin-selective reuptake inhibitors (SSRIs) as monotherapy (Shi et al., 2004) – unfortunately, also among the recognized patients, this proportion was 50% (Birnbaum et al., 2003; Shi et al., 2004). However, treatment latency might not have an effect on the efficacy of treatment. Shorter treatment latency has been connected to greater morbidity before lithium treatment; while in treatment, the patients with shorter treatment latency had better response but a similar proportional change in outcome as patients with longer delay (Baldessarini et al., 1999).

4.5.5 Screening for bipolar disorder

At present, the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000; Hirschfeld, 2001) appears to be the most useful screening instrument for detecting BD I and II. Nevertheless, it may be somewhat less specific than originally intended (Hirschfeld et al., 2000; Isometsä et al., 2003; Miller et al., 2004), without modification not be optimally sensitive for BD II patients (Hirschfeld et al., 2003a; Isometsä et al., 2003; Miller et al., 2004; Zimmerman et al., 2004), and some other screens may be better for detecting bipolar spectrum. Use and development of different diagnostic screens for BD and bipolar spectrum are useful not only for purposes of research, but also clinically to improve correct and early diagnosis of BD and to direct diagnostic attention to patients at the highest risk of BD. Thus, finding a suitable screen depends on the target group to be screened as well as on the purpose of screening; for instance, high-risk adolescents might require a different screen than that for depressed adult inpatients. However, a diagnosis of BD should not be based exclusively on any screen, but on careful and often repeated diagnostic evaluation, with several informants, and preferably with a prospective follow-up of mood (Zimmerman et al., 2004; Akiskal and Benazzi, 2005; Baldassano, 2005; Hirschfeld et al., 2005; Phelps, 2006).

5. AIMS OF THE STUDY

We investigated the recognition, clinical characteristics, comorbidity, and outcome of 191 BD I and II patients with an acute phase in secondary level psychiatric care.

Specific aims of the study were as follows:

- I To obtain a comprehensive view of the clinical epidemiology of BD I and II in secondary level psychiatric settings.
- II To describe differences in current comorbidity between BD I and II and (unipolar) MDD, and between current and lifetime axis I and II comorbidities in BD.
- III To investigate predictors of missed or incorrect clinical diagnosis of psychiatric patients with BD I and II.
- IV To investigate whether the course of BD type II is more depressive than that of BD I, and if so, the underlying factors causing this difference.

6. METHODS

6.1 General study designs

The Jorvi Bipolar Study (JoBS) is a collaborative research project between the Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki, Finland, and the Department of Psychiatry, Jorvi Hospital, Helsinki University Central Hospital (HUCH), Espoo, Finland. The catchment area (pop. 261 116 in 2002) comprises the adjacent cities of Espoo, Kauniainen, and Kirkkonummi, and the Department of Psychiatry at Jorvi Hospital provides secondary care psychiatric services to the area's residents. The second report (Study II) also included major depressive disorder (MDD) patients from the Vantaa Depression Study (VDS). The VDS was carried out in conjunction with the Department of Psychiatry of the Peijas Medical Care District. The Ethics Committee of HUCH approved the study protocol of VDS in 1996 and of JoBS in 2001.

Because of the different focuses of the studies, the publications had different patient compositions as presented in Table 7.

Table 7. Composition of cohorts in the original publications

Cohort		
	Jorvi Bipolar Study (bipolar patients)	Vantaa Depression Study (major depressive patients)
		Total number of patients
Study I	Patients evaluated at baseline, N=191	191
Study II	Patients evaluated at baseline, N=191	Patients evaluated at baseline, N=269
Study III	Patients evaluated at baseline, excluding 8 BD NOS patients, N=183	183
Study IV	18-month follow-up, N=160	160

6.2 Screening

Using the Mood Disorder Questionnaire (MDQ), all in- and outpatients at the Department of Psychiatry at Jorvi Hospital who currently had a possible new phase of DSM-IV BD were sought from January 1, 2002 to February 28, 2003. During the given period, attending mental health professionals at the Department of Psychiatry screened with MDQ every patient aged 18-59 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. In addition, despite a negative MDQ screen, patients were included as positive if suspected to have BD due to a clinical diagnosis of BD or pertinent symptoms (N=28). A clinical diagnosis of ICD-10 schizophrenia was an exclusion criterion for screening. Based on the pilot study of the JoBS (Isometsä et al., 2003), the response to MDQ item 3 ("problems due to episodes") was ignored. The sampling procedure is presented in Figure 3. After a positive MDQ screen, or suspicion of BD, the patient was fully informed about the study project and written informed consent was requested. Altogether, 1630 patients were screened, 546 of whom proved to be MDQ-positive or suspected bipolar (Figure 3).

The detailed methodology of VDS has been reported elsewhere (Melartin et al., 2002). In brief, JoBS was planned to be comparable with the VDS. In the VDS, patients were screened for MDD in an acute mood episode, and all psychiatric patients aged 20-59 years 1) seeking treatment, 2) referred to treatment, or 3) already in treatment with an acute deteriorating clinical state were screened for MDD. The screening instruments in the VDS included the five screening questions for major depression from the Schedules for Clinical Assessment of Neuropsychiatry (SCAN) (Wing et al., 1990) and the Scale for Suicidal Ideation (SSI) (Beck et al., 1979). The screen was considered positive if the patient had a) one positive item among the five screening questions for depression from SCAN, or b) a score of six or more on SSI (Beck et al., 1979). Exclusion criteria in the VDS included BD I and schizophrenia. A total of 806 patients were screened; 703 screened positive, and 161/703 (22.9% of the screened) refused the interview.

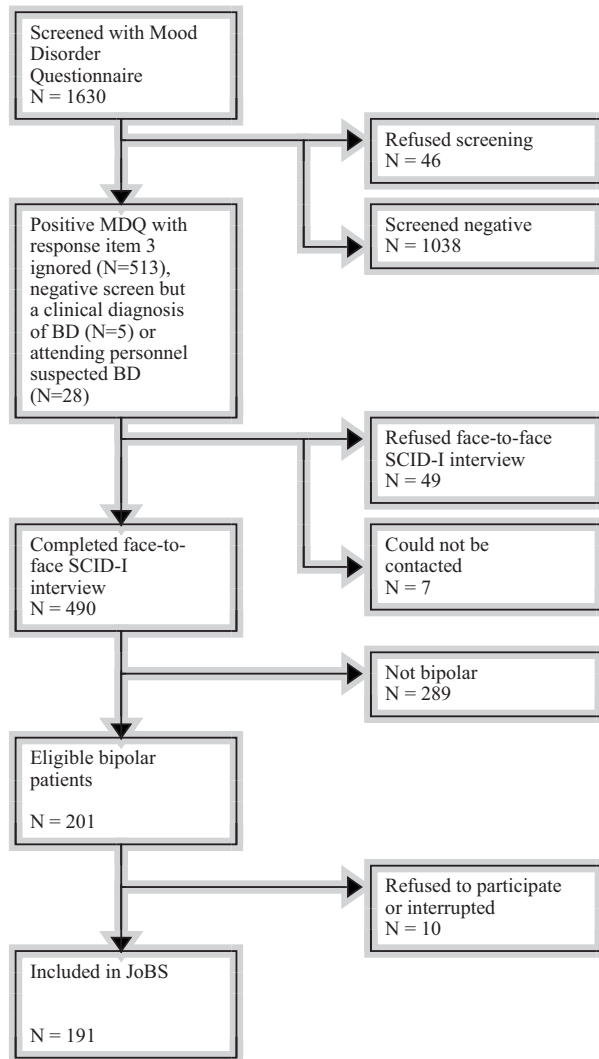


Figure 3. Screening of eligible bipolar patients in the Jorvi Bipolar Study

6.3 Baseline evaluation

6.3.1 Diagnostic measures

In the second phase of the JoBS, a diagnosis was made based on two separate interviews using all available information from the face-to-face interviews and psychiatric records; if the diagnosis was uncertain, attending personnel, family members, or other informants were contacted. BD was diagnosed using the Structured Clinical Interview for DSM-IV Disorders, researcher version with psychotic screen (SCID-I/P) (First et al., 2002). The SCID-I was supplemented with a section for diagnosing mixed episodes. Of the 546 patients with positive screens, 490 were interviewed (median delay from screening to interview 8.8 days), and 201 patients (12.3% of the screened, 38.4% of positive screens) were assigned a diagnosis of BD after the SCID-I interview. The diagnosticians were all psychiatrists (OM, HV, PA, KS, SL, Marita Pippingsköld), and weekly meetings were held to solve diagnostic problems. Of previously diagnosed patients, 12 were not considered bipolar at interview, 9 refused to participate, and 6 could not be contacted. The patients who refused to participate at some stage (N=105) were older than participants (median 44 vs. 37.7 years for the cohort). The final study group included in the analyses consisted of 191 DSM-IV bipolar I and II patients with a current phase. The current episode was defined according to DSM-IV criteria and could be monophasic or polyphasic. Also included as bipolar II were those bipolar NOS (not otherwise specified) patients with hypomania of 2-3 days, or depressive mixed states (DMX3=three or more simultaneous intra-episode hypomanic symptoms present for at least 50% of time during a major depressive episode) as defined by Benazzi and Akiskal (Benazzi and Akiskal, 2001), that clearly belonged to the bipolar II group. The soft bipolar spectrum was excluded.

Inter-rater reliability was tested using videotaped interviews that were then blindly assessed by another diagnostician. In order not to reveal the diagnosis made by the first interviewer, response to all items was requested and neither hints of inclusion or exclusion nor the diagnosis were allowed on the tape. In the 20 randomly selected, videotaped diagnostic interviews, agreement was complete (κ for BD overall= 1.0; also specifically, bipolar I=1.0 and bipolar II=1.0).

In the second phase of the VDS, a current episode of MDD was diagnosed (and BD excluded) using the World Health Organization (WHO) *Schedules for Clinical Assessment in Neuropsychiatry*, version 2.0 (SCAN) (Wing et al., 1990). To exclude substance-induced mood disorder, MDD patients who were currently abusing alcohol or other substances were interviewed after two to three weeks of abstinence. The final study group included in the analyses consisted of 269 MDD patients in VDS, all with a current episode. Inter-rater agreement in diagnostic interviews was excellent (κ =0.86) (Melartin et al., 2002) .

