



Hanna Valtonen

Suicidal Behaviour in Bipolar Disorder

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Hanna Valtonen

Academic Dissertation

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Hanna Valtonen, Itsetuhoinen käyttäytyminen kaksisuuntaisessa mielialahäiriössä
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TIIVISTELMÄ

Tämä tutkimus on osa Kansanterveyslaitoksen Mielenterveyden ja Alkoholitutkimuksen osaston ja Helsingin ja Uudenmaan sairaanhoitopiirin Jorvin sairaalan psykiatrian yksikön kaksisuuntaisen mielialahäiriön etenevää seurantatutkimusta (Jorvi Bipolar Study). Tutkimuksessa on seurattu kaksisuuntaista mielialahäiriötä sairastavia psykiatrisen erikoissairaanhoidon avo- ja sairaalapotilaita, joilla tutkimukseen otettaessa oli diagnosoitavissa meneillä oleva sairausjakso. Tutkimuksen tavoitteena oli tutkia itsetuhoisen käyttäytymisen esiintyvyyttä, itsemurhayritysten ilmaantuvuutta sekä itsemurhayritysten riskitekijöitä tässä potilasryhmässä.

Tutkimusta varten seulottiin 1630, iältään 18-59-vuotiasta potilasta käyttäen Mood Disorder Questionnaire (MDQ)-mielialahäiriökyselyä. Kyselyn perusteella positiiviseksi osoittautuneet 490 potilasta haastateltiin puoli-strukturoidulla haastattelumenetelmällä [the Structured Clinical Interview for DSM-IV Disorders, research version with psychotic screen (SCID-I/P)]. Tutkimukseen valikoitui lopulta 191 potilasta. Näillä oli diagnosoitavissa meneillään oleva kaksisuuntaisen mielialahäiriön sairausjakso, josta myöhemmin käytetään nimeä indeksijakso.

Potilaat haastateltiin uudestaan 6 ja 18 kuukauden kuluttua. Itsetuhoista käyttäytymistä tutkittiin sekä indeksijakson että seurannan aikana itsemurha-ajatuksia kartoittavan asteikon avulla ja haastattelukysymyksin. Tietoja kerättiin myös sairauskertomuksista. Tieto erilaisista sairausjaksoista seurannan aikana koottiin yksityiskohtaiseksi graafiseksi kuvaajaksi (life-chart).

Tässä tutkimuksessa ilmeni, että itsetuhoinen käyttäytyminen on erittäin yleistä kaksisuuntaista mielialahäiriötä sairastavilla potilailla. Indeksijakson aikana 20 % potilaista yritti itsemurhaa ja itsemurha-ajatuksia esiintyi 61 %:llä. Masennus, toivottomuus, samanaikainen muu psykiatrisen sairastavuus ja aikaisempi itsemurhayritys osoittautuivat keskeisiksi riskitekijöiksi itsetuhoiselle käyttäytymiselle indeksijakson aikana. Itsetuhoisen käyttäytymisen esiintyvyys kaksisuuntaisen mielialahäiriön päätyyppien, tyyppi I:n ja II:n, välillä oli samanlaista.

Indeksijakson aikana tehdyt itsemurhayritykset sijoituivat sairauden masennus- ja sekamuotoisiin vaiheisiin. Itsemurha-ajatuksia esiintyi eniten sekamuotoisten jaksojen aikana. Toivottomuus ennusti itsemurhayrityksiä masennusjakson aikana. Sekamuotoisen vaiheen aikana itsearvioitu masennuksen syvyys ja alhaisempi ikä olivat itsemurhayritysten itsenäisiä riskitekijöitä.

18 kuukauden seurannan aikana 20 % potilaista yritti itsemurhaa. Aikaisemmat itsemurhayritykset, toivottomuus, masennusjakso tutkimukseen ottohetkellä ja alhaisempi ikä ennustivat itsemurhayrityksiä seuranta-aikana. Potilaista 55 % oli yrittänyt itsemurhaa joko ennen tutkimukseen ottoa, tai yritti sitä indeksijakson tai seurannan aikana.

Seuranta-aikana itsemurhayritysten ilmaantuvuus oli 37-kertainen sekamuotoisen jakson ja 18-kertainen masennusjakson aikana verrattuna muihin jaksoihin. Aikaisempi itsemurhayritys sekä masennus- tai sekamuotoisessa jaksossa vietetty aika ennustivat itsemurhayritystä seuranta-aikana.

Tutkimus osoittaa kaksisuuntaisesta mielialahäiriöstä kärsivien potilaiden olevan huomattavan itsetuhoaltis ryhmä: yli puolet potilaista on yrittänyt itsemurhaa. Kliinisesti on erittäin tärkeää tunnistaa kaksisuuntainen mielialahäiriö ja hoitaa sekamuotoiset jaksot ja masennusjaksot mahdollisimman nopeasti ja tehokkaasti, koska näihin molempiin liittyy huomattavan korkea itsemurhayritysten riski.

Avainsanat: kaksisuuntainen mielialahäiriö, itsemurha-ajatukset, itsemurhayritys.

ABBREVIATIONS

ANOVA	One-Way Analysis of Variance
APA	American Psychiatric Association
BD	Bipolar Disorder
BD I	Bipolar Disorder type I
BD II	Bipolar Disorder type II
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BHS	Beck Hopelessness Scale
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBT	Cognitive-Behavioural Therapy
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CT	Computed Tomography
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition
ECA	Epidemiological Catchment Area Study
ECT	Electroconvulsive Therapy
ESEMED	European Study on the Epidemiology of Mental Disorders
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
FFT	Family-Focused Therapy
HAM-D	Hamilton Rating Scale for Depression
HPA axis	Hypothalamic-Pituitary-Adrenal axis
HR	Hazard Ratio
HSD	Honestly Significant Difference Test
5-HTT	Serotonin transporter
HUCH	Helsinki University Central Hospital
ICD-10	International Classification of Diseases, 10 th edition
IPSRT	Interpersonal and Social Rhythm Therapy
JoBS	Jorvi Bipolar Study
LIFE	Longitudinal Interval Follow-up Evaluation
MDQ	Mood Disorder Questionnaire
MRI	Magnetic Resonance Imaging
NCS	National Comorbidity Survey

NCS-R	National Comorbidity Survey Replication
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NICE	National Institute for Health and Clinical Excellence
NIMH	National Institute of Mental Health
ODIN	Outcome of Depression International Network
OR	Odds Ratio
PET	Positron Emission Tomography
PIF	Psychoses in Finland
PSSS-R	Perceived Social Support Scale-Revised
RR	Relative Risk
SCID	Structured Clinical Interview for DSM-IV
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
SMR	Standardized Mortality Ratio
SOFAS	Social and Occupational Functioning Assessment Scale of DSM-IV
SPECT	Single-Photon Emission Computed Tomography
SPSS	Statistical Package for the Social Sciences for Windows
SSI	Scale for Suicidal Ideation
SSRI	Selective Serotonin Reuptake Inhibitors
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
SUPRE	Suicide Prevention
VDS	Vantaa Depression Study
WFSBP	The World Federation of Societies of Biological Psychiatry
WMH	World Mental Health
WHO	World Health Organization
WHO/SUPRE-MISS	Suicide Prevention-Multisite Intervention Study on Suicide
YMRS	Young Mania Rating Scale

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1. ABSTRACT

The Jorvi Bipolar Study (JoBS) is a collaborative ongoing bipolar research project between 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. The JoBS is a prospective, naturalistic cohort study of secondary level care psychiatric out-and inpatients with a new episode of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) bipolar disorder (BD).

Altogether, 1630 patients (aged 18-59) years were screened using the Mood Disorder Questionnaire (MDQ) for a possible new episode of DSM-IV BD. 490 patients were interviewed with semi-structured interview [the Structured Clinical Interview for DSM-IV Disorders, research version with Psychotic Screen (SCID-I/P)]. 191 patients with new episode of DSM-IV BD were included in the bipolar cohort study. Psychiatric comorbidity was evaluated using semi-structured interviews. At 6- and 18-month follow-up, the interviews were repeated and life-chart methodology was used to integrate all available information about nature and duration of all different phases. Suicidal behaviour was examined both at intake and follow-up by psychometric scale [Scale for Suicidal Ideation (SSI)], interviewer's questions and medical and psychiatric records. The aim of this thesis was to evaluate prevalence of suicidal behaviour and incidence of suicide attempts, and examine the wide range of risk factors for attempted suicide both, at intake and follow-up, in representative secondary-level sample of psychiatric in- and outpatients with BD.

In this study suicidal behaviour was common among psychiatric patients with BD. During the episode when patients were included into cohort study (index episode), 20% of the patients had attempted suicide and 61% had suicidal ideation. Severity of depressive episode and hopelessness were independent risk factors for suicidal ideation, whereas hopelessness, comorbid personality disorder and previous suicide attempt predicted suicide attempts during the index episode. There were no differences in prevalence of suicidal behaviour between bipolar I and II disorder; the risk factors were overlapping but not identical.

During the index episode, suicide attempts took place during depressive, mixed and depressive mixed phases. Furthermore, there were marked differences regarding level of suicidal ideation during different phases, with the highest levels during the mixed phases of the illness. Hopelessness was independently associated with suicidal behaviour during the depressive phase. A subjective rating of severity of depression (Beck Depression Inventory) and younger age predicted suicide attempts during mixed phases.

During the 18-month follow-up 20% of patients attempted suicide. Previous suicide attempts, hopelessness, depressive phase at index episode and younger age at intake were independent risk factors for suicide attempts during follow-up. Taken altogether, 55% patients attempted suicide before index episode, during index episode or during follow-up.

The incidence of suicide attempts was 37-fold during combined mixed and depressive mixed states and 18-fold during major depressive phase as compared with other phases. Prior suicide attempt and time spent in combined mixed phases - mixed and depressive mixed - and depressive phases independently predicted the suicide attempt during follow-up.

More than half of the patients have attempted suicide during their lifetime, a finding which highlights the public health importance of suicidal behaviour in bipolar disorder. Clinically, it is crucial to recognize BD and manage the mixed and depressive phases of bipolar patients fast and effectively, as time spent in depressive and mixed phases involves a remarkably high risk of suicide attempts.

Keywords: bipolar disorder, suicidal ideation, suicide attempt.

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 Valtonen H, Suominen K, Mantere O, Leppämäki S, Arvilommi P, Isometsä E.
Suicidal ideation and attempts in bipolar I and II disorders.
J Clin Psychiatry 2005;66:1456-1462.
- II Valtonen HM, Suominen K, Mantere O, Leppämäki S, Arvilommi P, Isometsä E.
Suicidal behaviour during different phases of bipolar disorder.
J Affect Disord 2007;97:101-107.
- III Valtonen HM, Suominen K, Mantere O, Leppämäki S, Arvilommi P, Isometsä E.
Prospective study of risk factors for attempted suicide among bipolar disorder patients.
Bipolar Disord 2006;8:576-585.
- IV Valtonen HM, Suominen K, Haukka J, Mantere O, Leppämäki S, Arvilommi P, Isometsä E.
Differences in incidence of suicide attempts during phases of bipolar I and II disorders.
Submitted.

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3. INTRODUCTION

Bipolar disorder is episodic, lifelong and a clinically severe mood disorder. Bipolar disorder poses a major public health concern due to high rate of mortality, morbidity, psychosocial impairment, psychosocial disability, health care costs, higher unemployment, decreased work productivity and secondary substance abuse (Altshuler et al., 2002; American Psychiatric Association, 2002; Angst et al., 2002; Coryell et al., 1987; 1993; Goetzl et al., 2003; Judd et al., 2002; 2003a; 2003b; 2005; Shi et al., 2004; Simon, 2003; Ösby et al., 2001). Rihmer and Angst (2005) have estimated the lifetime prevalence of bipolar disorder to be from 0.1% to 4.8%. There appear to be relatively few gender differences in bipolar disorder. The age of onset of bipolar disorder, most commonly around 20 years of age, is substantially (about 10 years) lower than that of unipolar depression (Rihmer and Angst, 2005). Bipolar disorder is associated with increased mortality due to cardiovascular diseases and particularly suicide (Ahrens et al., 1995; Angst et al., 2002; Ösby et al., 2001).

In the year 2000, approximately one million people died from suicide: a "global" mortality rate of 16 per 100 000, or one death every 31 seconds. In the last 45 years suicide rates have increased by 60% worldwide. Suicide is now among the three leading causes of death among those aged 15-44 years (both sexes) (WHO). Over 90% of suicide victims have a psychiatric disorder at the time of death (Harris and Barraclough, 1997). Risk for suicides varies according to type of psychiatric diagnosis. Approximately 60% of all suicides occur in relation to mood disorders (Mann and Currier, 2005). Other psychiatric disorders associated with an increased risk of suicide are schizophrenia, alcoholism and those personality disorders which are associated with impulsivity (Mann and Currier, 2005).

A meta-analysis (Harris and Barraclough, 1997) and two recent nationwide studies from Scandinavia (Ösby et al., 2001; Høyer et al., 2000) indicate a standardized mortality ratio of about 20 for BD sufferers. Bipolar disorder (BD) is associated with a significant risk of attempted suicide (Hawton et al., 2005). It is commonly estimated that 25-50% of them attempt suicide at least once (Goodwin and Jamison, 1990; Jamison, 2000; Slama et al., 2004), and 30-75% have suicidal ideation (Suppes et al., 2001; MacKinnon et al., 2005). A comprehensive view of risk factors related to suicidal behaviour in bipolar disorder is still emerging. Identifying the predictors of suicidal behaviour is a key for suicide prevention.