6.3.2 Observer and self-report scales

In the JoBS, only patients with BD were further evaluated. In the third phase, the current symptomatology of the index episode was evaluated using the *Young Mania Rating Scale* (YMRS) (Young et al., 1978) and the 17-item *Hamilton Depression Scale* (Ham-D-17) (Hamilton, 1960); the patient filled in the 21-item *Beck Depression Inventory* (BDI) (Beck et al., 1961) and the Beck Anxiety Inventory (BAI) (Beck et al., 1988). In bipolar patients, some delay occurred from screening to estimating symptom scores in the first interview, which especially in 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; they were by interview euthymic (N=2) or had shifted to depression, but did not fulfill the time criteria of two weeks (N=8).

6.3.3 Other characteristics

Information on demographic characteristics, variables for prior illness history, and preceding treatment using a graphic retrospective life chart was collected. *Age at illness onset* was defined as the time of onset of the first mood episode fulfilling DSM-IV criteria. *Age at treatment* was the first contact with psychiatric care irrespective of diagnosis; if this was not caused by a mood episode, the delay from episode to treatment could be negative (N=5). Definitions of *adequate acute-phase pharmacotherapy* were based on published treatment guidelines (Sachs et al., 2000; APA, 2002; Grunze et al., 2002; Goodwin and Young, 2003; Grunze et al., 2003). The treatments were defined irrespective of dosage, serum concentration, or duration of treatment as follows: 1. Adequate treatment for bipolar depression – monotherapy with lithium or lamotrigine or combinations of lithium, valproate, carbamazepine, or olanzapine with an antidepressant. The combination of lamotrigine with an antidepressant was interpreted as inadequate treatment in bipolar I patients. 2. Adequate treatment for mania/hypomania – monotherapy or combinations of lithium, valproate, carbamazepine, atypical antipsychotics, or haloperidol. Treatment was interpreted as inadequate if an antidepressant was used. 3. Adequate treatment for mixed/depressive mixed state – defined the same as for mania, except that treatment was interpreted as inadequate if a conventional antipsychotic was used. 4. Treatment for rapid cycling – monotherapy or combinations of lithium, valproate, or carbamazepine. Treatment with lamotrigine was interpreted as adequate for BD II patients. Treatment was classified as inadequate if an antidepressant was used. At baseline, mood stabilizing treatment was prescribed to 56% of patients (89/160) followed up for 18 months and to 87% of patients (84/97) with a correct diagnosis of BD I or BD II. The adequacy of psychopharmacological therapy at acute phase is described in detail elsewhere (Arvilommi et al., 2007), and psychopharmacologic and psychosocial treatments during follow-up will be reported and discussed in detail in a subsequent paper. Patients were rated as clinically recognized or unrecognized. To avoid diagnostic bias caused by the study itself, the clinical bipolar diagnosis had to have been made before the research MDQ screening.

6.3.4 Assessing comorbidities in Study II

Current comorbid psychiatric diagnoses were assigned during an acute phase of MDD or BD. However, in case of a manic or mixed episode severe enough to require hospitalization, the second diagnostic interview was conducted when the patient was discharged from the hospital, typically after about three weeks. The researcher made full DSM-IV axis I diagnoses (SCID-I in JoBS, SCAN in VDS). Due to differences between the diagnostic tools in the JoBS and the VDS, substance use disorders are comparable only concerning current alcohol dependence, which also influences the total axis I comorbidity. The SCID-II for DSM-III-R (Spitzer et al., 1990a) (VDS) or DSM-IV (First et al., 1997) (JoBS) personality disorders was used to assess all comorbid diagnoses on axis II, which were modified for between-group analyses in two diagnoses. Antisocial personality disorder was adapted to DSM-IV criteria by deleting items "irresponsible parenting" and "failure to sustain a monogamous relationship", and fusing two items exploring consistent responsibility from DSM-III (VDS). DSM-IV borderline personality disorder was changed to DSM-III-R by deleting item "stress-related paranoid ideation". This affected the prevalences in BD vs. MDD comparisons, excluding no MDD patients with antisocial personality disorder, but 8 BD patients with borderline personality disorder were lost. Within the bipolar group, unmodified DSM-IV criteria were used in within-group analyses.

6.4 Follow-up procedure

6.4.1 Study drop-outs

Of the total of 191 subjects with a current phase initially included in the study, at six months, 5 (2.6%) refused to participate, 15 (7.9%) were missing, and 171 (89.5%) were interviewed. Of missing patients, reliable information was available for 5 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 1 year) follow-up were excluded. Thus, 160/188 living patients (85.1%) were included in the 18-month analyses.

Of BD II patients, 7 converted to BD I due to mania, 3 due to a mixed phase *during the follow-up* (between beginning of index phase and 18 months later). Gender distribution and age of patients who had converted were similar to those who had not converted. In analyses, all patients were treated according to their baseline diagnosis (results were similar in alternative analyses with 18-month diagnoses). In addition, based on a similar clinical picture, 8 BD NOS patients at intake were included in the analysis as BD II patients. Of these BD NOS patients, 7 were followed up for 18 months, with two (29%) converting to BD II.

The patients included in the 18-month analysis were older (median 38.0 vs. 28.8 years, $U=1799.5$, $p=0.013$), more often had professional education (105/160 (65.6%) vs. 10/31 (32.3%), $\chi_1^2=12.1$, $p=0.001$), had a longer duration of illness before intake (12.2 vs. 9.2 years, $U=1924$, $p=0.048$), and had an older age at first hospitalization (31.5 vs. 23.5 years, $U=474$, $p=0.021$) than patients not included in this analysis. No difference between BD I and II was detected in the rate of attrition. Baseline characteristics of the 160 BD patients who completed the 6- and 18-month follow-ups are shown in Study IV, Table 1. The mean time to the 18-month follow-up interview in the total sample was 20.3 ± 4.6 months, for BD I 20.4 ± 4.7 months and for BD II 20.2 ± 4.6 months ($t_{158}=0.326$, $p=0.7$) (Study IV, Table 1).

6.4.2 Integration of information into a life chart

After baseline assessments, the outcome was investigated at 6- and 18-month interviews, which typically lasted 2-3 hours. 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. Besides information on symptom ratings and visits to attending personnel, change points in the psychopathologic states were also inquired about using probes related to important life events in order to improve the accuracy of the assessment. All available data were then integrated into a graphic life chart based on DSM-IV criteria, analogous to the life chart used in the VDS (Melartin et al., 2004). The onset of index phase and the index episode were evaluated retrospectively.

6.4.3 Definitions for time periods of life chart

An episode, defined according to DSM-IV criteria, can be *monophasic* or *polyphasic*. Here, *a phase* refers to a monophasic episode or a single phase of a polyphasic episode, and similarly, *an episode* 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 2 days (Angst, 1998; Judd et al., 2003a; Akiskal and Benazzi, 2005). *Depressive mixed phases* (=three or more simultaneous intra-episode hypomanic symptoms present for at least 50% of time during a major depressive episode), as defined by Benazzi and Akiskal (Benazzi and Akiskal, 2001), were also evaluated. A *mood episode* will be used here to mean any monophasic depressive, manic, hypomanic, mixed, or depressive mixed phase, or a polyphasic episode, ending when the full criteria of the final phase are no longer fulfilled. *Substance-induced mood episodes* had the same definitions for a phase as above, but were induced by any psychoactive substance; they were not included in the analyses of numbers or durations of time periods. *States of subsyndromal symptoms* (including prodromal or residual symptoms) were rated when the patient was not euthymic and did not fulfill the criteria of a phase; durations of more than 1 week for hypomanic symptoms, and more than 2 weeks for depressive symptoms and cyclothymia were required. A state of euthymic mood was used as a state variable when the duration of euthymia was more than 2 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*, while full criteria of a DSM-IV mood episode were not met, some symptoms were present; in *full remission*, no DSM symptoms were present. In statistical analysis, the patient had reached remission if, as in the DSM-IV, in at least 2 consecutive months criteria were not met for a mood episode. *Relapse* was defined as a return of a mood episode after a period of less than 2 months with symptoms below the mood episode threshold. *Recurrence* was defined as emergence of symptoms sufficiently severe to satisfy criteria for a new mood episode after at least 2 consecutive months of partial or full remission.

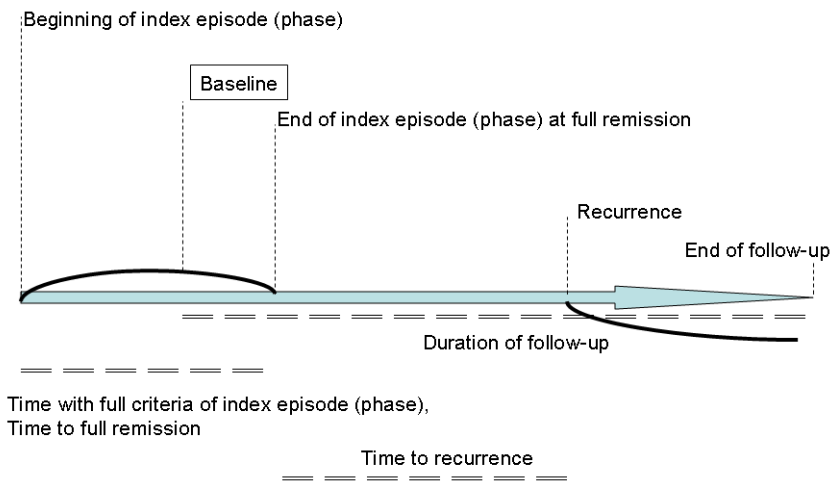


Figure 4. Definitions for time periods of life chart; an example of a monophasic patient with full remission