The Jorvi Bipolar Study (JoBS) is a prospective, naturalistic cohort study of 191 secondary-level care psychiatric out- and inpatients with a new episode of DSM-IV BD. In the JoBS the predictors of chronicity, recurrences, suicidal behaviour as well as work and functional disability are investigated and the adequacy of treatment evaluated. The present thesis focuses on suicidal behaviour among bipolar patients followed up for 18 months.

4. REVIEW OF THE LITERATURE

4.1 Bipolar Disorder

4.1.1 Definition of bipolar disorder

Bipolar disorder, or manic-depressive illness as it was previously named, is mental disorder characterized by recurrent episodes of mania, hypomania, mixed states and depression. Bipolar disorder is divided to bipolar I and bipolar II disorders. *Bipolar I disorder* is characterized by one or more manic or mixed episodes usually accompanied by major depressive episodes. *Bipolar II disorder* is characterized by one or more major depressive episodes and at least by one hypomanic episode. The soft bipolar spectrum includes cyclothymic depressions (BD-II½), antidepressant-associated hypomania (BD-III), hyperthymic depressions (BD-IV) and hyperthymic temperament (BD-V) (Akiskal et al., 2006). Bipolar disorder ranges from a pattern of mild depression and brief hypomania to one severe rapid cycling or predominant mania with psychotic features (Müller-Oerlinghausen et al., 2002).

4.1.2 Diagnosis of bipolar disorder

In Finland the tenth edition of the International Classification of Diseases (ICD-10) is used (WHO, 1993). DSM-IV is frequently used in psychiatric research (American Psychiatric Association, 2000). A semi-structured interview (SCID) was developed to increase diagnostic validity and it is based on DSM criteria (First et al., 1997). In this thesis DSM-IV criteria was used. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) divides *mood disorders* into the following categories: unipolar depression, bipolar disorders, mood disorder due to a general medical condition and substance induced mood disorder.

Major depressive episode is characterized by depressive mood or loss of interest or pleasure in nearly all activities most of the day for at least two consecutive weeks (Table 1). The main symptoms are accompanied by changes in appetite or weight, sleep and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans or attempts. Further, the episode must be accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning. There are no differences in DSM-IV criteria regarding unipolar depression or major depressive episode of bipolar disorder.

Manic episode is characterized by abnormally and persistently elevated, expansive or irritable mood lasting at least one week (or less if hospitalisation is required) (Table 2). The mood disturbance is accompanied by inflated self-esteem or grandiosity, decreased need for sleep, pressure of speech, flights of ideas, distractibility, increased involvement in goal-directed activities or psychomotor agitation and excessive involvement in pleasurable activities with a high potential for painful consequences. The disturbance must be sufficiently severe to cause marked impairment in social, occupational functioning or to require hospitalisation, or it is characterized by the presence of psychotic features.

Mixed episode is characterized by a period of lasting at least one week in which the criteria are met both for a manic episode and for a major depressive episode nearly every day (Table 3). Further, the disturbance must be sufficiently severe to cause marked impairment in social, occupational functioning or to require hospitalisation, or it is characterized by the presence of psychotic features.

Hypomanic episode is characterized by persistently elevated, expansive or irritable mood lasting at least four days (Table 4). The mood disturbance is accompanied by inflated self-esteem or grandiosity, decreased need for sleep, pressure of speech, flights of ideas, distractibility, increased involvement in goal-directed activities or psychomotor agitation and excessive involvement in pleasurable activities with a high potential for painful consequences. Hypomanic episode must be clearly different from the individual's usual nondepressed mood, and there must be a clear change in functioning that is not characteristic of the individual's usual functioning, and changes in mood and functioning must be observable by others.

Depressive mixed state is characterized by three or more simultaneous intra-episode hypomanic symptoms present for at least 50% of time during a major depressive episode (Benazzi and Akiskal, 2001).

Differential diagnosis is important to chart potential hypomanic and manic episodes when investigating depressive patients, the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000) may be a useful tool but is not sufficient without careful diagnostic interview to make an adequate diagnosis. The pilot study for the Jorvi Bipolar Study found that the sensitivity of MDQ was relatively high (0.85), but specificity only moderate (0.50). However, the optimal cut-off within this sample was found to be eight symptoms but accepting also minor problems due to episodes (sensitivity 0.90, specificity 0.61) (Isometsä et al., 2003). When an individual aged over 50 years has first manic or hypomanic episode possibility of organic aetiology of mood episode must be evaluated.

Table 1. DSM-IV criteria for Major Depressive Episode

- A. Five (or more) of following symptoms have been present during the same two week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure:
- (1) depressed mood most of the day, nearly every day
 - (2) markedly diminished interest or pleasure, in all, or almost all, activities most of the day, nearly every day
 - (3) significant weight loss or gain or decrease or increase in appetite nearly every day
 - (4) insomnia or hypersomnia nearly every day
 - (5) psychomotor agitation or retardation nearly every day (observable by others)
 - (6) fatigue or loss of energy nearly every day
 - (7) feelings of worthlessness or excessive or inappropriate guilt nearly every day
 - (8) diminished ability to think or concentrate, or indecisiveness, nearly every day
 - (9) recurrent thoughts of death, recurrent suicidal ideation without a specific plan or a suicide attempt or a specific plan for committing suicide.
- B. The symptoms do not meet criteria for a Mixed Episode.
- C. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
- D. The symptoms are not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical condition.
- E. The symptoms are not better accounted for by bereavement.
-

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

Table 2. DSM-IV criteria for Manic Episode

- A. A distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least one week (or less if hospitalisation is required).
- 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
 - (3) more talkative than usual or pressure to keep talking
 - (4) flights of ideas or subjective experience that thoughts are racing
 - (5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimulus)
 - (6) increased involvement in goal-directed activities or psychomotor agitation
 - (7) excessive involvement in pleasurable activities with a high potential for painful consequences.
- C. The symptoms do not meet criteria for a Mixed Episode.
- D. The disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalisation 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., drug of abuse, a medication) or a general medical condition.
-

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

Table 3. DSM-IV criteria for Mixed Episode

- A. The criteria are met for both a Manic Episode and for a Major Depressive Episode (except duration) nearly every day during at least a 1-week period.
 - B. 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 hospitalisation to prevent harm to self or others or there are psychotic features.
 - C. The symptoms are not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical condition.
-

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

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
 - (3) more talkative than usual or pressure to keep talking
 - (4) flights of ideas or subjective experience that thoughts are racing
 - (5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimulus)
 - (6) increased involvement in goal-directed activities or psychomotor agitation
 - (7) excessive involvement in pleasurable activities with a high potential for painful consequences.
 - 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 hospitalisation and there are no psychotic features.
 - F. The symptoms are not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical condition.
-

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

4.1.3 Epidemiology of bipolar disorder

Lifetime prevalence of bipolar I disorder is often assumed to be about 1%, whereas there is no reliable estimate of prevalence of bipolar II disorder, mainly because the challenge for diagnosis of hypomania in general population surveys. However, Rihmer and Angst (2005) have estimated the lifetime prevalence of bipolar disorder to be from 0.1% to 4.8%. Recent Finnish general population study, the Psychoses in Finland (PIF), which is based on the Health 2000 Study, found that lifetime prevalence for bipolar I disorder was 0.24% (Perälä et al., 2007) (Table 5). Perälä et al. (2007) noticed in their comment that the inclusion of register diagnosis of BD I disorder for the nonresponse group would lift the prevalence to 0.42%.

In the National Institute of Mental Health (NIMH) Epidemiological Catchment Area Study (ECA), the lifetime prevalence rate of bipolar I disorder was 0.8%, and of bipolar II 0.5% (Rihmer and Angst, 2005; Weissman et al., 1988). The National Comorbidity Survey Replication (NCS-R) is a nationally representative face-to-face household survey of English-speaking household residents aged 18 years and older in the United States (N=9282) conducted between February 2001 and April 2003 using the fully structured World Health Organization (WHO) World Mental Health (WMH) Survey version of the Composite International Diagnostic Interview (CIDI) (Kessler et al., 2004). Lifetime prevalence of DSM-IV/ WMH-CIDI Disorders in Total NCS-R Sample was 3.9 for bipolar disorder (I-II) (Kessler et al., 2005a) and 12-month prevalence of DSM-IV and WMH-CIDI Disorders was 2.6 for bipolar I and II disorders (Kessler et al., 2005b). In a previous National Comorbidity Survey (NCS) lifetime prevalence of bipolar I disorder was estimated to be 1.6% and 12-month prevalence only slightly lower (Kessler et al., 1994)

The Netherlands Mental Health Survey and Incidence Study (NEMESIS) is a prospective survey in the Dutch general population aged 18-64, with three assessment points in 1996, 1997 and 1999. A total of 7076 respondents were interviewed. The lifetime prevalence of bipolar disorder found in the NEMESIS was 1.9% (ten Have et al., 2002). National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) found that prevalence of 12-month and lifetime DSM-IV bipolar I disorder were 2.0% (95% CI=1.82 to 2.18) and 3.3% (95% CI=2.76 to 3.84) (Grant et al., 2005). Community studies conducted in European countries found 12-month prevalence of bipolar disorder range from 0.2% to 1.1% (Wittchen and Jacobi, 2005; Pini et al., 2005).

An Australian general population survey study reported 12-month prevalence for bipolar disorder to be 0.5% (Mitchell et al., 2004). In recent Chinese study according the lifetime prevalence of DSM-IV/WMH-CIDI Disorders study found 0.1% lifetime prevalence for bipolar disorder (I-II) (Lee et al., 2006). The Zurich cohort study (22-35 years young adults) identified a 5.5% prevalence of DSM-IV hypomania/mania and a further 2.8% for brief hypomania (recurrent and lasting 1-3 days) (Angst, 1998).

In the Finnish study which was based on the Finnish Hospital Discharge Register from 1987 to 1994, Räsänen et al. (1998) reported the annual rate of all hospitalized patients with bipolar disorder was 0.03%. In their conclusions, they hypothesized the low prevalence and incidence of bipolar disorder in Finland may be due to late onset-age. Sorvaniemi and Salokangas (2005) reported the 1-month and 12-month prevalence of BD were 0.9% and 2.1% respectively. In community mental health centres, the corresponding figures were 4.4% and 7.6% (Sorvaniemi and Salokangas, 2005). Kieseppä et al. (2004) estimated the annual incidence of bipolar disorder I was 5.8/100 000 (95% CI=5.4 to 6.3).

Delays of diagnosis of bipolar disorder

Bipolar disorder is often misdiagnosed. First, there is a long delay before a correct diagnosis is made. Second, there are patients who switch to bipolar disorder from unipolar disorder just during follow-up. In a survey of bipolar members of the United States National Depressive and Manic-Depressive Association, a third (34%) of respondents had had more than 10 years of treatment before receiving a bipolar diagnosis and 69% were misdiagnosed, with the most frequent misdiagnosis being unipolar depression (Hirschfeld et al., 2003). Mantere et al. (2004) reported that in Jorvi Bipolar Study (JoBS) 25.6% of bipolar I patients and 50.5% of bipolar II were previously undiagnosed. Respectively, Baldessarini et al. (1999) reported that the time from illness onset to maintenance treatment takes on average 8 years (7 years for type I, 10 years for type II syndromes). Furthermore, bipolar disorder begins often with depressive episode and thus cannot be diagnosed as bipolar disorder before first mixed, manic or hypomanic episode.

Table 5. Prevalence of bipolar disorder

Lifetime prevalence of bipolar disorder (I and II)

NCS-R	3.9 %	Kessler et al., 2005a	United States	N=9282
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Lifetime prevalence of bipolar I disorder

NCS	1.6 %	Kessler et al., 1997	United States	N=8098
NEMESIS	1.9 %	ten Have et al., 2002	Netherlands	N=7076
NESARC	3.3 %	Grant et al., 2005	United States	N=43093
PIF	0.2 %	Perälä et al., 2007	Finland	N=8028

12-month prevalence of bipolar disorder (I and II)

NCS-R	2.6 %	Kessler et al., 2005b	United States	N=9282
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12-month prevalence of bipolar I disorder

NESARC	2.0 %	Grant et al., 2005	United States	N=43093
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Switching from unipolar to bipolar disorder

Angst and colleagues (2005) reported that a diagnostic change from depression to bipolar I occurred in about 1% of the patients per year and to bipolar II disorders in about 0.5% per year. In their over an average of 20 years follow-up a diagnostic change from depression to bipolar disorder occurred in 39.2% of cases (121/309), in 75 of them (24.3%) changing to BD-I and in 46 (14.9%) changing to BD-II (Angst et al., 2005). Risk factors for a change from depression to BD-I were male gender and an early onset of the disorder; risk factors for a change from depression to BD-II were female gender, a later onset of the disorder and a positive family history of mania (Angst et al., 2005). Goldenberg et al. (2001a) reported in a 15-year follow-up that 27% of the study group (N=74) had developed one or more distinct periods of hypomania, while another 19% had at least one episode of full bipolar I mania. In the Finnish Vantaa Depression Study (VDS) the 18-month follow-up 13 of unipolar depressed patients 269 (5%) switched to bipolar disorder (Melartin et al., 2004).

4.1.4 Aetiology and pathogenesis of bipolar disorder

The aetiology of bipolar disorder is multifactorial and poorly known. Bipolar disorder is probably determined by multiple genetic loci and environmental influences also play an important role in it's development (Taylor et al., 2002; Smoller and Finn, 2003). Independent of familial loading, life events increase the liability to mood disorders in children of patients with bipolar disorder but the effects slowly diminish with time (Hillegers et al., 2004).