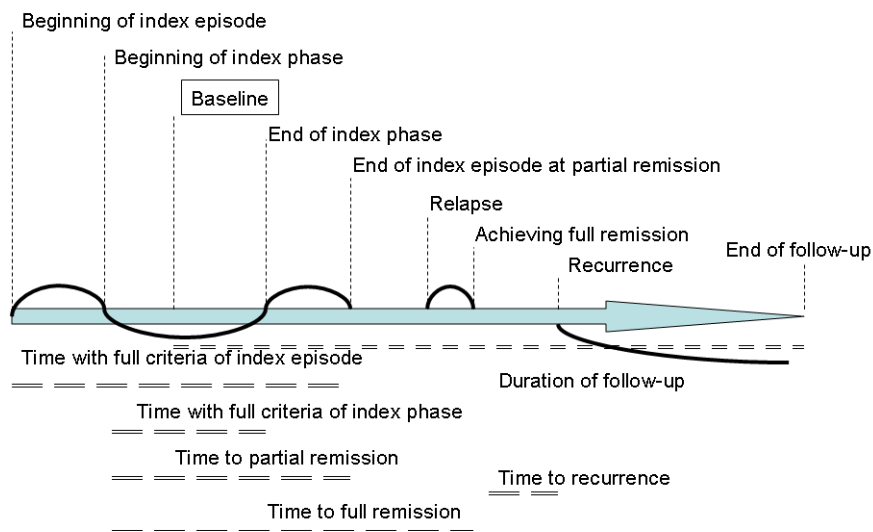


Figure 5. Definitions for time periods of life chart; an example of a polyphasic patient with partial remission preceding full remission

6.4.4 Principal outcome measures

Five principal outcome measures were evaluated (Figures 4 and 5). 1) *The proportion of time in different symptom states during follow-up* is time spent in any state divided by the duration of follow-up. 2) *Time with full criteria of the index phase* was counted from the onset of the index phase to a state not fulfilling the full criteria of that phase. 3) *Time with full criteria of the index episode* was counted from the onset of the index episode to the end of the last phase that met the criteria of a depressive, manic, hypomanic, mixed, or depressive mixed phase. 4) *Time to full remission* is time from the beginning of the index phase to onset of a state of full remission lasting at least 2 consecutive months. 5) *Time to recurrence from the beginning of remission* is the time from onset of remission lasting at least 2 consecutive months to onset of a new episode.

6.5 Statistical methods

The Pearson's chi-square statistic and Fisher's exact test were used to evaluate categorical and nonparametric data, the Mann-Whitney U-test or Kruskal-Wallis test to compare continuous variables not normally distributed, and the two-sample t-test for continuous variables normally distributed. Logistic regression models were used to adjust for confounding factors. Only those who completed the whole 18-month follow-up were included in the analyses of outcome. Despite multiple testing, for descriptive purposes, the results in univariate analyses are reported as significant at $p \leq 0.05$. The logistic regression models (Study I, II, and III) or the Kaplan-Meier analyses, Cox models, and linear regression models (Study IV) constitute the main findings. SPSS software, version 11.0 or 12.01, was used.

7. RESULTS

7.1 Clinical characteristics of bipolar I and II disorders (Study I)

The final sample consisted of 90 bipolar I and 101 bipolar II patients (Table 8), the latter including eight bipolar NOS patients. Overall, approximately half (52.9%) of the patients were women; significantly more men had BD I and women BD II. The mean age of the cohort was 37.7 years, and BD I patients tended to be older than BD II patients (Table 8). The men were significantly older. Every fourth patient (25.7%) was divorced or widowed. Two of five patients (39.8%) had no professional education, BD I less than BD II; on the other hand, one of six patients (16.2%) had university-level education, BD I more often.

7.1.1 Analysis of screening

The effect of the ignored response to MDQ item 3 (distress from symptoms) in the sample was evaluated. Of the cohort, 18% of BD I and 27% of BD II patients would have been excluded using the standard cut-off of 3-4 in item 3 (1 BD I and 4 BD II patients responded "1"; 15 BD I and 23 BD II patients responded "2"), and 38 patients had left the item unanswered. Overall, two of five patients (42%) would have gone undetected without the modification. The screening considerably increased the detection rate of BD, by an estimated 51%.

7.1.2 Clinical history

An average patient in the cohort had an age at onset of about 20 years and now, being near 40 years, had gone through about 5 lifetime episodes (Table 8). Over half (58.4%) of BD II and a quarter (25.6%) of BD I patients had no prior hospitalizations, with BD I patients having more hospitalizations. Most patients (85%) had had at least one polyphasic episode during their lifetime. BD I patients had accumulated more (hypo)mania and polyphasic episodes than BD II patients. Lifetime psychotic symptoms were reported in half (N=95/191, 49.7%) of the cases, twice as often in BD I (Table 8).

Table 8. Main differences between BD I and BD II in the Jorvi Bipolar Study in sociodemographic and clinical characteristics at intake (N=191)

Characteristics ¹	BD I (N=90)	BD II (N=101)	Total BD (N=191)	Test of significance Test statistic	p
Sociodemographic characteristics					
Male	50 (55.6%)	40 (39.6%)	90 (47.1%)	$\chi^2=4.86$, df=1	p=0.027
Age at entry, years	39.5±12.0,37.9	36.0±12.1,35.0	37.7±12.1,36.5		NS
Not cohabiting	25 (27.8%)	36 (35.6%)	61 (31.9%)	$\chi^2=7.2$, df=1	NS
No professional education	30 (33.3%)	46 (45.5%)	76 (39.8%)		NS
Disability pension	28 (31.1%)	15 (14.9%)	43 (22.5%)		p=0.007
Family history of BD	15 (16.7%)	22 (21.8%)	37 (19.4%)		NS
Illness characteristics					
Age at onset of first episode, years	24.1±10.5,21.2	23.3±9.2,21.2	23.7±9.8,21.2		NS
Number of lifetime phases	18.9±35.1,10	16.1±21.5,10	17.4±28.7,10.0		NS
Number of lifetime major depressive phases	8.0±13.2,5.0	8.0±11.1,5.0	8.0±12.1,5.0	$\chi^2=22.2$, df=1	NS
Psychotic symptoms during lifetime	62 (63.9)	35 (36.1)	97 (50.8)		p<0.001
History of treatment					
Age at psychiatric care, years	30.6±10.8,27.3	30.6±11.4,27.4	30.6±11.1,27.3		NS
Age at first hospitalization, years	32.3±10.7,30.6	32.9±10.6,32.9	32.6±10.6,31.4		NS
Number of hospitalizations if hospitalized	5.2±6.3,3.0	2.9±3.1,2.0	4.3±5.4,2.0	U=953.5, Z=-2.89 $\chi^2=21.0$, df=1	p=0.004
No previous hospitalization	23 (25.6%)	59 (58.4%)	82 (42.9%)		p<0.001
Delay from first episode to treatment, years	6.5±9.0,2.6	7.3±9.3,4.2	6.9±9.1,3.5		NS
Correct diagnosis of BD					
No bipolar diagnosis	23 (25.6%)	51 (50.5%)	74 (38.7%)	$\chi^2=12.7$, df=1	p<0.001
Age at diagnosis, years	35.4±10.9,32.2	35.2±11.6,34.7	35.3±11.2,33.5		NS
Delay from first episode to diagnosis, years	9.7±9.7,7.0	12.3±9.7,9.9	10.8±9.6,7.8		NS
Delay from first contact to psychiatric care to diagnosis, years	4.6±6.0,3.0	5.7±7.9,2.3	5.1±6.9,2.7		NS
Characteristics at intake					
Current episode					NS
Depression	15 (16.7%)	27 (26.7%)	42 (22.0%)	$\chi^2=4.49$, df=1	p=0.034
Hypomania	2 (2.2%)	9 (8.9%)	11 (5.8%)		
Mania	20 (22.2%)	NA	20 (10.5%)		
Mixed ²	7 (7.8%)	13 (12.9%)	20 (10.5%)		
Polyphasic	46 (51.1%)	52 (51.5%)	98 (51.3%)		
Psychotic symptoms currently	20 (22.2%)	11 (10.9%)	31 (16.2%)		
Rapid cycling preceding intake	28 (31.1%)	34 (33.7%)	62 (32.5%)		
Beck Depression Inventory score of depressive patients	26.7±9.3	25.7±9.8	26.2±9.6		
Hamilton Depression Rating Scale score of depressive patients	21.9±5.6	20.2±7.4	21.0±6.7		
Young Mania Rating Scale of manic and hypomanic patients	20.6±12.8	14.4±5.1	18.7±11.3		

1 N (%) or mean±standard deviation, median, NS=nonsignificant

2 Mixed episode in BD I and depressive mixed state in BD II

7.1.3 Missing clinical diagnosis and delays in diagnosis

Clinical history revealed two major delays: in seeking treatment and in achieving the correct diagnosis (Table 8). The former explains a major part of the latter, but the pre-diagnosis treatment time was still considerable. Diagnosed BD II patients had a longer delay from the first episode to diagnosis than BD I patients, but there was no difference in median delay from treatment to diagnosis or delay range. More strikingly, a quarter (25.6%) of BD I patients were previously undiagnosed, and over half (50.5%) of BD II patients. Men were more often diagnosed than women (74.4% vs. 49.5%). The disparity between BD I and II remained after adjustment for gender.

7.1.4 Current episode and phase

Half (51.3%) of the patients were currently in a polyphasic episode. Rapid cycling accounted for one-third (32.5%) of the cohort. The distribution of phases was different in mono- and polyphasic episodes in BD I patients; mania seemed to be principally monophasic in the index episode – only 3/23 episodes were polyphasic. Current psychotic symptoms were observed in 16.2% of patients, more in BD I (Table 8). More BD I than BD II patients were currently hospitalized; still, over half of BD I subjects were outpatients. Most mixed BD I patients (N=11/15, 73.3%) as well as some manic patients (N=6/23, 26.1%) were treated in outpatient settings. Despite similar symptom severity, more depressive BD I patients were hospitalized than depressive BD II patients (46.8% vs. 25.4%).

7.1.5 Symptom severity

In depression, the symptom scores differed only according to the treatment setting, not the type of BD (Study I, Table 4). The YMRS score was, as expected, higher in mania than hypomania. In a mixed phase in BD I and a depressive mixed phase in BD II, BAI scores were significantly higher than in other phases or in purely depressed patients.