Heritability

Bipolar disorder is highly heritable (McGuffin et al., 2003). Family, twin and adoption studies have been essential in defining the genetic epidemiology of bipolar disorder (Hayden and Nurnberger, 2006; Smoller and Finn, 2003; Taylor et al., 2002). Kieseppä et al. (2004) demonstrated the high heritability of bipolar disorder in a nationwide population-based twin sample assessed with structured personal interviews. The model of genetic and specific environmental variance was the best-fitting model, with a heritability estimate of 0.93 (Kieseppä et al., 2004). Family studies have documented that first-degree relatives of affected individuals have an excess risk of the disorder, while twin studies (and to a lesser extent, adoption studies) suggest that genes are largely responsible for this familial aggregation (Smoller and Finn, 2003). Taylor et al. (2002) report in their review that family studies have shown the approximate lifetime risk of a first-degree relative of a bipolar proband to be 5% to 10%. Moreover, studies of monozygotic twins show that their risk of contracting the disease is as much as 75 times greater than that for the general population. In addition, adoption studies have demonstrated that biological relatives of bipolar patients are substantially more likely to have the disorder than are adoptive relatives (Taylor et al., 2002).

Structural brain imaging

Neuroimaging studies can be divided into structural studies and functional brain imaging studies. Computed tomography (CT) and magnetic resonance imaging (MRI) are used in structural studies. Several recent neuroimaging studies of mood disorders have concluded that bipolar disorder is associated with structural brain changes, but their results have been inconsistent (McDonald et al., 2004). The recent meta-analysis by McDonald et al. (2004) of regional morphometric MRI studies was based on 26 studies comprising volumetric measurements on up to 404 independent patients with bipolar disorder. The authors reported that patients with bipolar disorder had enlargement of the right lateral ventricle, but no other regional volumetric deviations which reached significance (McDonald et al., 2004). Strong heterogeneity existed for several regions, including the third ventricle, left subgenual prefrontal cortex, bilateral amygdala and thalamus (McDonald et al., 2004). White matter hyperintensities are relatively non-specific lesions reported to occur with increased frequency in BD, although this is a matter of debate (Sublette et al., 2006). It has been hypothesized that white matter hyperintensities may produce mood disorders by interrupting relevant brain pathways (Soares and Mann, 1997). Furthermore, there is growing awareness of the effect of white matter hyperintensities on neuropsychological functioning (Singh et al., 2005).

Functional brain imaging

Positron emission tomography (PET), single-photon emission computed tomography (SPECT) and, more recently, functional magnetic resonance imaging (fMRI), provide methods for defining the anatomy of brain function. These technologies can be used to produce brain maps that correspond to changes in brain metabolism or blood flow (representing brain 'activation'), which are obtained at rest or during cognitive tasks designed to study specific neural networks (Strakowski et al., 2005). Functional imaging studies report activation differences between bipolar and healthy controls in anterior limbic regions (Strakowski et al., 2005).

Neurochemistry

There is considerable evidence that dopamine and noradrenalin system abnormalities are present in bipolar disorder (Singh et al., 2005; Manji et al., 2003). Furthermore, evidence from neuroimaging post-mortem and genetic studies suggests that bipolar disorder is associated with abnormalities of the serotonin transporter (5-HTT) system (Cannon et al., 2006; Ichimiya et al., 2002; Mann et al., 2000). The direction of abnormality in the brainstem was opposite to that found in the cortex, thalamus, and striatum. Elevated 5-HTT binding in the cortex may be related to anxiety symptoms and syndromes associated with BD (Cannon et al., 2006). Also, cholinergic system abnormalities are present in bipolar disorder (Manji et al., 2003). More recently, research into the pathophysiology and treatment of mood disorders has moved from a focus on neurotransmitters and cell surface receptors to intracellular signalling cascades (Manji et al., 2003). Conceptual and experimental evidence suggests that abnormalities in the regulation of signal transduction

cascades and neuroplasticity could, more primarily than abnormalities monoamine neurotransmitter systems, underlie the pathophysiology of BD (Manji et al., 2003). Magnetic resonance spectroscopy investigations have also revealed abnormalities of membrane and second messenger metabolism (Strakowski et al., 2005).

Neuroendocrinology

The hypothalamus integrates disparate information about the milieu and is the primary coordinator of mass-sustained organismic functions (e.g., circadian rhythms, appetite and motivational states, which may be experienced as mood) (Seidman, 2005). The hormone axes are critical components of hypothalamic-regulated homeostatic adaptation (Seidman, 2005). Activation of the hypothalamic-pituitary-adrenal (HPA) axis modulates cognitive processes, pain and sleep (Seidman, 2005). Stress is primarily mediated by HPA axis (Singh et al., 2005). One prevailing etiological theory in BD proposes abnormalities of an interactive system, whereby hypothalamic releasing factors trigger pituitary production of adrenocorticotropic hormone, stimulating the adrenal gland to produce corticosteroids that provide feedback to the brain (Sublette et al., 2006).

4.1.5 Course and outcome of bipolar disorder

Longitudinal course of bipolar disorder is chronic and dominated by depressive features of disorder and affective symptoms below the threshold of major depressive episode and mania (Judd et al., 2002; 2003a; 2003b; Post et al., 2003; Perlis et al., 2006; Mantere et al., in press). *Relapse* is usually defined as a return of a mood episode after a period of less than 2 months with symptoms below the mood episode threshold. *Recurrence* is usually 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.

In the Stanley Foundation Bipolar Network Study, a prospective follow up, over half of patients (62.8%) had 4 or more episodes/year and nearly third of patients (30.6%) had more than 8 episodes/year (Post et al., 2003). In the multicentre Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study during up to 2 years of follow-up, nearly half of patients (48.5%) experienced recurrences; the majority of recurrences (70%) were to the depressive pole, with a ratio of 2.5:1 for depressive recurrence versus manic/mixed/hypomanic episodes (Perlis et al., 2006). Recurrence was frequent and associated with the presence of residual mood symptoms at initial recovery (Perlis et al., 2006). In the McLean-Harvard First-Episode Mania Study within 2 years of syndromal recovery, 40% experienced a new episode of mania (20%) or depression (20%) and 19% switched phases without recovery (Tohen et al., 2003). Syndromic recovery was defined by Tohen et al. (2003) as patient no longer met DSM criteria for a manic, mixed, or depressive syndrome. Predictors of mania recurrence were initial mood-congruent psychosis, lower premorbid occupational status and initial manic presentation. Predictors of depression onset were higher occupational status, initial mixed presentation and any comorbidity (Tohen et al., 2003).

In the National Institute of Mental Health (NIMH) Collaborative Depression Study, a mean of 13.4 years of prospective follow-up, depressive symptoms dominated the course of bipolar II disorder; patients experienced approximately 39 times more depressive symptoms (50.3% of all follow-up weeks) than hypomanic symptoms (1.3% of all follow-up weeks) and patients were symptomatic 53.9% of all follow-up weeks (Judd et al., 2003a). In their analogous study regarding bipolar I patients they found that patients were symptomatically ill 47.3% of weeks throughout a mean of 12.8 years of follow-up (Judd et al., 2002).

Symptom severity and psychosocial disability fluctuate together during the course of illness (Judd et al., 2005; Altshuler et al., 2002). Each increase or decrease in depressive symptom severity is associated with a highly significant stepwise increase or decrease in psychosocial disability (Judd et al., 2005). Likewise, patients with BD-I show a similar pattern of significant stepwise change in impairment as their level of manic symptom severity changes between mild subsyndromal symptoms and hypomania or between hypomania and mania (Judd et al., 2005).

Recent review reported that predictors of episodes of bipolar disorder include stressful life events, increased number of previous episodes, decreased interval between episodes and persistence of affective symptoms and episodes. Factors associated with longer survival times include psychotherapy, social support and medication adherence (Altman et al., 2006). A growing body of evidence suggests that bipolar patients exhibit neuropsychological impairment that persists even during the euthymic state, which may be a contributory factor to a poor psychosocial outcome (Robinson and Ferrier, 2006). The weight of evidence suggests that greater neuropsychological dysfunction in bipolar disorder is associated with a worse prior course of illness, particularly the number of manic episodes, hospitalisations and length of illness (Robinson and Ferrier, 2006).

4.1.6 Comorbidity of bipolar disorder

The majority of patients with bipolar disorder, of all ages and both genders, have at least one comorbid psychiatric or medical disorder and many have more than one (Krishnan, 2005). Axis I comorbidity is associated with severity of illness, earlier age at onset, rapid cycling, family history of alcoholism, drug abuse and suicidal behaviour (McIntyre et al., 2006; Nolen et al., 2004; Frye et al., 2003; McElroy et al., 2001). Somatic comorbidity is also correlated with several indicators of poorer prognosis and outcome e.g. longer duration and higher severity of depression (measured by HAM-D) in bipolar I disorder (Thomson et al., 2006).

In the Stanley Foundation Bipolar Network Study 65% of the patients met DSM-IV criteria for at least one lifetime comorbid disorder, and 33% met criteria for at least one current comorbid disorder; 24% patients had three or more lifetime disorders (McElroy et al., 2001). McElroy et al. (2001) found that 42% of patients met criteria for a comorbid anxiety disorder, 42% for comorbid substance use disorder and 5% for an eating disorder. Bipolar disorder is associated with high prevalence of alcohol and substance abuse or dependence.

Chengappa et al. (2000) reported 57.8% subjects with bipolar I disorder abused, or were dependent on one or more substances or alcohol, and Frye et al. (2003) found 38% of patients met the criteria for a lifetime history of alcoholism and the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Study (ECA) found that over 60% of patients with bipolar I disorder developed a substance use disorder during their lifetime.

On the basis of The National Hospital Discharge Register in Finland, Sorvaniemi and Hintikka (2005) studied the recorded prevalence of psychiatric comorbidity among bipolar inpatients by clinicians and the associated factors. Of the 2687 hospital stays in 1998, 82% had no other recorded psychiatric diagnosis except an episode of bipolar disorder. Psychiatric comorbidity was recorded in 18% of hospital stays, of which 20% had two comorbid psychiatric diagnoses. Substance-related disorders (11%) were the most commonly recorded comorbid disorders. Personality disorders were recorded in 6%, and anxiety disorder in 1% of the hospital stays (Sorvaniemi and Hintikka, 2005). Studies based on discharge register records indicate that comorbidity disorders of BD are under recognized in clinical task. Mantere et al. (2006) have also reported high rates of comorbidity related to BD based on Structured Clinical Interview for DSM-IV Disorders (both Axis I and II). Of the patients, 70% had a current comorbid disorder; on Axis I 60%, Axis II 43%. Anxiety disorders were prevalent in 45%, substance use disorders in 20% and eating disorders 8% (Mantere et al., 2006).

4.1.7 Treatment of bipolar disorder

The goals of treatment of bipolar disorder are the treatment of acute phase and prevention of future episodes. Treatment of bipolar disorder should always consist of pharmacotherapy and psychosocial interventions. Pharmacotherapy of bipolar disorder is usually divided to acute phase treatment and maintenance treatment. Following recommendations of pharmacotherapy are based on Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for management of patients with bipolar disorder and it's update in 2007 (Yatham et al., 2005; 2006), National Institute for Health and Clinical Excellence (NICE) clinical guideline (2006): The management of bipolar disorder in adults, children and adolescents in primary and secondary care, The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment (Grunze et al., 2004) and American Psychiatric Association: Practice guideline for the treatment of patients with Bipolar disorder (APA, 2002). Response, regarding pharmacotherapy, means that the patient has experienced at least a 50% reduction in symptoms as assessed on a standard psychiatric rating scale, for instance, Hamilton Depression Rating Scale. Remission is used when no DSM symptoms are present and the patient is actually well.

4.1.7.1 Pharmacotherapy

Acute phase pharmacotherapy

Manic episode

Lithium, divalproex sodium, atypical antipsychotics are recommended as a first-line acute pharmacological treatment of manic episode. Lithium is superior to placebo and comparable in efficacy to conventional antipsychotics and anticonvulsant agents, with response occurring in about 50-70% of patients. Lithium has also been shown to be as effective as the atypical antipsychotics, olanzapine, risperidone and quetiapine, and the conventional antipsychotic, haloperidol. In a meta-analysis, the efficacy of divalproex was superior to placebo and equivalent to lithium and carbamazepine in the treatment of mania. Clinically, divalproex sodium is preferred because it has fewer gastrointestinal side effects compared with divalproex and valproic acid. In two studies examining the efficacy of divalproex compared with olanzapine in acute mania, one showed similar efficacy while the other showed statistically the significant superiority of olanzapine. A pooled analysis comparing an oral loading of divalproex to lithium or olanzapine showed no differences in early efficacy between these agents. Atypical antipsychotic monotherapy with olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole are also recommended for the first-line treatment of acute mania.

The combinations of lithium or divalproex with various atypical antipsychotics (risperidone, quetiapine or olanzapine) have demonstrated significant beneficial effects compared with lithium or divalproex monotherapy. If therapy with one of the first-line agents (lithium, divalproex or an atypical antipsychotic) at optimal doses is inadequate or not tolerated, the next step should involve switching to or adding-on an alternate first-line agent. In patients who are inadequately responsive to first-line agents, second-line choices would include other anticonvulsants such as carbamazepine and oxcarbazepine, the combination of lithium plus divalproex or electroconvulsive therapy (ECT). If a patient is taking an antidepressant at the onset of an acute manic episode, the antidepressant should be stopped. Benzodiazepines are recommended as adjunctive therapy rather than as primary antimanic agents. Monotherapy with gabapentin, topiramate, lamotrigine, verapamil, tiagabine, risperidone and carbamazepine are not recommended for the treatment of acute mania.