7.2 Differences in axis I and II comorbidity between bipolar I and II disorders and major depressive disorder (Study II)

7.2.1 Comorbidity in bipolar disorder versus major depressive disorder

Nearly all comorbid disorders had a slightly different distribution in BD patients than in MDD patients. In univariate analyses, MDD had significantly more current comorbid axis I disorders (69.1% vs. 57.1%), anxiety disorders, and cluster A and C personality disorders. BD had more eating disorders, somatoform disorders, and cluster B personality disorders. More MDD patients had phobic anxiety disorders (BD I vs. BD II vs. MDD 20.0% vs. 26.7% vs. 37.9%, respectively; $\chi_2^2=11.6$, $p=0.003$), also when comparing only depressed MDD and BD patients.

In nominal regression models with the main categories of comorbidity, after adjusting for level of depression, gender, and age, the differences in anxiety disorder, eating disorder, and personality clusters A and B remained significant (Table 9). The other aspects of severity had no effect on the results and were thus omitted from the final model.

Table 9. Multinomial regression model for current axis I comorbidity in 269 unipolar depressive patients in the Vantaa Depression Study and 191 bipolar patients in the Jorvi Bipolar Study

Variable	Unipolar ¹ OR	BD II OR	95%CI	Wald χ^2	p	BD I OR	95%CI	Wald χ^2	p
Sociodemographic characteristics									
Age	1.0	0.98	0.96-1.0	4.0	0.05	1.00	0.98-1.02	0.036	0.85
Gender	1.0	2.0	1.2-3.4	6.8	0.009	3.3	1.9-5.7	17.6	<0.001
Clinical status									
Beck Depression Inventory	1.0	0.96	0.93-0.98	10.9	0.001	0.94	0.91-0.95	20.1	<0.001
Axis I									
Any anxiety disorder	1.0	0.90	0.54-1.5	0.18	0.67	0.54	0.31-0.95	4.5	0.03
Any eating disorder	1.0	30.9	5.8-163.7	16.3	<0.001	21.4	3.2-140.9	10.1	0.001
Axis II									
Cluster A	1.0	0.28	0.12-0.65	8.7	0.003	0.26	0.11-0.063	9.1	0.003
Cluster B	1.0	2.3	1.1-4.6	5.2	0.02	6.1	3.0-12.4	25.5	<0.001

¹ Reference category

7.2.2 Comorbidity in bipolar disorder

The overall current (Table 10) and lifetime (Table 11) comorbidity in BD was high. In BD patients overall, 69.8% had a current comorbid disorder (unmodified proportions, see methods); on axis I 60.2% (BD I 54.4%, BD II 65.3%) and on axis II 42.9% (42.2%, 43.6%, respectively). Anxiety disorders were currently present in 44.5%, substance use disorders in 19.9%, and eating disorders in 7.9% of BD patients. BD II patients had more anxiety disorders, posttraumatic stress disorder, and binge eating. In a logistic regression model with BD I and II, after adjusting for gender, age, and Beck Depression Inventory findings, no significant differences emerged. In substance use disorders, current prevalences were one-third of lifetime prevalences, but in anxiety disorders these two rates were rather consistent.

The comorbidity in BD was distributed according to current illness phase (Study II, Table 4). Manic and hypomanic patients had the lowest prevalences in all main categories of disorders, and mixed and depressive mixed patients combined the highest, with prevalences of total comorbidity of 56.8% and 82.9%, respectively. One-fifth of (hypo)manic patients had an anxiety disorder. This proportion was twofold in depressive and threefold in mixed patients.

Table 10. Current DSM-IV axis I and II comorbidity in 191 bipolar patients in the Jorvi Bipolar Study

	BD I (N=90)		BD II (N=101)		Total BD (N=191)	
	N	%	N	%	N	%
Any comorbid axis I diagnosis	49	54.4	66	65.3	115	60.2
Any anxiety disorder ¹	32	35.6	53	52.5	85	44.5
Panic disorder	17	18.9	29	28.7	46	24.1
Agoraphobia without panic	3	3.3	1	1.0	4	2.1
Social phobia	13	14.4	21	20.8	34	17.8
Simple phobia	5	5.6	10	9.9	15	7.9
OCD	3	3.3	1	1.0	4	2.1
PTSD ²	5	5.6	15	14.9	20	10.5
Eating disorder	4	4.4	11	10.9	15	7.9
Bulimia	3	3.3	6	5.9	9	4.7
Anorexia	1	1.1	0	0.0	1	0.5
Binge eating ³	0	0.0	5	5.5	5	2.6
Any somatoform disorder	3	3.3	6	5.9	9	5.2
Substance use disorder	19	21.1	19	18.8	38	19.9
Alcohol abuse	3	3.3	3	3.0	6	3.1
Alcohol dependence	15	16.7	12	11.9	27	14.1
Drug abuse	0	0.0	1	1.0	1	0.5
Drug dependence	1	1.1	3	3.0	4	2.1
No comorbid axis I or II disorder	30	33.3	26	25.7	56	29.3

¹ $\chi^2=5.5$, df=1, p=0.019

² $\chi^2=4.4$, df=1, p=0.036

³ $\chi^2=4.6$, df=1, p=0.032

Table 11. Lifetime DSM-IV axis I and II comorbidity in 191 bipolar patients in the Jorvi Bipolar Study

	BD I (N=90)		BD II (N=101)		Total BD (N=191)	
	N	%	N	%	N	%
Any comorbid axis I diagnosis	73	81.1	77	76.2	150	78.5
Dysthymia	5	5.6	5	5.0	10	5.2
Any anxiety disorder ¹	41	45.6	61	60.4	102	53.4
Panic disorder	24	26.7	37	36.6	61	31.9
Agoraphobia without panic	4	4.4	2	2.0	6	3.1
Social phobia	19	21.1	31	30.7	50	26.2
Simple phobia	6	6.7	10	9.9	16	8.4
OCD	4	4.4	5	5.0	9	4.7
GAD	12	13.3	17	16.8	29	15.2
PTSD ²	8	8.9	23	22.8	31	16.2
Eating disorder	10	11.1	21	20.8	31	16.2
Bulimia	9	10.0	14	13.9	23	12.0
Anorexia	4	4.4	2	2.0	6	3.1
Binge eating ³	0	0.0	5	5.0	5	2.6
Substance use disorder	52	57.8	45	44.6	97	50.8
Alcohol abuse	11	12.2	7	6.9	18	9.4
Alcohol dependence	39	43.3	36	35.6	75	39.3
Drug abuse	2	2.2	1	1.0	3	1.6
Drug dependence	5	5.6	7	6.9	12	6.3
Any comorbid axis II diagnosis	38	42.2	44	43.6	82	42.9
Cluster A	10	11.1	9	8.9	19	9.9
Cluster B	28	31.1	26	25.7	54	28.3
Cluster C	18	20.0	26	25.7	44	23.0
No comorbid axis I or II disorder	11	12.2	20	19.8	31	16.2

1 $\chi^2=4.2$, df=1, p=0.04
2 $\chi^2=6.7$, df=1, p=0.009
3 $\chi^2=4.6$, df=1, p=0.032

7.3 Clinical predictors of unrecognized bipolar I and II disorders (Study III)

In univariate analyses, diagnostic status was found to be related to gender. In BD I, unrecognized patients had a higher work status, with a disability pension ten times less common than in recognized patients (4.3% vs. 41.8%, $\chi_3^2=11.6$, p=0.009). In BD II, unrecognized patients were more often professionally educated (66.0% vs. 43.5%, $\chi_1^2=4.7$, p=0.029). No other sociodemographic differences were observed.

In BD I patients, the clinical factors associated with poor recognition in univariate analyses (Study III, Table 1) were lower age at first symptoms and age at onset, rapid cycling, less manic and more depressive episodes, more lifetime anxiety disorder, and less lifetime substance use disorder. Unrecognized BD I patients had a longer delay from

illness onset to psychiatric treatment, shorter time in treatment, and less hospitalizations (all had had hospitalizations only in depressed or mixed episodes) than their recognized peers. In BD II patients, lack of psychotic symptoms, fewer depressive episodes, and shorter time in treatment were correlated with missed bipolar diagnosis.

In final models explaining unrecognized BD type I (Study III, Table 2), rapid cycling (OR=11.6), no hospitalizations (OR=10.6), and no psychotic symptoms (OR=4.4) remained significant. In BD II patients (Study III, Table 3), no psychotic symptoms (OR=3.3), female gender (OR=3.0), and shorter time in treatment (OR=1.1) predicted unrecognized BD.

7.4 Outcome of bipolar disorder (Study IV)

7.4.1 Proportion of time in different symptom states during follow-up

The proportions of time spent in most states differed according to type of disorder (Table 12). BD II patients spent a significantly greater proportion of time in any mood episode and in a depressive phase or depressive symptoms. BD I patients spent more time euthymic. No differences were detected between BD I and BD II patients in the proportions of time spent in manic/hypomanic or mixed/depressive mixed states when different degrees of states were considered together.

Table 12. Differences between BD types I and II in proportion of time spent in specific clinical states and mean number of new specific states in 160 bipolar patients followed up for 18 months

	BD I (N=75)	BD II (N=85)	Total BD (N=160)	Test statistic	p
Proportion of time spent in specific states during follow-up, mean %					
Any mood episode	37.7	47.5	42.9	U=2508	0.02
Depressive states	41.7	58.0	50.4	U=2306	0.003
Major depressive phases ¹	29.0	38.7	34.2	U=2357	0.004
Depressive symptoms ²	12.7	19.3	16.2	U=2384	0.005
Hypomanic and manic states	5.5	5.7	5.6		NS
Manias ^{3,4}	2.7	0.8	1.7	U=2341	<0.001
Hypomanias ⁵	2.1	4.1	3.2	U=2567	0.02
Hypomanic symptoms ²	0.7	0.8	0.8		NS
Mixed states	3.9	3.9	3.9		NS
Mixed phases ^{3,4}	2.1	0.6	1.3	U=2551	<0.001
Depressive mixed phases ⁶	1.7	3.4	2.6	U=2681	0.02
Euthymic phases ³	48.7	31.7	39.6	U=2279	0.002
Other states	49.0	32.4	40.2	U=2319	0.003
Cyclothymic phases ³	0.3	0.5	0.4		NS
Substance-induced mood episodes ³	0.0	0.2	0.1		NS
Mean number of new phases according to type of phase⁷					
Mean number of new episodes	2.4	3.2	2.8		NS
Mean number of new phases	0.82	0.87	0.8		NS
Mean number of specific phases					
Major depressive ¹	1.11	1.69	1.42	U=2400	0.006
Manic ^{3,4}	0.28	0.096	0.18	U=2649	0.004
Hypomanic ⁵	0.61	1.7	0.86		NS
Mixed ^{3,4}	0.19	0.060	0.12	U=2758	0.005
Depressive mixed ⁶	0.19	0.24	0.22		NS

1 Phases defined using DSM-IV criteria, separated depressive mixed phases

2 Symptoms without full DSM-IV criteria, including prodromals and residuals

3 DSM-IV criteria

4 Patients with a switch from BD II to BD I during follow-up included

5 DSM-IV criteria, except duration of 2 days accepted

6 Three or more simultaneous intra-episode hypomanic symptoms present for at least 50% of time during a major depressive phase; the states not included in depressive states

7 Weighted with time in follow-up; Mann-Whitney U-test

7.4.2 Factors underlying more time ill

Most patients (78.1%) had new phases (of a polyphasic episode, relapse or recurrence) during the follow-up; no differences in the number of new episodes or phases overall were observed between BD I and II patients (Table 11). However, more BD II patients had a new depressive phase, and they also had a greater number of depressive phases (Table 11). When manias and hypomanias as well as mixed and depressive mixed phases were considered together, no differences between BD I and II patients were detected in the presence or number of these phases. While the index phase was most often a major depressive episode with similar proportions in BD I and II (Study IV, Table 1), subsequent phases also comprised mainly depressions, but more so in BD II. The duration of a depressive phase did not differ between BD I and II, and the same was true for all other states, with the exception of euthymia (Study IV, Table 3). When only patients with a depressive index phase were compared, no differences were detected between BD I and II in the numbers of new phases, episodes, or depressions. However, among patients with other than depressive index phases, BD II patients had a significantly higher number of new phases and hypomanias than BD I patients.

The proportion of all patients meeting full criteria of a mood episode until the end of follow-up was one of ten (11.3%); one-third (33.1%) did not reach full remission (Study IV, Figure 1), and three-quarters (73.2%) of patients with full or partial remission had a relapse or recurrence. More BD I than II patients reached full remission (BD I vs. BD II 76.0% vs. 58.8%, $\chi_1^2=5.7$, $p=0.017$), and a greater proportion of BD II patients reached at best only partial remission (12.0% and 30.6%, respectively, $\chi_1^2=8.7$, $p=0.003$).

7.4.3 Other principal outcome measures

Median *time with full criteria of the index phase* overall was 3.5 months and median *time with full criteria of the index episode* overall was 8.5 months. No difference between BD I and II patients was evident in the duration of index phase or episode, both of which were mainly determined by the type of index phase. Also, median durations of distinct types of phases did not differ between BD I and II. Median *time to full remission* (lasting at least 2 consecutive months) from the beginning of the index phase was overall 11.1 months (Study IV, Table 3). BD II patients needed 3.0 months more to achieve full remission, but the difference was not statistically significant. Median *time to recurrence after 2 months of (full or partial) remission* was 8.9 months (Study IV, Table 3).

7.4.4 Effect of index phase

Type of index phase had a significant effect on most outcome measures. Type of index phase affected the proportion of time in different symptom states (Study IV, Table 4). Patients with a depressive or depressive mixed index phase had the highest proportion of time spent in any mood episode and in depressive states during follow-up. Patients with a manic index phase spent the smallest proportion of time ill, in any depressive states, and in mixed

plus depressive mixed phases. Moreover, they spent 72.2% of time euthymic compared with 34.4% in patients with a depressive index phase during follow-up. Patients with a hypomanic and mixed phase were in an intermediate position compared with other phases. A depressive index phase had the longest and a hypomanic index phase the shortest duration (Study IV, Table 3). Mixed index phases were more similar to depressive index phases than to manic phases in all principal outcome measures, with no statistically significant differences in post hoc analyses between depressive and mixed index phases. Full remission during the 18-month follow-up was most prevalent after mania (Study IV, Table 5). In addition, patients with a manic index phase had the least new phases, episodes, and specifically, depressive and hypomanic phases in follow-up (Study IV, Table 4).

7.4.5 Effect of a polyphasic episode at intake

Polyphasic index episodes were detected overall (at baseline or continuing from intake) in 103/160 patients (64.4%), with no (statistically) significant differences being present between BD I and II patients. Different types of index phases were preceded and followed by a polyphasic episode with different distributions, and this was an important modifying factor in outcome. Only one-fourth of manic index phases were polyphasic (*either preceding or continuing from intake*), in contrast to all other phases ($\chi_3^2=18.4$, $p<0.001$) (Study IV, Figure 2). While a depressive index phase was most likely to be polyphasic *preceding* the index phase ($\chi_3^2=14.5$, $p=0.002$), mixed and depressive mixed index phases were most likely to *continue being* polyphasic ($\chi_3^2=13.7$, $p=0.003$).

7.4.6 Effect of clinical diagnosis and adequate acute-phase pharmacotherapy at intake on principal outcome measures

In the total sample, having a clinical diagnosis of BD at intake had a significant influence on outcome only in one measure, time to full remission, which was significantly longer for clinically undiagnosed patients. Comparing diagnosed BD I and II patients, median duration of index episode, time to recurrence after 2 months of remission, and proportion of time ill (31.8% vs. 50.8% $U=767$, $Z=-2.8$, $p=0.005$) showed better outcome for BD I. Accordingly, BD I patients with adequate acute-phase pharmacotherapy had a better outcome than BD II patients with adequate pharmacotherapy in terms of time to full remission. Comparing undiagnosed BD I and II groups, time to full remission was the only statistically significant difference, being longer for BD I. No differences were detected between inadequately treated BD I and II.

BD I patients with a diagnosis and adequate acute-phase pharmacotherapy did better than undiagnosed or inadequately treated BD I patients. Duration of index phase, duration of index episode, time to full remission, and proportion of time ill (21.4% vs. 50.7%, $U=327$, $Z=-2.7$, $p=0.008$) showed better outcome for the diagnosed BD I patients, even more than

duration of index episode, time to full remission, and proportion of time ill (21.4% vs. 46.2%, $U=479$, $Z=-2.2$, $p=0.025$) for adequately treated BD I patients. Surprisingly, no differences were found when comparing diagnosed BD II with undiagnosed BD II, or adequately treated BD II with inadequately treated BD II.

7.4.7 Linear regression models and survival analyses of differences between bipolar I and II patients in the five principal outcome measures

A linear regression model was constructed for the proportion of time in different symptom states during follow-up; the differences between BD I and II did not reach significance. Two similar linear regression models were then created explaining, specifically, time in depressive states (Table 13). In the first model, the effect of index phase was controlled for dimensionally (with baseline HAM-D and YMRS scores), and in the second model, categorically (major depressive vs. other phase); in both, all nonsignificant variables except age and gender were removed. In both models, BD II predicted more time in depressive states. Besides having BD II, higher number of comorbid axis I disorders, and in the final dimensional model, also higher HAM-D score, and in the final categorical model, depressive index phase significantly and independently predicted higher proportion of time in depressive states.

For the four other principal outcome measures (time with full criteria of the index phase, time with full criteria of the index episode, time to full remission from the beginning of the index episode, and time to recurrence from the beginning of remission), Kaplan-Meier models and Cox regression models, adjusted for age and gender, gave no statistically significant differences between BD I and II.

Table 13. Linear regression models with type of index phase controlled for dimensionally and categorically for total time spent in depressive symptoms or major depressive phases during 18-month follow-up of 160 BD patients

	B	SE	Beta	t	p
Dimensional model					
Type I or II disorder	13.7	5.0	0.2	2.8	0.007
Age	0.22	0.21	0.076	1.1	0.29
Gender	5.0	5.0	0.072	1.0	0.32
HAM-D score at baseline	1.7	0.31	0.39	5.4	<0.001
Number of axis I disorders	6.1	3.1	0.15	2.0	0.048
Categorical model					
Type I or II disorder	10.8	5.2	0.16	2.1	0.038
Age	0.24	0.22	0.08	1.1	0.28
Gender	5.2	5.1	0.075	1.0	0.31
Index phase MDE	19.8	5.0	0.29	4.0	<0.001
Number of axis I disorders	11.2	3.1	0.027	3.6	<0.001

8. DISCUSSION

8.1 Main findings

Even in this psychiatric setting, BDs were usually either unrecognized or recognized only after a long delay. A significant proportion of not only BD II, but also BD I patients had never been hospitalized. Furthermore, polyphasic episodes and rapid cycling were commonly present among both BD I and II patients. Depressive mixed states were at least as common among BD II patients as mixed episodes among BD I patients.

Patterns of psychiatric comorbidity of BD and MDD differed somewhat qualitatively. MDD patients had more current axis I disorders, specifically anxiety disorders, and more cluster A personality disorders. In contrast, BD patients had more cluster B personality disorders. BD I and II patients were quite similar in comorbidity. Among BD patients, the prevalence of psychiatric comorbidity was strongly associated with the current illness phase.

The classic presentations of BD with hospitalizations, manic episodes, and psychotic symptoms lead clinicians to correctly diagnose BD I in psychiatric care. When the classic presentations are absent, as in BD II patients, but also in a large proportion of BD I patients, the disorder is recognized less often. Time of follow-up elapsed in psychiatric care but none of the clinical features seemed to explain correct diagnosis of BD II, suggesting reliance on cross-sectional presentation of illness. In addition, rapid cycling among BD I patients and female gender among BD II patients were correlated with unrecognized BD. It is noteworthy that of unrecognized BD patients, only one-third had ever been hospitalized, and four-fifths were currently outpatients. Thus, the problems in diagnosis were most evident in outpatient settings.