Mixed episode

The simultaneous presentation of manic and depressive symptoms presents significant treatment challenges. Lithium is not as effective in mixed states as it is in classic mania, while divalproex appears to be equally effective in both mixed episodes and pure mania. Atypical antipsychotics alone or in combination with lithium or divalproex have shown conflicting results, but for the most part appear to be as effective in patients with mixed episodes as in those with classic mania. Conventional antipsychotics are not recommended for treatment of mixed states. Antidepressants also are not recommended during mixed states.

Depressive episode

Lithium remains a recommended first-line therapy for acute bipolar depression with response rates ranging from 64% to 100%. Long-term lithium treatment is associated with reduced risk of suicide and suicide attempts among bipolar disorder patients (Baldessarini et al., 2003; 2006a; Tondo et al., 2000; 2003; Cipriani et al., 2005; Müller-Oerlinghausen et al., 2005; Kessing et al., 2005). Thus, lithium is indicated for depressive and suicidal BD patients. Antidepressants may be useful as adjunctive therapy for bipolar depressed patients who cannot tolerate high serum lithium levels, or who have depressive symptoms that are refractory to lithium. Lamotrigine and quetiapine monotherapy are also recommended as a first-line therapy for depressive episode. Olanzapine plus Selective Serotonin Reuptake Inhibitors (SSRI) and lithium or divalproex plus SSRI/bupropion continue to remain the other first-line options by the update of CANMAT 2007. Antidepressants should be avoided for patients with depressive episode who have rapid cycling. Gabapentin is not recommended for treatment of depressive episode.

Maintenance treatment

Maintenance treatment has multiple goals: prevent relapses, reduction of subthreshold symptoms, reduction of suicide risk and reduction of cycling frequency and mood instability as well as improvement of functioning (American Psychiatric Association, 2002). Four medications have been approved by the United States Food and Drug Administration (FDA) for maintenance treatment of bipolar disorder: lithium, lamotrigine, olanzapine and aripiprazole. All these medications have been studied as long-term relapse prevention monotherapy in bipolar disorder (Keck, 2006). However, lamotrigine has not been recommended as a single, first-line agent in bipolar I disorder, but only for patients with mild manias.

4.1.7.2 Psychosocial interventions

Various forms of psychosocial intervention have been found efficacious as adjunctive treatments for bipolar disorder. These include Family-Focused Therapy (FFT), Interpersonal and Social Rhythm Therapy (IPSRT), Cognitive-Behavioural Therapy (CBT) and individual or group psychotherapy (Miklowitz et al., 2000; Miklowitz, 2006; Colom et al., 2003; Lam et al., 2005; Frank et al., 2005).

The psychosocial interventions usually have same common features (Keck, 2006). Firstly, they emphasize the need for medication, education about medication and adherence. Secondly, they emphasize detection of early warning signs for recurrence. Thirdly, they stress the importance of helping patients cope with and anticipate stressors that trigger mood episodes. Fourthly, it is considered important to identify and treat comorbid illnesses (Keck, 2006). Interpersonal therapy with a social rhythm component IPSRT may also help promote periods of euthymia in bipolar patients (Frank et al., 2005).

Patients with bipolar I disorder suffering from frequent relapses were randomly assigned into a cognitive therapy plus medication group or a controlled condition of medication only (Lam et al., 2005). Patients in the cognitive therapy group had significantly fewer days in bipolar episodes after the effect of medication compliance was controlled. The results showed that cognitive therapy had no significant effect in relapse reduction over the last 18 months of the study period (Lam et al., 2005). In disagreement, Scott et al. (2003) compared the effectiveness of treatment as usual with Cognitive Behavioural Therapy. They found that more than half of the patients had a recurrence by 18 months and they found no significant differences between these two groups (Scott et al., 2003).

Patients assigned to FFT plus mood stabilizing medication had fewer relapses and longer delays before relapses during the study year, compared with intervention involving two family education sessions and follow-up crisis management plus mood stabilizing medication. Patients in FFT also showed greater improvements in depressive (but not manic) symptoms (Micklowitz et al., 2000).

Yet cognitive behavioural psychotherapies and psychoeducational approaches do not appear to be frequently or systematically employed in clinical practice, and this may contribute to the considerable residual morbidity and mortality associated with conventional treatment (Post and Leverich, 2006). As Miklowitz and Taylor (2006) report there is a need for randomized clinical trials of Family-Focused Therapy, or other adjunctive psychosocial interventions, to investigate the effectiveness of these treatments to reduce suicidal behaviour of bipolar patients.

4.2 Suicidal behaviour

The concept of suicidal behaviour ranges from suicidal ideation to suicide attempts and completed suicide (Table 6). Suicidal behaviour may vary with respect to manifestation, performance, seriousness and lethality. Suicidal behaviour is characterized with a variety of terminology in the literature. The American Psychiatric Association's (APA) definitions of terms were used in this thesis (APA, 2003).

4.2.1 Classification of suicidal behaviours

Table 6. Classification of suicidal behaviour by Beck (1986)

I.	Suicide Ideation Thinking, planning Impulse or desire A. Intent to die (High, medium, low, none)
II.	Suicide attempt A. Intent B. Lethality C. Method
III.	Completed suicide A. Intent B. Method

4.2.2 Risk factors of suicidal behaviour and stress-diathesis model

Suicidal behaviour is a result of the interaction between psychological, social and biological factors (van Heeringen et al., 2000). Nongenetic familial factors that may contribute to risk of suicidal behaviour include the effect of parenting, sexual and physical abuse. Suicidal behaviour is the result of the triggering of psychobiological defeat scripts as a consequence of the perception of uncontrollable rejection or loss. It is highlighted by the fact that the environment appears to exert its influence even in the antenatal, perinatal and early postnatal periods, and thus affects our ability to deal with stressors at a later age (van Heeringen et al., 2000).

There is clear evidence that the activity of three neurobiological systems have a role in the pathophysiology of suicidal behaviour. This includes (van Heeringen, 2003; Mann, 2003): hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis, dysfunction of the serotonergic (5-HTTergic) system and excessive activity of the noradrenergic system. Hyperactivity of the hypothalamo-pituitary-adrenal axis and high activity of the noradrenergic system appear to be involved in the response to stressful events (van

Heeringen, 2003). Dysfunction of the serotonergic system is thought to be trait-dependent and associated with disturbances in the regulation of anxiety, impulsivity and aggression (van Heeringen, 2003; Mann and Currier, 2005). Postmortem studies of suicide victims have revealed decreased serotonin activity in the ventrolateral prefrontal cortex (Mann et al., 1999). Prefrontal localized hypofunction and impaired serotonergic responsivity are proportional to the lethality of the suicide attempt and may mediate the effects of suicide intent and impulsivity on lethality (Mann, 2003). There is disagreement regarding a possible link between plasma polyunsaturated fatty acid status and suicidal behaviour (Sublette et al., 2006; Hakkarainen et al., 2004).

A number of psychological variables have been found associated with suicidal behaviour: impulsivity, dichotomous thinking (tendency to think in terms of all or nothing), cognitive rigidity, hopelessness, problem-solving deficits, over-general autobiographic memory (tendency to remember events in a summarized and over-general way) and biases in future judgement (Beck, 1986; Williams and Pollock, 2000). Freud proposed that most individuals cope with the loss of a loved person through the experience of mourning. However, he believed there are other certain vulnerable individuals for whom the loss experience is unbearable and generates enormous anger. The individual feels ambivalence but preserves the mental image of the loved person by internalization and it becomes part of the ego. Feelings of anger towards the lost object are not possible to express and so they are transformed into self-censure and the wish to harm oneself. When these feelings reach a critical pitch they lead to the urge to destroy the self (Williams and Pollock, 2000).

Hopelessness is a key psychological variable of suicidal behaviour (Beck et al., 1986; 1989; 1990). Hopelessness can be a state or trait-related variable (Mann et al., 1999). Hopelessness has proven to be a better predictor of suicidal intent than depression, and is believed to mediate the association between depression and suicidal behaviour (Beck, 1986). Hopelessness, or the absence of rescue factors such as positive expectancies, thereby may also occur independent of depression, or apparent excess of degree of depression. Whether hopelessness leads to suicidal behaviour depends upon the presence or absence of risk and protective factors. However, little is known about factors that protect against the development or occurrence of hopelessness in depressed individuals (van Heeringen et al., 2000).

Stress-diathesis model

Mann and colleagues (1999) have proposed a stress-diathesis model to explain the relationship between the risk factors affecting the threshold for suicidal behaviour and the precipitants that trigger it. This model understands the diathesis as a predisposition to suicidal behaviour in individuals. That is, a set of enduring conditions or traits constitutes a diathesis, the presence of which makes an individual more likely to engage in suicidal behaviour when encountering a stressor, than someone without the diathesis (Mann et al., 1999). Thus, aggressive and impulsive traits and tendency to pessimism (more suicidal ideation, hopelessness, subjective depression, a perception of fewer reasons for

living) are two elements of the diathesis (Mann et al., 1999). Among the many types of stressors, the onset or acute worsening of psychiatric disorder is nearly always present in suicide attempters (Mann and Currier, 2005). Furthermore, Mann and colleagues (1999) suggest that a patient must have at least one major risk factor from each domain (stressor and diathesis) to be at high risk for suicide.

4.2.3 Suicidal ideation

4.2.3.1 Definition of suicidal ideation

Suicide ideators are commonly defined as individuals who have thoughts and wishes of suicide, but have not made any overt suicide attempt (Beck, 1986). Suicidal ideation includes suicide threats, suicidal preoccupations and expressions of the wish to die as well as indirect indicators of suicide planning. Suicidal ideation appears to be an important marker for identifying patients at risk for suicide (Brown et al., 2000) and suicide attempts (Mann et al., 1999). In a 20-year prospective study of risk factors for suicide in psychiatric outpatients, Brown and his co-workers found patients who scored three or higher on the Scale for Suicidal Ideation (SSI) were approximately seven times more likely to commit suicide than patients who scored less than three (Brown et al., 2000).

4.2.3.2 Epidemiology of suicidal ideation

Weissman et al. (1999) reported that the lifetime prevalence of suicidal ideation varies from 2% to 18%, whereas Bertolote et al. (2005) found that the rate for suicidal ideation varies from 2.6% to 25.4% in the general population. Kessler et al. (2005c) reported no statistically significant differences between the National Comorbidity Survey (NCS) and the National Comorbidity Survey Replication (NCS-R) in the 12-month prevalence of suicidal ideation (2.8% vs. 3.3%), suicide plans (0.7% vs. 1.0%) or suicide gestures (suicide attempt without intention) (0.3% vs. 0.2%). Suicidal ideation can be measured by one item of Beck Depression Inventory (BDI) or Scale for Suicidal Ideation (SSI). Furthermore, suicidal ideation can be charted during a different time period. These factors explain the differences of epidemiology of suicidal ideation

The Outcome of Depression International Network (ODIN) study involves five countries in Europe (N=12 000). Adults aged between 18 and 64 were selected from the general population and screened for possible depressive disorder using the Beck Depression Inventory (BDI). As a part of this study Casey et al. (2006) recently found suicidal ideation to be reported at 7.4% in Norway, 2.3% in Spain, 7.4% in Wales, 9.8% in Finland and 14.6% in Ireland based on detailed analysis of item 9 of the BDI, which measured the severity of suicidal ideation.

The European Study on the Epidemiology of Mental Disorders (ESEMED) is a cross-sectional household survey carried out in six European countries (Belgium, France, Germany, Italy, the Netherlands and Spain). In this study 21,425 respondents (aged 18 years or older) were interviewed between January 2001 and August 2003. Lifetime prevalence of suicidal ideation was 7.8% (Bernal et al., 2006).

The Finnish 12-month follow-up study of suicidal ideation, Hintikka et al. (2001), reported that the 12-month incidence was (4.6%) and prevalence of suicidal ideation (14.7%) in the general population. Suicidal ideation was higher in men than in women (9.2% and 3.1%, respectively). Sixty-nine per cent of those men and 59 % of those women who had suicidal ideation at baseline continued to have suicidal thoughts on follow-up (Hintikka et al., 2001).

4.2.3.3 Risk factors of suicidal ideation

Studies of nonfatal suicidal behaviour have focused mainly on risk factors for suicide attempts and only few studies focused on suicidal ideation. Suicidal ideation can appear at any time in life, and most individuals who report suicidal ideation will never attempt suicide (Bernal et al., 2006). The risk for suicidal ideation is increased by depression (Casey et al., 2006; Hintikka et al., 2001), but decreased by being older (age ≥ 30 years), being married, having someone who is concerned for you and having people to count on (Casey et al., 2006). In NCS and NCS-R surveys suicidal ideation was related to younger age, being female and low level of education (Kessler et al., 2005c).

Sokero et al. (2003) reported hopelessness, alcohol dependence or abuse, low level of social and occupational functioning and poor received social support to be significant independent risk factors for suicidal ideation among psychiatric in- and outpatients with DSM-IV major depressive disorder. Sokero et al. (2006) have also reported that a decline in suicidal ideation among patients with major depressive disorder is predicted by a preceding decline in hopelessness and depressive symptoms.

4.2.4 Suicide attempt

4.2.4.1 Definition of suicide attempt

Suicide attempt is defined as a self-injurious behaviour with a nonfatal outcome accompanied by evidence (either explicit or implicit) that the person intended to die (APA, 2003). Suicide attempts vary in both lethality and suicidal intent (Mann and Currier, 2005). A suicide attempt may or may not result in injuries (O'Carroll et al., 1996). An *aborted suicide* attempt refers to an event in which an individual is one step away from attempting suicide, but does not complete the act, and thus incurs no physical injury (APA, 2003; Barber et al., 1998). By definition, an aborted suicide attempt had to involve at least some degree of intent to die, a change of mind immediately before the actual attempt and the absence of injury. Suicidal *intent* is defined as subjective

expectation and desire for a self-destructive act to end in death (APA, 2003). *Lethality* of suicidal behaviour is objective danger to life associated with a suicide method or action (APA, 2003).

Deliberate self-harm is defined as wilful self-inflicting of painful, destructive or injurious acts without intent to die (APA, 2003). This term is used in the United Kingdom for all episodes of survived self-harming behaviours regardless of intent (Skegg, 2005). In North America this term refers to episodes of bodily harm without suicidal intent, especially if the behaviour is repetitive (Skegg, 2005). Furthermore, in North America this term usually excludes overdoses and methods of high lethality (Skegg, 2005). Parasuicide is used in the World Health Organization (WHO) /European study on parasuicide and this term includes all suicide attempts. WHO's definition of parasuicide is the following: "an act with nonfatal outcome, in which an individual deliberately initiates a nonhabitual behaviour that, without intervention by others, will cause self-harm, or ingests a substance in excess of the prescribed or generally recognized therapeutic dosage, and which is aimed at realizing changes which he/she desired via the actual or expected physical consequences" (World Health Organization, 1986). Simple alcohol intoxication is not regarded as parasuicide.

4.2.4.2 Epidemiology of suicide attempt

Official statistics on suicide attempts are not usually collected annually, as in the case of completed suicides. However, there are several epidemiologic surveys. The World Health Organization Suicide Prevention-Multisite Intervention Study on Suicide (WHO/SUPREMISS) investigates suicidal behaviours in a number of nations. Bertolote et al. (2005) reported that prevalence of suicide attempts varies from 0.4% to 4.2%. Kessler et al. (2005c) reported there were no significant changes that occurred between 1990-1992 and 2001-2003 in the 12-month prevalence of suicide attempts in the general population (0.4% vs. 0.6%).

The World Health Organization/EURO Multicentre Project on Parasuicide included sixteen centres in 13 European countries. The highest average male age-standardized rate of suicide attempts was found in Helsinki, Finland (314/100,000), and the lowest rate (45/100,000) was for Guipuzcoa, Spain, representing a 7-fold difference. The highest average female age-standardized rate was found for Cergy-Pontoise, France (462/100,000) and the lowest (69/100,000) again for Guipuzcoa, Spain. With only one exception (Helsinki), the person-based suicide attempt rates were higher among women than men. In the majority of centres, the highest person-based rates were found in the younger age groups. More than 50% of the suicide attempters made more than one attempt, and nearly 20% of the second attempts were made within 12 months after the first attempt (Schmidtke et al., 1996).

In a sample of the Finnish general population (N=4868), the self-reported prevalence of parasuicide was 0.9% in women and 1.1% in men (Hintikka et al., 1998).

4.2.4.3 Risk factors of suicide attempt

Kessler et al. (1999) reported that based on the National Comorbidity Survey (NCS) the risk factors of a suicide attempt were significantly related to being female, being previously married (divorced or widowed), being born in a recent cohort (year of birth 1966-1975) and having a low educational level. In replication survey, younger age and being previously married were associated with suicide attempts. Females as compared to males had consistently higher rates for suicide attempts in most countries in National Institute of Mental Health (NIMH) Epidemiological Catchment Area Study (ECA) (Weissman et al., 1999).

It has been reported that more than 90 % of suicide attempters have suffered from mental disorders (Suominen et al., 1996; Beautrais et al., 1996; Haw et al., 2001; Hawton et al., 2003a). In both surveys, NCS and NCS-R, nearly 90% of suicide attempters met criteria for one or more of the 12-month DSM disorder (Kessler et al., 2005c). Major depression was the most common individual disorder among people with suicide-related behaviours in both surveys, whereas anxiety disorders were the most common class of disorders (Kessler et al., 2005c). Suominen et al. (1996) reported that at least one Axis I diagnosis was made in 98% of suicide attempters. Depressive syndromes were more common among females, whereas alcohol dependence was more common among males (Suominen et al., 1996). Suominen et al. (2000) found suicide attempters with personality disorders more often had a history of previous suicide attempts and lifetime psychiatric treatment than comparison subjects. However, suicide attempts did not differ in terms of suicide intent, hopelessness, lethality or impulsiveness between subjects with or without personality disorders.

Past suicidal behaviour is a strong indicator of future suicide attempts (Borges et al., 2006; Zahl and Hawton, 2004). A mortality follow-up study was conducted on 11 583 people who presented themselves to the general hospital in Oxford in the UK between 1978 and 1997 (Hawton et al., 2003b). Of the cohort, 10.2% persons had died by the end of 2000 and 2.6% of the cohort had died by suicide or probable suicide. The most frequent method of suicide was self-poisoning, with little difference between the genders in the distribution of this and other methods of suicide. The majority, however, had used a method different from that used in the index episode of self-harm (Hawton et al., 2003b). A follow-up of this cohort study was conducted to examine risk of death from a range of causes during a follow-up period of between 3 and 23 years (Hawton et al., 2006). The number of deaths (1,185, 10.2%) was 2.2 times the expected number, the excess being significantly greater in males than females (Hawton et al., 2006).

Sokero et al. (2003) reported that severity of depression and current alcohol dependence or abuse in particular, but also younger age and low level of social and occupational functioning independently predicted suicide attempts among psychiatric in- and outpatients with DSM-IV major depressive disorder.

4.2.5 Suicide

4.2.5.1 Definition of suicide

Suicide is defined as a self-inflicted death with evidence (either explicit or implicit) that the person intended to die (APA, 2003). This term should be utilized only in the case of death.

4.2.5.2 Epidemiology of suicide

Global suicide rates per 100 000 population have been estimated and published since 1950. There is great variation between countries regarding death rates of suicide (Schmidtke, 1997; WHO). Suicide rates are usually higher in male than in female for all age-groups. In Finland the suicide rate is among the highest in Europe (17.9/100 000 in 2005). For example, in Sweden, the suicide rate is 13.2 /100 000 in 2002 and in Hungary 27.7/100 000 in 2003 (WHO).

4.2.5.3 Risk factors of suicide

Repetition is one of the core characteristics of suicidal behaviour. Among those who commit suicide, up to 37% have attempted suicide previously (Harris and Barraclough, 1997). A suicide attempt is the strongest known predictor for completed suicide (Nordström et al., 1995; Harris and Barraclough, 1997; Möller, 2003; Owens et al., 2005). Owens et al. (2002) reported suicide risk among self-harm patients is hundreds of times higher than in the general population. Isometsä and Lönnqvist (1998) reported 56% of suicide victims were found to have died at their first suicide attempt, thus even if a suicide attempt is a powerful single predictor of completed suicide, it's sensitivity as a risk factor is limited.

The psychological autopsy method offers the most direct technique currently available for examining the relationship between particular antecedents and suicide (Cavanagh et al., 2003). The review of psychological autopsy studies indicated that mental disorder was the most strongly associated variable of those that have been studied with suicide (Cavanagh et al., 2003). Likewise, Arsenault-Lapierre et al. (2004) reported in their meta-analysis that on average 87% of the subjects who committed suicide had a mental disorder. Approximately 60% of all suicides occur in relation to mood disorders (Mann and Currier, 2005). Other psychiatric disorders associated with increased risk of suicide include schizophrenia, alcoholism and personality disorders (Mann and Currier, 2005). Furthermore, Harris and Barraclough (1997) calculated a Standardized Mortality Ratio (SMR) for each psychiatric disorder. In their conclusion they write that virtually all mental disorders have an increased risk of suicide excepting mental retardation and dementia (Harris and Barraclough, 1997).

Hopelessness is a key psychological factor in suicidal behaviour (Beck, 1986). Hopelessness is associated with completed suicide in many studies (Fawcett et al., 1987; 1990; Beck et al., 1989; 1990; Keller and Wolfersdorf, 1993; Nordentoft et al., 1993). Hopelessness is defined as a state of negative expectations (Beck et al., 1974). In a 20-year prospective study of risk factors for suicide in psychiatric outpatients, Brown and his co-workers (2000) found patients who scored a nine or above on the Beck Hopelessness Scale (BHS) (Beck et al., 1974) were approximately four times more likely than patients who scored eight or below to commit suicide within a given year of follow-up. Beck et al. (1985) reported of hospitalised patients because of suicidal ideation, the Hopelessness Scale and the pessimism item of the Beck Depression Inventory predicted the eventual suicides. A score of 10 or more on the Beck Hopelessness Scale correctly identified 91% of the eventual suicides (Beck et al., 1985). Hopelessness is usually measured by the Beck Hopelessness Scale (BHS) which consists of 20 true-false statements that assess the extent of negative expectancies about the future. The possible range of scores is from 0 to 20 (Beck et al., 1974). Suicide attempters' reaction to survival is also found to be a risk factor for eventual suicide (Henriques et al., 2005).

The time period after discharge from a psychiatric hospital is known to be a high risk time for completed suicide for up to one year (Kapur et al., 2006; Qin and Nordentoft, 2005; Pirkola et al., 2005; Ho, 2003; Goldacre et al., 1993). In a Danish population-based nested case-control study based on register data, unemployment, low income, being single and a history of mental illness necessitating hospital admission, were associated with increased risk of suicide. However, in the multivariate analysis, the strongest risk factor was mental illness necessitating hospital admission; risk of suicide was especially high during admission (relative risk 62.6) and during the year after discharge (6.51)(Mortensen et al., 2000).

In a Finnish study, Suokas and Lönnqvist (1991) investigated self-poisoned patients who were treated in the emergency room of Helsinki University Central Hospital. By the end of a 5-year follow-up period, 3.2% of these had committed suicide. Risk factors were being male of advancing age, having mental disorders, previous suicide attempts, a nonimpulsive index suicide attempt, moderate to very serious lethality and severe intention to die during the index suicide attempt (Suokas and Lönnqvist, 1991).

In a Finnish study concerning patients who attempted suicide and who were treated in general hospitals, Suominen et al. (2004a) reported 8% of attempters committed suicide during the 12-year follow-up. The only statistically significant risk factor for eventual suicide was high scores on the Beck Suicidal Intention Scale (Suominen et al., 2004a). Furthermore, suicides continued to accumulate almost four decades after suicide attempt (Suominen et al., 2004b).

Pirkola et al. (2005) reported the register-based study collected in a comprehensive dataset covering all suicides in Finland during 1980-2001. On the basis of the available information on previously hospitalized victims, they found that subjects committing

suicide soon after discharge from hospital treatment for psychiatric disorders differed from later suicides of previously hospitalised patients; in more often being female, having more often received treatment for a schizophrenia spectrum or affective disorder and less often for a substance-related disorder. They had more often used suicide methods of easier availability (particularly drowning and jumping from heights), had more often been an employee and had more often had a higher grade of education (Pirkola et al., 2005).

4.2.6 Prevention of suicidal behaviour

In 1999 WHO launched Suicide Prevention (SUPRE), it's worldwide initiative for prevention of suicide. The overall objectives of the SUPRE project are to reduce mortality and morbidity due to suicidal behaviours, to break the taboo surrounding suicide and to bring together national authorities and the public in an integrated manner to overcome the challenges.

Specific objectives are: To bring about a lasting reduction in the number of suicides and suicide attempts, with emphasis on developing countries and countries in social and economic transition. To identify, assess and eliminate at early stages, as far as possible, factors that may result in young people taking their own lives. To raise the general awareness about suicide and provide psychosocial support to people with suicidal thoughts or experiences of attempted suicide, and to their relatives and close friends, as well as to those of people who committed suicide.

Mann et al. (2005) recently reviewed suicide prevention strategies. They found that physician education in depression recognition and treatment, and restriction of access to lethal methods (particularly firearms) reduced suicide rates. Other methods including public education, screening programs and media education needed more evidence of efficacy. Furthermore, Mann and Currier (2005) have suggested that in formulating a treatment and management strategies for suicidal patients, three principal aspects require attention: diagnosis and treatment of existing psychiatric disorder, assessment of suicide risk and removal of the means for suicide, specific treatment to reduce the diathesis or propensity to attempt suicide.

The Finnish Department of Mental Health and Alcohol Research of the National Public Health Institute has been active in both development of suicide preventive strategies in Finland and suicide research (Lönqvist et al., 1995). The national suicide prevention project in Finland was carried out from 1986 to 1996 and consisted of a research phase from 1986 to 1991, an implementation phase from 1992 to 1996 and an internal evaluation phase from 1997 to 1998. The Finnish suicide rate increased during the first years of the project, followed by a reduction of 20% between 1991 and 1996 and finally dropping to 9% below the initial level (Upanne et al., 1999; Lehtinen and Taipale, 2001).