In medium-term follow-up, BD II patients spent about 40% more time depressed than BD I patients. The most important factors explaining this difference were higher proportions of BD II than BD I patients having depressive phases, a higher proportion of depressive phases among all phases in BD II, and a higher frequency of depressive phases in BD II during follow-up. Duration of the depressive phases was, however, equal. Although type of index phase was a major determinant of medium-term illness course, the finding of BD II patients spending more time in depression persisted even after controlling for this confounding factor.

8.2 Methods

The Jorvi Bipolar Study (JoBS) is the first clinical cohort study based on systematic screening for BD among psychiatric in- and outpatients within a geographically defined catchment area. The data on unrecognized BD are thus uniquely representative, and comparisons between BD I and II are unbiased by sampling. This is the first study to compare total axis I and II comorbidity between MDD, BD I, and BD II patients. The sampling of patients at the beginning of a new phase enabled investigation of the duration of different types of index phases and the effect of index phase on other outcome measures and comorbidity. No other study has contained patients with all types of index phases, including hypomanias and depressive mixed phases. The outcome of BD I and II has been compared in only a few cohorts.

8.2.1 Representativeness of the cohort sample

The present naturalistic study involved a relatively large (N=191) cohort that was representative of secondary care psychiatric BD patients with a new phase of BD, including both BD I and II, independent of clinical diagnosis. Finland has no private psychiatric hospitals, and public psychiatric care is free of charge. Probably, most BD I patients seek treatment or contact a psychiatrist in an acute phase, while more BD II patients may be treated by primary healthcare or private psychiatrists. Using the MDQ screen was a major strength of the study; most BD patients in psychiatric care in the area with an incident illness episode were likely found. After interviewing also patients with a previous clinical diagnosis or suspicion of BD, screening was more sensitive to patients with worse insight into the illness. Nevertheless, it is impossible to exclude the possibility that individual undiagnosed patients lacking insight or denying their illness might have remained undetected due to their consistent denial of all symptoms in the screen and diagnostic interviews. However, in order to significantly bias the findings, such cases would need to be numerous and also have characteristics markedly different from the current cohort. This possibility thus seems remote and merely theoretical. Moreover, the rate of refusals was low, estimated not to exceed 10% of all BD patients.

8.2.2 Screening

A large number of psychiatric patients (N=1630) were screened. The MDQ was used, but in order to increase sensitivity for BD II, the cut-off was modified by including as positive also patients without problems due to episodes. This modification of the cut-off in the screen was based on the pilot study of the JoBS (Isometsä et al., 2003), some other studies (Benazzi, 2003; Miller et al., 2004; Zimmerman et al., 2004), and the definition in the DSM-IV that hypomania is not severe enough to cause marked impairment in functioning. 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.

At the time of the study, the MDQ was the best instrument available to screen for BD. Using a screen profoundly influenced the composition of the sample compared with previous studies. Had the sampling been based on the specific type of current episode, the size of the cohort compared with its actual size would have been 16% for psychotic symptoms, 56% for depression, and 22% for mixed episodes. Based on inpatient status, 34% of patients would have been included, and based on clinical diagnosis 61%.

8.2.3 Diagnostic measures

All diagnoses were carefully assigned by psychiatrists with a minimum of 5 years of clinical experience using a semistructured interview (First et al., 2002), information from all patient records was available and completed with several informants in any case of uncertainty, and interrater reliability was assessed and found to be excellent (kappa 1.0 for both BD I and II). This kind of diagnostic procedure has been used as a golden standard in studies evaluating the validity of SCID-I (Shear et al., 2000), and thus evaluated, the BD I diagnosis should be both highly reliable and valid. The reliability of SCID-I for DSM-III-R BD was 0.84 (Williams et al., 1992); in the only study comparing the validity of diagnosis of BD by SCID the kappa was 0.89 (Fennig et al., 2004). The reliability or validity of SCID for BD II has not been evaluated. The reliability of SCID-II using DSM-IV criteria has been evaluated in one study to be from 0.83 to 0.98 for distinct disorders, but the validity was poor (Skodol et al., 1988); however, the number of patients in the study was only 22 (see also www.scid4.org). 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.

In Study II, two diagnostic interviews were used, SCAN (Wing et al., 1990) and SCID (First et al., 2002), with both generating DSM-IV axis I diagnoses. However, minor differences between these interviews could slightly affect the prevalences of single diagnostic groups. In BD-MDD comparisons, some criteria modifications to assure comparability on axis II were necessary because of the different versions of the SCID-II (Spitzer et al., 1990a; First et al., 1997) used. Current alcohol dependence instead of total substance use disorders was included in total axis I comorbidity, and modifications lowered total axis II comorbidity and the prevalence of borderline personality disorder in BD by 2-3%. The reliability of comorbid diagnoses was not evaluated.

8.2.4 Effect of current phase

Rating in an acute phase was done deliberately to investigate the persistence of comorbid disorders, duration of index phases, and effect of index phase on outcome in follow-up. However, including the patients in an acute phase could have had some impact on the results. Patients' beliefs about self and insight into illness differ between different phases of BD (Dell'Osso et al., 2002; Bentall et al., 2005), and this could affect patients' willingness to participate and the ability to report symptoms objectively. In addition, a current illness phase affects comorbidity ratings; for example, patients often

deny symptoms while in a manic state (Dell'Osso et al., 2000), and depression and anxiety seem to be related (Gaudio and Miller, 2005). However, patients were met twice, and comorbid disorders were assessed in a later subacute phase. In Study II, also depressed BD and MDD patients were compared, and in the regression models, adjustments were made for current illness phase. It should be emphasized that 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. Despite our best efforts, however, one cannot totally exclude the possibility that the current state might have colored the perception of personality. Compared with studies of strictly euthymic patients (Peselow et al., 1995; Ucock et al., 1998; Kay et al., 1999; Colom et al., 2000; Vieta et al., 2000; Vieta et al., 2001; Brieger et al., 2003; George et al., 2003), the overall level of axis II comorbidity here was intermediate. The study design was constructed as closely as possible to the situation where a clinician meets mood disorder patients during the acute phase.

8.2.5 Life chart and definitions of outcome

The life chart methodology is generally accepted as part of follow-up studies of BD. However, the aim was to assess the compatibility of life chart phases with DSM-IV criteria, which are part of everyday clinical practice and known to all clinicians. Thus, the graphic life chart 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 types I and II (Tondo et al., 1998; Dittmann et al., 2002; Judd et al., 2003b; Judd et al., 2003c; Post et al., 2003; Joffe et al., 2004). This kind of graphic life chart was planned and used in the VDS (Melartin et al., 2004). Similar to LIFE, change points in the psychopathologic state were inquired about using probes related to important events. Unlike with LIFE, in the interview 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) plus depressive mixed states, full remission with no symptoms of phases, and partial remission when criteria for neither mood episode nor full symptomatic remission were fulfilled. The life chart was constructed in the two follow-up interviews based on patients report, all available patient records, and other informants when needed. As in any study not based on daily prospective mood ratings (Judd et al., 2003b; Judd et al., 2003c), that the underreporting of some milder illness phases, such as short hypomanic or depressive mixed episodes, could not be excluded. However, there is unlikely to be any bias in the comparison of BD I and II in this respect.

8.3 General characteristics of the cohort compared with other cohorts with bipolar patients

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, and this affects comparability with other cohorts in many aspects. It is noteworthy that a considerable proportion of even BD I patients, mostly with mild manias but still unequivocal functional impairment at work or in family roles, had not been hospitalized or diagnosed. The cohort therefore represents a considerably larger proportion of actual bipolar patients in psychiatric care than previous studies. While this study is more representative of BD in psychiatric care than other naturalistic prospective studies on BD, the results may not be directly comparable because of the high proportion of clinically unrecognized or misdiagnosed patients, especially in BD II. However, the proportion of unrecognized patients was equal to that of patients not receiving mood stabilizing treatment in the CDS (Judd et al., 2003b; Judd et al., 2003c).

In this cohort, psychotic symptoms during the lifetime were present in half, but currently in only 16%, of all patients. These proportions are low compared with other, tertiary care samples (Benazzi and Akiskal, 2001; Suppes et al., 2001; Serretti et al., 2002a; Akiskal and Benazzi, 2003; Judd et al., 2003b; Schneck et al., 2004). Polyphasic episodes were common; nearly all (85.0%) BD I and II patients had had at least one polyphasic episode during their lifetime. The number was higher among BD I patients, as also reported earlier (Kilzieh and Akiskal, 1999). A polyphasic episode was currently present in 51% of patients, corresponding to previous cross-sectional studies (Coryell et al., 1987; Winokur and Kadmas, 1989; Maj et al., 2002), in 36% following intake and 64% overall (at baseline or continuing from intake). Rapid cycling was present at intake in 29% of patients, in contrast to less than 20% in earlier studies (Coryell et al., 1994; Angst et al., 2005), and during follow-up in 40%, on the upper border (15-38.2%) of other prospective follow-up studies (Maj et al., 1994; Baldessarini et al., 2000; Tondo et al., 2001; Coryell et al., 2003; Schneck et al., 2004; Kupka et al., 2005). Thus, in this naturalistic cohort, both polyphasic episodes and rapid cycling were highly prevalent, while prevalence of polyphasic episodes has not been reported comparably in previous studies. Especially rapid cycling might to some extent reflect factors related to treatment.

In the follow-up of the JoBS cohort, 10% of BD II patients (9.9% of the 101 BD II patients in the original sample, 11.8% of the 85 followed up for 18 months) converted to BD I during the 18-month follow-up due to a manic (N=7) or mixed (N=3) episode; this is a higher proportion than the 1-2% per year in longer follow-ups (Coryell et al., 1995; Angst et al., 2005).

8.4 Clinical differences between bipolar I and II patients

The difference in current psychotic features between BD I and II (22.2% vs. 10.9%) was less marked than that reported in a private clinic sample (80.9% vs. 5.6%) (Serretti et al., 2002a), in a large sample of hospitalized depressive patients (62.4% vs. 21.9%) (Benazzi and Akiskal, 2001; Akiskal and Benazzi, 2003), or in the CDS (54.8% vs. 18.3%) (Judd et al., 2003b). Lifetime prevalences (67.8% vs. 33.7%) were slightly more similar to results from other studies, 67% vs. 23% in the Stanley cohort (Suppes et al., 2001), and 56% vs. 14% in the STEP-BD (Schneck et al., 2004), the differences being greater in BD II.