Educational intervention for non-psychiatrically trained multidisciplinary staff to assess suicide risk and manage suicidal patients was carried out in England (Morriss et al., 1999). Suicide risk assessment and management skills such as problem solving, future coping and provision of immediate support were significantly improved after 1 month of training (Morriss et al., 1999). However, the suicide rate did not change before or after educational intervention. It seems that brief educational interventions to improve the assessment and management of suicide for front-line health professionals in contact with suicidal patients, may not be sufficient to reduce the population suicide rate (Morriss et al., 2005).

A 2-year intervention program was performed in Nuremberg at four levels: training of family doctors and support through different methods, a public relations campaign informing about depression, cooperation with community facilitators (teachers, priests, local media, etc.) and support for self-help activities as well as for high-risk groups (Hegerl et al., 2006). The effects of the 2-year intervention on the number of suicidal acts (completed suicides plus suicide attempts) were evaluated. Compared to the control region (Wuerzburg), a reduction in frequency of suicidal acts and suicide attempts was observed in Nuremberg during the 2-year intervention. The reduction was most noticeable for high-risk methods (e.g. hanging, jumping and shooting). Concerning completed suicides, there were no significant differences compared to the control region (Hegerl et al., 2006).

4.3 Suicidal behaviour in bipolar disorder

4.3.1 Epidemiology of suicidal behaviour in bipolar disorder

Bipolar disorder (BD) is associated with a significant risk of suicidal behaviour (Hawton et al., 2005; Baldessarini et al., 2006b). Chen and Dilsaver (1996) found in their study that patients with bipolar disorder are at higher risk of suicidal behaviour than those suffering from other Axis I disorders. Bipolar disorder is related with increased mortality due to cardiovascular diseases and particularly suicide (Ahrens et al., 1995; Angst et al., 2002; Ösby et al., 2001).

4.3.1.1 Epidemiology of completed suicide

Guze and Robins (1970), who were the first to systematically review the suicide risk of bipolar disorder (or manic-depressive illness), found that approximately 15% of all deaths among manic-depressive patients were the result of suicide. Goodwin and Jamison (1990) reported in their review that approximately 19% of manic-depressive patients died by suicide. In both of these analyses, bipolar disorder was not consistently discriminated from major unipolar depression. Furthermore, both studies were based on hospitalised patients. These two reviews have been criticized by Bostwick and Pankratz (2000) because both reviews calculated proportionate mortality (the percentage of the dead who died by

suicide) rather than case fatality (the percentage of the original sample who died by suicide) and because most of the studies included, in both estimates of lifetime suicide risk, had follow-up periods of only a few years. Proportionate mortality must provide a biased estimate of suicide risk because the risk of suicide is not constant across the history of affective disease (Bostwick and Pankratz, 2000). The risk is highest in the beginning of the onset of affective disorder and soon after discharge from hospital.

A meta-analysis of studies on suicide risk in all psychiatric disorders, Harris and Barraclough (1997), found the risk of suicide in bipolar disorder was 15 times the expected. This meta-analysis is criticized by Rihmer because it reviewed studies which had not considered bipolar II separately (Rihmer and Kiss, 2002). This overestimates the suicide risk for unipolar depression and underestimates the same risk for bipolar illness (Rihmer and Kiss, 2002). Tondo and co-workers (2003) indicate in their meta-analysis that the standardized mortality ratio to be (observed deaths/expected deaths) about 20 for BD sufferers. Estimates in samples of never-hospitalized patients with affective disorders have reported lifetime suicide rates of about 6% (Bostwick and Pankratz, 2000; Inskip et al., 1998). In one prospective follow-up of 220 bipolar inpatients there was an increased risk of death by suicide (SMR=12.28) (Angst et al., 2002). It is estimated that prevalence of completed suicide among bipolar patients ranges from 19% at the high end (Goodwin and Jamison, 1990) and to 4-6% at the low end (Inskip et al., 1998).

4.3.1.2 Epidemiology of attempted suicide

Retrospective and cross-sectional studies of attempted suicide in bipolar patients show that 25-50% attempted suicide at least once (Goodwin and Jamison, 1990; Jamison, 2000; Slama et al., 2004). Suicide attempts in bipolar disorder tend to be of high lethality: one completed suicide for three attempts in bipolar disorder compared with one completed suicide in 18 attempts in the general population (Tondo and Baldessarini, 2000). A recent study Galfalvy et al. (2006) reported the rate of suicide attempts to be 54% for bipolar I patients and 63% for bipolar II patients. Recent prospective studies from tertiary care settings have reported the rate of attempted suicide during follow-up to vary from 19% to 3.7% (Galfalvy et al., 2006; Marangell et al., 2006).

4.3.1.3 Epidemiology of suicidal ideation

It is estimated that 30-75% of bipolar patients have suicidal ideation (Stallone et al., 1980; Bottlender et al., 2000; Suppes et al., 2001; MacKinnon et al., 2005). There are only a few studies regarding prevalence and risk factors of suicidal ideation among bipolar patients.

4.3.2 Risk factors of suicidal behaviour in bipolar disorder

Hawton and colleagues recently made a systematic review of suicide and attempted suicide in bipolar disorder (Hawton et al., 2005). Studies were selected for inclusion in their review if they met the following criteria: an international classification of disease, at least 90% of the subjects were aged 16 years or over, the design of the study was a cohort study with a minimum follow-up period of one year, a case-control or a cross-sectional study, an outcome of suicide or attempted suicide was reported, specific risk factors for suicide or attempted suicide were investigated. They found 55 articles to fulfil these criteria. The included articles reported on 13 studies of suicide: the results for three studies for bipolar patients were supplied by author. The systematical review included 23 studies of attempted suicide, of which, only one was a prospective cohort study.

4.3.2.1 Risk factors for completed suicide

Hawton and co-workers (2005) found in their meta-analysis that male gender and history of attempted suicide and hopelessness at the index episode were associated with suicide. Marital status or employment was not related to suicide (Hawton et al., 2005). There were no statistically significant associations of suicide with personal, social or family history characteristics (Hawton et al., 2005). Completed suicide was not related to alcohol or drug abuse, rapid cycling, psychotic symptoms or expression of suicidal ideas (Hawton et al., 2005). Furthermore, suicide risk did not seem to vary according to whether the individual had a diagnosis of bipolar I or bipolar II disorder (Hawton et al., 2005).

Ösby et al. (2001) found the standardized mortality ratio for suicide was especially high for younger patients during the first years after the diagnosis. Høyer et al. (2000) found the risk of suicide was high both immediately after admission and immediately following discharge. Tsai and colleagues (2002) found in their logistic regression model that those bipolar I inpatients who have a first-degree family history of suicide, and who have had more suicide attempts (at least once in seven years of illness), are more likely to commit suicide (Tsai et al., 2002).

Isometsä and co-workers (1994) examined suicides of persons with bipolar disorder. Most suicides of persons with bipolar disorder occurred during a major depressive episode (79%), but in some cases it occurred during a mixed state (11%) or even during or immediately after remission of psychotic mania (11%) (Isometsä et al., 1994; Isometsä, 2005). Isometsä et al. (1995) have also reported that adverse life events: serious conflicts with family, substantial financial deterioration, job problems, somatic illness, residence change are related to suicide among bipolar patients.

4.3.2.2 Risk factors for attempted suicide

Hawton and co-workers (2005) found in their meta-analysis that attempted suicide was significantly more common in single individuals. Furthermore, they reported suicide attempts were associated with a family history of suicide, the earlier onset of bipolar disorder, admission to hospital resulting from depression, severity of episodes, mixed affective states at presentation, rapid cycling, comorbid anxiety disorder and alcohol and drug abuse (Hawton et al., 2005). However, there are only a few studies which have assessed a wide range of risk factors for attempted suicide.

Previous suicidal behaviour

History of attempted suicide is a strong indicator of a future suicide attempt (Bottlender et al., 2000; Nordström et al., 1995; Möller, 2003; Fawcett et al., 1990; Oquendo et al., 2000; 2004; 2006; Leverich et al., 2003; Harris and Barraclough, 1997). Suicidal ideation appears also to be an important marker for identifying patients at risk for suicide attempt (Mann, 1999). Bipolar patients with a history of suicide attempt had more severe suicidal ideation prior to admission (measured by SSI) (Oquendo et al., 2000; Galfalvy et al., 2006).

Sociodemographic characteristics

Women attempt suicide generally more often in the general population. The majority of studies have not found an association with suicide attempt and gender among bipolar patients (Galfalvy et al., 2006; Tondo et al., 1999; Tsai et al., 1999; Lopez et al., 2001; Dalton et al., 2003; Leverich et al., 2003). Oquendo and co-workers (2000) found that among hospitalized bipolar I patients men attempted suicide more often than women, whereas MacKinnon et al. (2003) reported female gender was associated with suicide attempts. The majority of previous studies have not found an association with suicide attempt and age (Tondo et al., 1999; Tsai et al., 1999; Oquendo et al., 2000). However, Galfalvy et al. (2006) recently reported younger age is related to suicide attempt among depressed bipolar patients.

Previous studies have not found an association between suicide attempt and marital status among bipolar patients (Galfalvy et al., 2006; Tsai et al., 1999; Lopez et al., 2001; Oquendo et al., 2000), instead the Stanley Foundation Bipolar Network Study found that those who attempted suicide were significantly more commonly single individuals (Leverich et al., 2003). Oquendo et al. (2000) could not find evidence that having children protected against suicidal behaviour.

The Stanley Foundation Bipolar Network Study found that patients with a history of a suicide attempt had less college education and less income (below \$ 20 000/year) (Leverich et al., 2003), whereas other studies have not found an association between suicide attempt and education (Oquendo et al., 2000; Galfalvy et al., 2006). Unemployment is similarly not associated with suicide attempt among bipolar patients (Tsai et al., 1999).

The age of onset of BD is associated with suicide attempt among bipolar disorder patients in many (Tsai et al., 1999; Lopez et al., 2001; Leverich et al., 2003; MacKinnon et al., 2003; Galfalvy et al., 2006), but not all studies (Oquendo et al., 2000; Dalton et al., 2003). Of sociodemographic factors, only the earlier onset of BD has independently predicted suicide attempt (Tsai et al., 1999).

Personal, social and family characteristics

Lifetime levels of aggression have been found to be higher among bipolar suicide attempters compared with non-attempters, measured by both the Buss-Durkee Scale and the Brown Goodwin Aggression History Scale (Oquendo et al., 2000; Galfalvy et al., 2006). However, hospitalized bipolar I attempters did not differ from non-attempters on the measure of impulsivity, the Barret Impulsive scale (Oquendo et al., 2000), whereas Galfalvy found baseline attempters manifested more impulsive traits reflected in evaluated impulsivity scores (Galfalvy et al., 2006).

In recent studies, attempted suicide is associated with a history of early physical abuse, early sexual abuse and lack of a confidant prior to illness onset (Leverich et al., 2002; 2003; Leverich and Post, 2006; Galfalvy et al., 2006). Early sexual abuse, as well as lack of a confidant prior to illness onset, remained independent risk factors for attempted suicide in multinomial statistics in the Stanley Foundation Bipolar Network Study (Leverich et al., 2003). Tsai and colleagues (1999) also reported that interpersonal problems and occupational problems predicted suicide attempt in their logistic regression model.

In the few previous studies, some aspects of family characteristics are associated with suicide attempt among bipolar patients. Leverich et al. (2003) found that a family history of substance abuse and a family history of suicide were associated with suicide attempt in bipolar patients, whereas some studies did not find any statistically significant association with family history of affective disorder or family history of suicide attempt (Dalton et al., 2003; Galfalvy et al., 2006). Lopez et al. (2001) reported family history of affective disorders to predict suicide attempt among bipolar disorder patients in their multinomial statistics (Lopez et al., 2001). Of personal, social and family characteristics, early sexual abuse, lack of a confidant prior to illness onset as well as both interpersonal and occupational problems and family history of affective disorders, has independently predicted suicide attempt.

Subtype of bipolar disorder

The prevalence of suicide attempt between bipolar I and II disorders is a controversial issue (Lester, 1993; Vieta et al., 1997; Rihmer and Pestality, 1999). Some studies (Stallone et al., 1980; Bulik et al., 1990; Tondo et al., 1999; Balazs et al., 2003) have reported higher rates of suicide attempt for bipolar II disorder, whereas the Stanley Foundation Bipolar Network Study (Leverich et al., 2003) and some other studies (Endicott et al., 1985; Coryell et al., 1987; Dalton et al., 2003) found no difference. In theory,

bipolar II could carry a higher risk if the longitudinal symptomatic course of BD II is dominated more by the depressive phase of illness (Judd et al., 2003a), implying more time at risk for suicidal acts. Alternatively, possible differences related to illness episodes, such as different severity of depression, lability of mood, level of hopelessness or other characteristics, such as comorbidity, could result in risk disparities between bipolar I and II.

Hopelessness

Hopelessness, which has been researched widely as a risk factor for suicide attempt in suicidology in general, has seldom been studied among BD patients. For instance, the comprehensive meta-analysis by Hawton did not mention hopelessness as a risk factor of attempted suicide. One study involving hospitalised bipolar I patients showed a trend towards higher levels of hopelessness (Oquendo et al., 2000), whereas in a recent study the hopelessness was not related to suicide attempts (Galfalvy et al., 2006). Fawcett and co-workers found in their prospective study of unipolar and bipolar patients that hopelessness was a risk factor of attempted and completed suicide (Fawcett et al., 1990).

Clinical state

Depressive aspects of illness have been related to suicide attempts: higher number of prior major depressive episodes (Oquendo et al., 2000; Fagiolini et al., 2004) higher levels of depression measured by subjective ratings (BDI) or objective ratings (HAM-D) prior to admission (Oquendo et al., 2000; Fagiolini et al., 2004; Galfalvy et al., 2006), history of hospitalisation during depressive episodes (Lopez et al., 2001) and current depressive or mixed episodes (Oquendo et al., 2000; Tondo et al., 1999), whereas psychotic features have not found to be related to suicide attempts (Lopez et al., 2001). Rapid cycling is related to suicide attempt in some studies (Dalton et al., 2003; MacKinnon et al., 2003; 2005), but not in all (Wu and Dunner, 1993; Serretti et al., 2002). Of clinical characteristics, history of hospitalization during depressive episodes has independently predicted suicide attempts.

Comorbidity

The Stanley Foundation Bipolar Network Study found suicide attempters to have a greater mean number of Axis I comorbid disorders (Leverich et al., 2003). Some previous studies (Simon et al., 2004; 2007; Leverich et al., 2003), but not all (MacKinnon et al., 2003), have found comorbid anxiety or anxiety symptoms to be related to suicide attempt. Likewise, comorbid alcohol dependence or abuse is associated with suicide attempts in many (Tondo et al., 1999; Potash et al., 2000; Goldberg et al., 2001b; Lopez et al., 2001; Slama et al., 2004), but not all studies (Oquendo et al., 2000; Leverich et al., 2003). Also, drug dependence/abuse (Dalton et al., 2003, Goldberg et al., 2001b; Tondo et al., 1999) eating comorbidity (Leverich et al., 2003), personality disorder, according SCID-II among bipolar I patients (Ucok et al., 1998), and among bipolar II patients (Vieta et al., 1999), and Axis II comorbidities based on a self-rated questionnaire, (Leverich et al., 2003) have been associated with suicide attempts.

Risk factors of attempted suicide based on prospective studies

In the few published prospective studies, risk factors for suicide attempt have included a history of suicide attempts (Fawcett et al., 1990; Nordström et al., 1995; Oquendo et al., 2004; Galfalvy et al., 2006; Gonzalez-Pinto et al., 2006; Marangell et al., 2006), higher number of suicide attempts (Galfalvy et al., 2006), suicidal ideation (Fawcett et al., 1990; 1995; Oquendo et al., 2004; Galfalvy et al., 2006; Marangell et al., 2006), subjective rating of depression severity (Oquendo et al., 2004; Galfalvy et al., 2006), hopelessness (Fawcett et al., 1990; Oquendo et al., 2004), higher rates of illness recurrence (Gonzalez-Pinto et al., 2006), higher number of previous hospitalisations (Galfalvy et al., 2006; Gonzalez-Pinto et al., 2006), few reported reasons for living (Galfalvy et al., 2006), more days spent depressed, anxious, irritable over the past year (Marangell et al., 2006), rapid cycling (Coryell et al., 2003), comorbid alcohol dependence or abuse (Fawcett et al., 1990), cigarette smoking (Oquendo et al., 2004), borderline personality disorder (Galfalvy et al., 2006), younger age (Galfalvy et al., 2006; Gonzalez-Pinto et al., 2006), being single (Gonzalez-Pinto et al., 2006), aggression/impulsivity (Oquendo et al., 2004; Galfalvy et al., 2006), less adherence to lithium treatment (Gonzalez-Pinto et al., 2006) and family history of mood disorder (Gonzalez-Pinto et al., 2006).

Limitations of previous prospective studies

However, these prospective studies have mostly (Coryell et al., 2003) or exclusively (Nordström et al., 1995) included inpatients with mixed and often undifferentiated types of affective disorders (Fawcett et al., 1990; Nordström et al., 1995; Oquendo et al., 2004), that have had small bipolar sample sizes (<70) (Nordström et al., 1995; Oquendo et al., 2004; Galfalvy et al., 2006) or are from tertiary care setting (Galfalvy et al., 2006). Thus, the generalizability of these findings e.g. to bipolar patients in outpatient settings, remains somewhat unclear.

Findings from multivariate statistics according prospective studies of attempted suicide

Few previous studies, except the studies by Oquendo et al. (2004), Galfalvy et al. (2006) and Marangell et al. (2006), have assessed the wide range of risk factors for attempted suicide or used multivariate statistics. Oquendo et al. (2004) found history of suicide attempts, subjective rating of the severity of depression and cigarette smoking to independently predict suicide attempt in their prospective study. Further, Galfalvy et al. (2006) found family history of suicidal acts and comorbid borderline personality disorder to predict an early attempt, while younger age, high hostility scores, higher number of past attempts, subjective pessimism as reflected in depression and suicidal ideation and few reported reasons for living, predicted suicidal acts during the whole period. Marangell et al. (2006) reported that percent days depressed in past year and history of suicide attempts independently predicted suicide attempt.

4.3.2.3 Risk factors for suicidal ideation

Few studies have examined risk factors for suicidal ideation in bipolar patients. Positive family history for affective disorder, severe depression, psychotic symptoms (Bottlender et al., 2000), past suicide attempt (Bottlender et al., 2000; Goldberg et al., 1999), current comorbid anxiety disorders (Simon et al., 2007), comorbid alcohol abuse or dependence (Goldberg et al., 1999), comorbid personality disorders in bipolar II disorder (Ucok et al., 1998; Vieta et al., 1999), panic spectrum symptoms in bipolar I disorder (Frank et al., 2002), any Axis I comorbidity (Vieta et al., 2000; 2001) and earlier age at onset (Carter et al., 2003) have been associated with suicidal ideation. Two studies comparing bipolar I and II disorder (Stallone et al., 1980; Vieta et al., 1997) found no significant differences in suicidal ideation regarding the prevalence of bipolar disorder.

4.3.3 Prevention of suicidal behaviour in bipolar disorder

Long-term lithium treatment is associated with reduced risk of suicide and suicide attempts among bipolar disorder patients (Baldessarini et al., 2003; 2006a; Tondo et al., 2000; 2003; Cipriani et al., 2005; Müller-Oerlinghausen et al., 2005; Kessing et al., 2005). A recent meta-analysis, involving 85 229 person-years of risk-exposure, including both open label and randomized controlled trials of 31 studies published since 2001, found the overall risk of suicides and attempt were five times less among lithium-treated subjects than among those not treated with lithium (Baldessarini et al., 2006a).

Gray and Otto (2001) recommended, in their review of psychosocial approaches to suicide prevention, the following as standard elements of a suicide prevention program for patients with bipolar disorder: vigorous treatment of bipolar disorder, over-rehearsal of help options for times of distress, training in problem-solving skills, cognitive restructuring of hopelessness-based cognitions, enhancement of reason for living, training in emotional tolerance/regulation skills.

4.3.4 Summary of previous studies regarding suicidal behaviour in bipolar disorder

There is a lack of studies regarding prevalence and incidence of suicidal behaviour in BD. Previous studies have assessed neither aborted suicide attempts, nor suicide attempts which (despite intent to die) were not communicated to professionals. Moreover, previous studies have not examined the incidence of suicide attempts, or differences in incidence during various phases of bipolar disorder.

Many single risk factors for suicidal behaviour have been investigated in previous cross-sectional and retrospective studies, but a comprehensive view of risk factors related to suicidal behaviour in bipolar disorder is still emerging. Suicidal behaviour and the depressive aspects of BD have been consistently associated with suicide attempts

in previous studies. The findings for instance regarding subtype of BD, alcohol and substance dependence or abuse, smoking and rapid cycling, by contrast, have been much less consistent.

Overall, there are only few prospective studies regarding suicidal behaviour in BD. None of previous studies have investigated time-varying risk factors and included time at risk estimations when estimating overall suicide risk. Thus, there is a need for prospective studies to investigate the wide range of risk factors, including both static and time-varying risk factors, of suicidal behaviour and use of multivariate statistics, which is needed to differentiate independent risk factors from confounding associations.

5. AIMS OF STUDY

The aim of this study was to evaluate prevalence of suicidal behaviour (suicidal ideation and suicide attempt) and incidence of suicide attempts, and examine a wide range of risk factors for attempted suicide both cross-sectionally and prospectively in a representative secondary-level sample of psychiatric in- and outpatients with BD.

The specific aims of the study were:

1. To investigate cross-sectionally the prevalence of suicide attempts and suicidal ideation in bipolar I and II disorders, and to examine independent risk factors for suicide attempts and suicidal ideation in a representative secondary-level sample of psychiatric in- and outpatients with BD.
2. To investigate cross-sectionally the differences in prevalence and risk factors for suicidal behaviour during different phases of BD.
3. To investigate prospectively the prevalence of suicide attempters, and to examine independent predictors for suicide attempts among a representative secondary-level sample of psychiatric in- and outpatients with BD.
4. To investigate whether the incidence of attempted suicide is higher during depressive and mixed phases than in other phases, and to examine if common risk factors associated with suicidal behaviour (comorbid anxiety disorders, comorbid personality disorders, comorbid substance dependence/abuse, hopelessness, severity of depression and lifetime psychotic features) modify this risk during depressive and mixed phases.

6. METHODS

6.1 General study design

The Jorvi Bipolar Study (JoBS) is a collaborative bipolar research project between 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. The Department of Psychiatry of Jorvi Hospital provides secondary-care psychiatric services to all citizens of Espoo, Kauniainen and Kirkkonummi (261,116 inhabitants in 2002). The ethical committee of HUCH approved the study protocol.

6.2 Screening

Using the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000), the aim was to identify all in- and outpatients at the Department of Psychiatry at Jorvi Hospital who currently had a possible new phase of DSM-IV BD from January 1, 2002 to February 28, 2003. Attending mental health professionals in the department screened every patient aged 18-59 years for seeking treatment, being referred or already receiving care and now showing signs of deteriorating clinical state. In addition, despite a negative MDQ screen, patients were included as positive if suspected to have BD due to their clinical diagnosis of BD or pertinent symptoms (N=28). A clinical diagnosis of ICD-10 schizophrenia was an exclusion criterion for screening. Based on pilot study (Isometsä et al., 2003), the response to MDQ item 3 ("problems due to episodes") was ignored. The sampling procedure is presented in Figure 1. After a positive MDQ-screen, or suspicion of a BD, the patient was fully informed about the study project and their written informed consent requested. Altogether, 1630 patients were screened, of whom 546 were MDQ-positive or suspected bipolar. Of 546 patients, 49 refused a face-to-face interview, and seven could not be contacted.

6.3 Baseline evaluation

6.3.1 Diagnostic measures

In the second phase of sampling, 490 patients were interviewed face-to-face by a researcher (OM, HV, PA, KS, SL, MP) using the Structured Clinical Interview for DSM-IV Disorders, research version with psychotic screen (SCID-I/P) (First et al., 2001). Two hundred and one patients were diagnosed with DSM-IV bipolar disorder and had a current episode of bipolar disorder. Ten patients refused to participate, leaving 191 patients in the bipolar cohort study. Inter-rater reliability was assessed via videotaped interviews, which were blindly assessed by another rater. In order not to reveal the diagnosis made by the first interviewer, all items were asked 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 found to be complete (κ for bipolar disorder overall=1.0; also specifically, for bipolar I=1.0 and bipolar II=1.0). The Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) (First et al., 1996) was also used in the JoBS to assess diagnoses on Axis II. Bipolar II depressive mixed states was defined according to Benazzi and Akiskal (2001): three or more simultaneous intra-episode hypomanic symptoms present for at least 50% of the time during a major depressive episode. The soft bipolar spectrum was excluded.

6.3.2 Observer and self-report scales

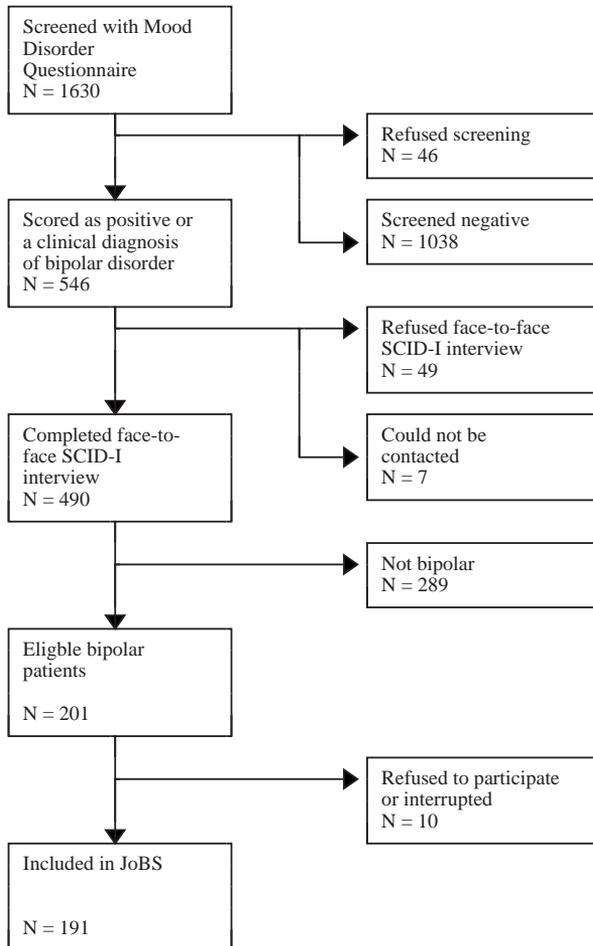
In the third phase the current symptomatology of the index episode was evaluated using the following observer scales: Young Mania Rating Scale (YMRS) (Young et al., 1978), 17-item Hamilton Depression Scale (HAM-D) (Hamilton, 1960), Scale for Suicidal Ideation (SSI) (Beck et al., 1979), and Social and Occupational Functioning Assessment Scale of DSM-IV (SOFAS) (Goldman et al., 1992). The self-report scales included the 21-item Beck Depression Inventory (BDI) (Beck et al., 1961), Beck Anxiety Inventory (BAI) (Beck et al., 1988), Beck Hopelessness Scale (BHS) (Beck et al., 1974) and Perceived Social Support Scale-Revised (PSSS-R) (Blumenthal et al., 1987). There was some delay from screening to estimating symptom scores in the first interview, which especially in cases of short hypomanias, meant that the patient had often passed the index episode.