Despite somewhat different clinical pictures, BD I and II did not differ significantly in terms of comorbidity profile (McElroy et al., 2001; Suppes et al., 2001; Dittmann et al., 2002; Judd et al., 2003b). This was true even regarding anxiety disorders, a finding that is supported by many (McElroy et al., 2001; Suppes et al., 2001; Dittmann et al., 2002) but not all (Henry et al., 2003; Judd et al., 2003b) comparative studies. In contrast, the current index phase of BD strongly affected comorbidity, with axis I prevalences highest in patients with a current mixed or mixed depressive episode and lowest in a (hypo)manic episode (Dell'Osso et al., 2000). Although anxiety disorders were associated with depressive or mixed phases, the ratio of current vs. lifetime comorbidity still seemed high. Thus, as also reported earlier (Bauer et al., 2005a), anxiety disorders appeared rather chronic, whereas the prevalences of distinct and total substance use disorders were currently only one-third of lifetime prevalences, suggesting a more episodic nature. It is also noteworthy that among bipolar patients some comorbid disorders cluster together (McElroy et al., 2001; Boylan et al., 2004; Simon et al., 2004a; Bauer et al., 2005a), with patterns similar to those in MDD (Melartin et al., 2002). Only a few patients had, for instance, current alcohol use disorder alone, whereas anxiety disorders were the most common as a single disorder. Axis I and II disorders also frequently coexisted. The marked cross-sectional and longitudinal complexity of not only the mood disorder per se, but also the concurrent disorders is a major challenge for clinicians.

8.5 Differences in comorbidity between bipolar disorder and major depressive disorder

Both unipolar and bipolar mood disorders appear to be highly comorbid, but their profiles of comorbidity are somewhat different. Overall, a current axis I comorbidity was more prevalent in MDD than BD (70% vs. 57%). In the MDD patients of the VDS, the prevalences were convergent with those previously reported, the prevalence of personality disorders being somewhat lower and that of alcohol disorders being higher than the weighted means reported elsewhere (Melartin et al., 2002). In the bipolar cohort, the prevalence of any comorbidity on axis I was relatively high (McElroy et al., 2001; Simon et al., 2004a), and on axis II (42.9%) intermediate compared with clinical studies of euthymic phase patients (Peselow et al., 1995; Ucek et al., 1998; Kay et al., 1999; Colom et al., 2000; Vieta et

al., 2000; Vieta et al., 2001; Brieger et al., 2003; George et al., 2003). This is the largest clinical study reporting differences in anxiety and the first to examine differences in alcohol dependence and eating disorders between BD and MDD. In line with the previous literature, MDD patients had more anxiety disorders (Pini et al., 1997; Yerevanian et al., 2001), while BD had more panic disorders (Chen and Dilsaver, 1995b; Simon et al., 2003). Panic disorder and posttraumatic stress disorder were especially prevalent in BD II. The similarity of prevalences of alcohol dependence was unexpected (Regier et al., 1990; Angst, 1998; Cassidy et al., 2001b; de Graaf et al., 2003). However, for methodological reasons, a possible difference in abuse cannot be excluded.

As hypothesized, the three clusters on axis II appeared differently distributed between MDD and BD. Unlike previous reports on inpatients, in which MDD had more axis II comorbidity (Rossi et al., 2001; Schiavone et al., 2004), no significant differences were found in total prevalences of axis II disorder. However, more borderline personality disorder was found among BD than MDD patients, which is in accordance with one outpatient (Benazzi, 2000) but not inpatient (Rossi et al., 2001; Brieger et al., 2003; Schiavone et al., 2004) studies. Furthermore, among BD patients, borderline personality disorder was associated with substance use disorders, anxiety disorders, and cluster A personality disorders, showing "complex comorbidity" as reported in an earlier study by Zanarini et al. (Magill, 2004). Also, BD patients seemed to have eating disorders more often than those with MDD. In contrast, phobic anxiety disorders were associated with cluster B and C personality disorders among MDD patients but not among BD patients. Overall, the findings are convergent with the idea that the temperamental profile underlying clusters of personality disorders might be more concentrated in cluster B in BD, but broader in MDD, including more clusters C and A. Finally, in line with a previous report (Henry et al., 2003), no evidence was found for the theory that increasing any aspect of severity would markedly increase overall comorbidity.

8.6 Recognition of bipolar disorder

This is the first study where psychiatric patients were first screened and then formally diagnosed to include clinically recognized and unrecognized BD. Underrecognition of BD was even more evident than expected from indirect sources (Lish et al., 1994; Ghaemi et al., 1999; Ghaemi et al., 2000; Hirschfeld et al., 2003b); the extent in secondary care has not been investigated using structured diagnostic tools. Surprisingly, as many as 26% of bipolar I cases had remained undiagnosed. Long delays both in seeking treatment and in diagnosing BD, as previously reported (Lish et al., 1994; Hantouche et al., 1998; Tondo et al., 1998; Ghaemi et al., 1999; Ghaemi et al., 2000; Goldberg and Ernst, 2002; Baethge et al., 2003; Baldessarini et al., 2003; Hirschfeld et al., 2003b; Morselli and Elgie, 2003), emerged. The former largely explained the latter, but the delay in achieving a correct diagnosis in treatment was still considerable.

Correlates of unrecognized BD were also reported. Two previous studies surveyed reasons for misdiagnosis, but the current and previous diagnoses plus reasons for misdiagnosis were based on patient report only (ten Have et al., 2002; Hirschfeld et al., 2003b). Some studies have estimated prevalence of misdiagnosis using the MDQ screen in case definition. Although the MDQ is not a diagnostic tool (Zimmerman et al., 2004; Phelps, 2006), diagnoses were made with diagnostic interviews only in one study (Hirschfeld et al., 2005), which did not report predictors of misdiagnosis. Our findings are in line with previous studies where women (Lish et al., 1994; Baethge et al., 2003; Baldessarini et al., 2003; Hirschfeld et al., 2003b) and BD II patients (Akiskal et al., 2003; Baethge et al., 2003; Baldessarini et al., 2003) often remained undiagnosed or were diagnosed only after a longer delay. Longer delay was correlated with less severe forms of BD (Baethge et al., 2003; Baldessarini et al., 2003) and lower age at onset (Goldberg and Ernst, 2002). The findings suggest that BD I is better diagnosed largely due to the manic and psychotic phases of illness leading to hospitalizations, whereas BDI patients who are not hospitalized or have better functional status more often are misdiagnosed. BD II, by contrast, does not lead to the dramatic contacts with healthcare that are typical of BD I. These patients seem to instead be treated as outpatients with a diagnosis of unipolar major depressive disorder, without attention to intermittent hypomanic phases, and only receive a correct diagnosis after years in treatment. This is somewhat understandable since the first episode of BD is most often depression (Lish et al., 1994; Tondo et al., 1998; Morselli and Elgie, 2003); BD II patients, in particular, spend most of their time in depression (Judd et al., 2003a) and have more depressive episodes before the first hypomania (Tondo et al., 1998). Although the role of the patient was not investigated here, it seems to be important, especially in BD II (ten Have et al., 2002; Hirschfeld et al., 2003b), in which the patient may not perceive hypomanic phases as disturbing or pathological, and may in fact view them as periods of improved functioning (Judd et al., 2005). Overall, therefore, it seems that at least partly different processes lead to correct diagnosis of BD I and BD II, the former diagnosis occurring sooner in hospitalized phases of the illness, the latter occurring as a function of time as an outpatient.

8.7 Differences in outcome between bipolar disorder I and II

Overall, BD II patients were more chronically ill; they spent a greater proportion of time ill and in depressive states, more time in partial remission, and less time in full remission. The finding that BD II patients did spend more time depressed in follow-up is in line with the CDS cohort where more BD II than I patients were not receiving mood stabilizing treatment. Other studies where treatment was more strictly controlled showed no differences between BD I and II (Post et al., 2003; Joffe et al., 2004). BD I patients did not spend more time in manic/hypomanic or mixed/depressive mixed states, unlike in some other studies (Judd et al., 2003b; Judd et al., 2003c; Joffe et al., 2004), perhaps because our study was the only one to include patients with hypomanic and depressive mixed phases at intake. Two of the three possible explanations for a depressive picture were not

true: depressive phase in BD I and II had the same duration, as reported earlier (Tondo et al., 1998), and the frequency of depressive phases was the same in BD I and II. However, BD II patients more often had at least one new depressive phase (Judd et al., 2003b), and the proportion of depressions among new phases was higher. Thus, the difference between BD I and II was the more depressive course of BD II due to the higher proportion of depressions among the new phases.

This study is unique in that the effect of patient sampling and several confounding factors that might influence the difference between BD I and II could be investigated. The patients were sampled during an acute phase, reflecting natural differences in proportions of all phases between BD I and II. The effect of index phase on outcome was evident in several ways. In line with previous studies (Keller et al., 1993; Coryell et al., 1998; Tondo et al., 1998; Judd et al., 2003b), a depressive phase lasted longer than other phases, more often ended in residual symptoms, and if full remission was achieved, a slightly longer time was needed. At intake, depression was equally prevalent in BD I and II, and when only the depressive patients were compared, no differences in outcome between BD I and II were detected. However, the differences in the prevalence of other index phases were significant; the existence of manic phases, in particular, might partly explain the differences in outcome. A manic phase was most likely to end and stay in full remission; patients with a manic index phase had the lowest number of new phases and spent two times longer being euthymic than those with a depressive index phase.

Several potential confounding factors (age, gender) and other factors known to correlate with outcome (axis I and II comorbidity, duration of illness, age at onset, psychotic symptoms) were taken into account. For instance, a manic index phase was also correlated with better recognition of the disorder and receiving mood stabilizing treatment (Keller et al., 1993; Coryell et al., 1998; Nolen et al., 2004). However, the higher proportion of time depressed in BD II was evident even after controlling for these factors. Treatment was not the main focus of this naturalistic study, and only acute-phase treatment was analyzed here, but some interesting findings did appear. When only the recognized or adequately treated patients were compared, BD II was more chronic, resembling the results of the CDS (Judd et al., 2003b). Surprisingly, no differences in the principal outcome measures were found according to clinical diagnosis or acute-phase pharmacotherapy in BD II, a finding clearly different from BD I. Overall, the course of BD II tends to involve a higher proportion of depressive phases with a poorer outcome, whereas manic phases in BD I more often evolve into sustained full remission and better outcome. In theory, this could in part be explained by manic phases leading to better recognition of BD and treatment. In addition, the available treatments for bipolar depression, particularly for BD II, might be less effective, at the very least opinions about the optimal treatment are varied (Hadjipavlou et al., 2004). However, based on these results, it is unlikely that the more depressive course of BD II is only due to the confounding effects of clinical diagnosis or treatment.

8.7.1 Depressive mixed phases

At intake, a depressive mixed phase was currently prevalent in 25.7% of BD II patients. A current mixed episode in BD I was evident in 16.7% of cases, a figure lower than in studies with hospitalized manic patients (Marneros, 2001a; Sato et al., 2002; Gonzalez-Pinto et al., 2003; Berk et al., 2005) This is the first follow-up study to include patients with depressive mixed index phases. Thus, it is interesting that BD I and II equally often had new depressive mixed phases, that the durations of new mixed and depressive mixed phases were similar, and that no statistically significant difference between BD I and II was noted in the proportions of time in mixed and depressive mixed phases when these states were considered together. Mixed and depressive mixed phases seemed more similar to each other than manic and hypomanic phases in predicting outcome.

8.8 Contributions to the validity of distinction of bipolar disorder I and II

Several demographic factors, clinical history, symptom profiles, diagnostic stability, differences in comorbidity and outcome, and response to treatment (only grossly) were evaluated, all of which can be used to ascertain the validity of distinguishing between BD I and BD II. A clear difference between these two was found in outcome; BD II had a more depressive course. This was evident even after controlling for differences between BD I and II in correct clinical diagnosis and adequate treatment as well as other potential confounding factors. Surprisingly, no difference in outcome between clinically diagnosed and undiagnosed BD II patients or adequately and inadequately treated BD II patients was evident. Since treatment was not the main focus of this naturalistic study and adequacy of treatment was not evaluated in terms of patient compliance or laboratory tests, for instance, this cannot be seen as evidence of a difference in treatment response of BD I and II. It suggests, however, that separate cohorts of BD I and II are needed in treatment trials. The clinical usefulness of treating BD I, by contrast, is well established based on the literature and this study; with treatment, the outcome is clearly better.

Strikingly few other clinical differences between BD I and II were evident. Most of the differences (hospitalizations, psychotic features, severity of symptoms) arise from the definitions of diagnostic criteria. Only minor differences were evident in comorbidity between BD I and II.

Diagnostic stability was good; 10 BD II patients switched to BD I in the 18-month follow-up. The interrater reliability in the JoBS was excellent also in distinguishing BD I and II, but the proportion of clinically undiagnosed patients, especially BD II patients, was alarmingly high. The clinical reliability of the diagnostic categories could be questioned; however, more attention should be focused on improving the diagnostic skills and resources of clinicians rather than questioning the validity of BD II as a diagnostic category. The results suggest that clinicians find it more difficult than researchers to accept the concept of BD II. One way to explain this could be that clinicians have a prototype view of BD in general that best corresponds to BD I.

9. CONCLUSIONS AND FUTURE IMPLICATIONS

9.1 Conclusions

In the Jorvi Bipolar Study (JoBS), BD was poorly detected. In terms of resources in psychiatric care and primary health care, the cities of Espoo, Kirkkonummi, and Kauniainen, where the cohort was collected, are among the best in Finland. Thus, the likelihood of bipolar patients being correctly and quickly diagnosed is probably even smaller in other parts of the country. The results on recognition, comorbidity, and outcome can be generalized also to other countries: the subjects are representative of secondary care patients, and the findings of this study are in line with the previous literature.

Some implications for the validity of categorical diagnoses of MDD and BD, as well as BD I and II, were evident. Patterns of psychiatric comorbidity of BD and MDD are likely to differ somewhat qualitatively. BD I and II patients appear to differ little in terms of comorbidity, and the clinical differences in prevalence of psychotic features and hospitalizations reflect the diagnostic criteria of the disorders. However, the differences in outcome are clear and not explained solely by differences in mood at intake or differences in recognition or treatment. BD II compared with BD I patients more often had any depressive phase, higher proportions of depressive phases among all phases, and higher frequency of these phases during the follow-up, whereas duration of the depressive phases per se was equal. As a result, BD II patients spent about 40% more time depressed than BD I patients in medium-term follow-up.

Effect of the type of current phase at evaluation is evident in several ways. The prevalence of psychiatric comorbidity is strongly related to the current illness phase of BD, the depressive and mixed patients having the highest prevalences of anxiety disorders. If the patient is currently manic or psychotic, the BD is correctly recognized in most cases, but if the patient is seeking help for a depressive phase, all too often only this current status serves as the basis for diagnosis and treatment. A depressive phase predicts the poorest outcome in terms of several outcome measures after medium-term follow-up.

9.2 Clinical implications

Recognition of BD is a major challenge even for psychiatrists. The evaluation of diagnosis and treatment of BD should be done in psychiatric care. Greater diagnostic precision concerning the type of mood disorder (MDD, BD I, or BD II) as well as in evaluating comorbid disorders is essential for improving the quality of treatment, and thus, the outcome and quality of life of patients. Instead of reliance on cross-sectional presentation of illness, professionals should consider the longitudinal course when making a diagnosis and planning treatment. Screening all depressive patients for BD is warranted to identify patients needing immediate diagnostic evaluation of BD, and the clinical diagnosis should be critically re-evaluated in case of treatment failure. Repeated diagnostic evaluation with other informants and longitudinal follow-up of mood in treatment are needed for every patient also to detect conversion from MDD to BD or from BD II to BD I and the emergence of new comorbid disorders.

Evaluation of recovery should happen at several levels; syndromatic, symptomatic, and functional recovery should be the target of professionals. Life chart methodology is a valuable tool for the professional as well as for the patient for learning to identify the type and course of illness at an individual level. Use of observer or self-report scales measuring severity of depressive and manic symptoms as well as functional status and suicidality is recommended to detect the longitudinal fluctuations in status. Repeated systematic evaluation of diagnoses and status may serve as a tool for psychoeducation of the patient, thus ensuring better compliance in treatment, and over time, increasing disease control.

BD affects individuals and society at many levels. BD is a major public health problem and is one of the most expensive disorders for society because of its recurrent and chronic nature and high mortality. Psychosocial and functional disability fluctuates in parallel with changes in affective symptom severity. Even subthreshold level symptoms are important for functional outcome and must be carefully evaluated to improve consequences of the disorder, including markedly increased healthcare use and costs, higher unemployment, work impairment, increased work absenteeism owing to illness, and thus, decreased work productivity and lower annual income. It may take years to find the optimal combination of treatments, biological as well as psychosocial, for individual patients. The response, outcome, and side-effects of individual patients show the adequacy and suitability of treatment. At the same time, individual patients have differing goals in life, and quality of life is a subjective experience not directly correlated with symptomatic recovery.

If mood disorder patients could be optimally diagnosed and the number of BD patients in treatment was twofold, this would have considerable consequences on psychiatric care. A need for new resources is evident in planning future treatment facilities for psychiatric patients. More time for the diagnostic evaluation of mood disorders is required, and a large group of patients needs repeated evaluation of treatment response by a psychiatrist and illness-specific psychosocial treatments. For instance, the disorder has a serious impact on social relations of the patient, and patients' experience of the quality of life

is most dependent on social support. Thus, not only the patient but also the family needs to be considered. Undiagnosed BD patients are known to need even more acute and long-term psychiatric treatment than patients with a correct diagnosis.

The evaluation, treatment, and prevention of manic and especially depressive episodes should be a special interest of clinicians. Also, the presence of mixed features should be carefully evaluated in both BD I and BD II patients given that depressive mixed states are at least as common among BD II patients as mixed episodes are among BD I patients. Both depressive and mixed features worsen the outcome, affect the recommended treatment, and increase the prevalence of suicidality.

9.3 Implications for future research

New challenges for research arise from patients without a clinical diagnosis not representing the whole bipolar population and important clinical differences existing between clinically diagnosed and undiagnosed bipolar patients. To truly reduce burden and costs of BD, the clinical picture of previously unrecognized BD patients should also be better known. To get a comprehensive picture of all bipolar patients, using a screen to select patients is warranted. Also long-term randomized controlled trials on both drug and psychosocial treatments should be carried out among ordinary BD patients with high comorbidity and chronic course of illness to separate type II disorder. In addition to efficacy of treatment, the effectiveness in every day medical practice should be evaluated. This better takes into account the common noncompliance of patients and the fact that the clinicians seldom prescribe medication as defined in the treatment guidelines. Uncovering details on the reasons for noncompliance of patients as well as on clinicians' views that lead to undiagnosed or inadequately treated BD is important for improving the overall outcome of patients. More information about the true prevalence and course of BD I and especially BD II is needed to plan healthcare resources to better respond to the needs of affected patients.

The limits of mood disorders and comorbid disorders require further clarification and validation. Both categorical and dimensional models of these disorders should be included in the same studies, ideally combining clinical, familial, and genetic information. To elucidate the relationship between mood disorders and comorbid disorders, more longitudinal information is needed to determine whether the same patients have the same profile of comorbidity when euthymic, and whether comorbid disorders differ in stability during follow-up. It also remains open whether the comorbidity profile affects the type and course of the current phase, and what specific effects different comorbidity profiles have on the longitudinal course.

Research on the predictors of outcome is important to detect those patients who are most vulnerable to poor outcome. Genetic, biological, developmental, and environmental risk factors contributing to contracting a mood disorder, to having BD I or BD II, and to determining the specific course of illness should be investigated simultaneously controlling for interactions and confounding factors.

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