6.3.3 Other characteristics

Information on demographic characteristics was gathered, variables for prior illness history and preceding treatment, using a graphic retrospective life-chart. *Age at illness onset* was defined as the time of onset of the first mood episode fulfilling DSM-IV criteria. Polyphasic episode was defined as an episode consisting of more than one distinct phase (depressive, hypomanic, manic, mixed or depressive mixed phase). The index

episode and index phase were defined respectively as the episode or phase respectively when the patients were included in the study. The majority of bipolar II (50.5%) and many bipolar I (25.6%) patients were previously undiagnosed; the remainder had a median 7.8 years delay from first episode to diagnosis (Mantere et al., 2004).

Figure 1. Screening of Eligible Bipolar Patients in the Jorvi Bipolar Study



6.3.4 Adequate acute-phase pharmacotherapy

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

6.3.5 Evaluation of baseline suicidal behaviour

Suicidal behaviour was examined in several ways. Current suicidal ideation was first investigated using the Scale for Suicidal Ideation (SSI), a 19-item observer-rated scale designed to quantify the intensity of current conscious suicide ideation (Beck et al., 1979). The patient was then asked whether they had ever seriously considered suicide during the current episode of bipolar disorder. Unless otherwise stated, suicidal ideation refers to patients who either scored ≥ 6 in the SSI or had seriously considered suicide during the index episode. In addition, the occurrence of a suicide attempt during the current episode of bipolar disorder was investigated, based on both the interview and psychiatric records. Furthermore, the information on lifetime suicidal behaviour was recorded according to interview and psychiatric records. By definition, a suicide attempt had to involve at least some degree of intent to die; self-harm with no such intent did not count.

6.4 Follow-up procedure

Follow-up

Life-chart methodology (Melartin et al., 2004; Mantere et al., in press) was used to integrate all available information about the nature and duration of different phases during the 18-month follow-up. The JoBS initially included 191 patients with DSM-IV bipolar disorder, 15 (8%) of whom, neither continued in treatment nor participated in the 6-month follow-up. Of the 176 included in the 6-month follow-up, three patients (2%) died between the 6-month and the 18-month follow-up (two [1%] by suicide), and 10 patients dropped out. Thus, both life-chart information, and information on suicide attempts, were obtained from 163 patients at the 18-month follow-up.

Integration of information into a life-chart

After baseline assessments, patients were prospectively followed up with a life-chart. The outcome was investigated at 6 and 18 months by repeated SCID-I/P (First et al., 2001) interviews. In addition, all observer and self-report scales were included at both follow-up assessments. All medical and psychiatric records were available. The duration of the phases of follow-up were examined by gathering all available data, which were then integrated into the form of a graphic life-chart based on DSM-IV criteria, analogous to the life-chart used in the Vantaa Depression Study (Melartin et al., 2004). This was created after reviewing all the patient information from the follow-up period at the 6- and 18-month interviews, which typically lasted 2-3 hours. Besides information of symptom ratings and visits to attending personnel, change points in the psychopathologic states using probes related to important life-events was also inquired into, in order to improve the accuracy of the assessment. Time after the baseline interview was divided into ten different time periods: euthymia, manic, hypomanic, major depressive, mixed, depressive mixed (according to Benazzi and Akiskal, 2001), cyclothymic, substance induced mood phase, and depressive and hypomanic symptoms (Mantere et al., in press).

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 the other prospective studies including and reporting on BD types I and II separately (Judd et al., 2003b; 2003c; Post et al., 2003; Dittman et al., 2002; Nolen et al., 2004; Joffe et al., 2004). As with the LIFE, change points in the psychopathologic state using probes related to important events were investigated. Unlike the LIFE, in the interview the life-chart was made directly comparable with the DSM-IV criteria, and classified the patients' follow-up time into periods of 4 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.

Definitions for time periods of life-chart

An *episode* was defined according to DSM-IV criteria and could be *monophasic* or *polyphasic*. Thus, a *phase* here 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), substance induced mood phase was induced by any psychoactive substance. *States of subsyndromal symptoms* (including prodromal or residual symptoms) was defined as a state where 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 is used as a state-variable when the duration of euthymia is more than 2 weeks.

Drop-out analysis

To ensure validity of the results, it is essential to verify that a greater proportion of suicidal patients did not exist among those who failed to complete the follow-up study than among those who were followed up, otherwise selective attrition could be expected to bias the findings and result in underestimates. This can be only estimated by investigating whether those who dropped out differ from those completing the study, in terms of their suicidal behaviour during and preceding the index episode at baseline. First, differences between patients who were (N=176), and who were not (N=15), included in the 6-month follow-up were analyzed regarding their suicidal behaviour during the index episode and before the index episode. Patients who were not included in the 6-month follow-up did not differ from patients who were included, in terms of suicide attempts, before the index episode (40% [6/15] vs. 45% [79/176]; $p=0.9$), suicide attempts during the index episode (33% [5/15] vs. 19% [34/176]; $p=0.3$) or suicidal ideation (40% [6/15] vs. 40% [71/176]; $p=1.0$). Second, differences between patients who were (N=163) and who were not (N=25) included in the 18-month follow-up were analyzed. The three patients who died were excluded from this drop-out analysis. Those who were not included in the 18-month follow-up differed from patients who were included in terms of suicide attempts during the index episode (40% [10/25] vs. 17% [28/163]; $\chi^2=5.7$, $p=0.02$), but not in suicide attempts before the index episode (44% [11/25] vs. 44% [72/163]; $p=1.0$), or suicidal ideation during the index episode (28% [7/25] vs. 42% [69/163]; $p=0.3$). Third, differences between patients who completed the 18-month follow-up study (N=163) vs. who were included in the 6- but not the 18-month follow-up (N=10), were analyzed regarding suicidal behaviour during the index episode and regarding the suicide attempts during the 6-month follow-up. Again, the three patients who died were excluded from this drop-out analysis. The patients who (N=163) completed the follow-up study differed from patients who (N=10) were included in the 6- but not the 18-month follow-up, in terms of suicide attempts during the index episode (17% [28/163] vs. 50% [5/10]; $\chi^2=4.6$, $p=0.03$), but not in suicide attempts before the index episode (44% [72/163] vs. 50% [5/10]; $p=1.0$), or suicide attempts during the 6-month-follow-up (14% [22/163] vs. 30% [3/10]; $p=0.3$). Thus, higher rate of attrition of previously suicidal patients was evident between the 6-month and the 18-month follow-up.

6.4.1 Follow-up procedure regarding suicidal behaviour

Information on suicide attempts was obtained for 176/191 patients (92%) at the 6-month follow-up and for 163/191 patients (85%) at the 18-month follow-up. Information about the occurrence of a suicide attempt during the follow-up was based on both the interview and the psychiatric and somatic records. Suicide attempt is defined as a self-injurious behaviour with a nonfatal outcome accompanied by evidence (either explicit or implicit) that the person intended to die (O'Carroll et al., 1996; APA, 2003); self-harm with no suicidal intention was not included. An aborted suicide attempt refers to an event in which an individual is one step away from attempting suicide but does not complete the act, and thus incurs no physical injury (Barber et al., 1998; APA, 2003). By definition, an aborted suicide attempt had to involve at least some degree of intent to die, a change of mind immediately before the actual attempt and the absence of injury. Since nonfatal suicidal behaviour was one of the main foci of the study, the suicidal behaviour of the patients was very carefully evaluated. Ten questions about suicidal behaviour at the 6-month follow-up, and 12 questions about suicidal behaviour at the 18-month follow-up were included in follow-up interviews. Patients were asked about aborted suicide attempts, suicide attempts with intention to die which were not communicated with professional staff, about suicide attempts which did not lead to contact to an emergency room, about timing of suicide attempts, the lethality of suicide attempts and questions of suicidal behaviour of relatives.

6.5 Statistical methods

The chi-square test with Yates' correction was used to evaluate categorical and non-parametric data, the Mann-Whitney, or Kruskal-Wallis, test to compare continuous variables not normally distributed and the two-sample t-test and One-Way Analysis of Variance (ANOVA) for continuous variables normally distributed. ANOVA post-hoc subgroup differences were tested using Tukey's Honestly Significant Difference test (HSD). Logistic regression models were used to adjust for confounding factors. Furthermore, multivariate nominal regression models were created, and suicidal behaviour, as the dependent variable, was classified into three mutually exclusive categories: non-suicidal patients (reference group), suicidal ideators without suicide attempts and suicide attempters. To avoid circularity, the suicidality items of the depression rating scale were omitted. The Poisson regression model was used to investigate univariate Relative Risks (RR). The Cox's proportional hazards regression model with individual frailty was used to investigate the relative importance of individual risk factors of attempted suicide. For continuous variables (age, HAMD, and BHS) hazard ratios (HR) were calculated for increment of 10 units. SPSS software version 11.5 was used.

7. RESULTS

7.1 Suicidal ideation and attempts in bipolar I and II disorders (study I)

7.1.1 Clinical and demographic characteristics of the sample

The characteristics of patients without suicidal behaviour, with suicidal ideation, or with suicide attempts during the index episode are presented in Table 7. Significant differences were found between the three groups in quality of affective state; severity of current episode (HAM-D, BDI scores); intensity of suicidal ideation; prevalence of rapid cycling; personality, anxiety and eating disorders; degree of anxiety and hopelessness and age at onset. In post-hoc subgroup comparisons, patients with current suicide attempts had a greater prevalence of comorbid personality disorder ($p<0.001$) and cluster C disorders ($p<0.001$), had more previous suicide attempts ($p=0.04$) and more suicidal ideation, according to SSI ($p=0.02$), than patients with suicidal ideation alone. Specifically, several item scores were higher among the suicide attempters, these included (item 8) attitude toward ideation (attempters [median 1.0] vs. ideators [median 1.0]; $Z=-2.0$, $p=0.04$), (item 9) control over suicidal action (attempters [median 1.0] vs. ideators [median 0.0]; $Z=-2.2$, $p=0.03$) and (item 17) suicidal note (attempters [median 0.0] vs. ideators [median 0.0]; $Z=-2.2$, $p=0.03$). There were no significant differences between patients with suicide attempts and suicidal ideation in severity of depression, measured by HAM-D, or hopelessness. Patients with suicidal ideation had significantly higher levels of depression (HAM-D $p<0.05$; BDI $p<0.05$), hopelessness ($p<0.05$), anxiety ($p<0.05$), fewer symptoms of mania (YMRS $p<0.05$), longer duration of last episode ($p<0.05$) and greater prevalence of comorbid anxiety disorders ($p=0.003$) than non-suicidal patients.

7.1.2 Suicidal ideation and attempts during the index episode

Overall, 116 (61%) of the 191 patients reported suicidal ideation during the index episode (66 females [65%] vs. 50 males [56%]; $\chi^2=1.5$, $df=1$, $p=0.20$). During the index episode 39 (20%) of the patients had attempted suicide, females more often than males (27 [27%] vs. 12 [13%]; $\chi^2=4.5$, $df=1$, $p=0.04$). Of those who attempted suicide, 36% (14/39) were referred to an emergency room and 33% (13/39) were hospitalised; the majority (11/13) were followed up for less than 24 hours at hospital. Most (30 [77%]) suicide attempters used non-violent methods. Of patients ($N=77$) with suicidal ideation alone (no suicide attempt) during the index episode, in the majority ($N=47$, 61%), it occurred during a depressive phase and in 23 (30%) during a mixed phase of illness.

Table 7. Characteristics of 191 Patients with Bipolar Disorder According to Suicidal Behaviours

	Non-Suicidal N=75	Suicidal Ideation (No attempt) N=77	Suicide Attempters N=39	χ^2	p
Bipolar disorder I/II					
I	40(53)	36(47)	14(36)		
II	35(47)	41(53)	25(64)		
Gender					
Male	40(53)	38(49)	12(31)		
Female	35(47)	39(51)	27(69)		
Age, mean \pm SD, y	38.7 \pm 12.8	38.7 \pm 11.5	33.7 \pm 11.9		
Last episode				47.6	<0.001
Monophasic episode	47(63)	36(47)	10(26)	14.7	0.001
Major depressive phase	15(20)	22(29)	5(13)		
Manic phase	18(24)	2(3)	0		
Hypomanic phase	10(13)	1(1)	0		
Mixed phase (Depressive and manic)	1(1)	4(5)	2(5)		
Mixed phase (Depressive and hypomanic)	3(4)	7(9)	3(8)		
Polyphasic episode	28(37)	41(53)	29(74)	14.7	0.001
Rapid cycling	16(21)	27(35)	19(49)	9.2	0.01
Current psychotic features	13(17)	13(17)	5(13)		
Duration of Last Episode, mean \pm SD, y ^a	0.6 \pm 1.3	1.8 \pm 3.0	1.5 \pm 2.6	16.2	<0.001
Duration of illness, mean \pm SD, y	13.3 \pm 10.7	15.4 \pm 10.7	12.5 \pm 9.0		
Previous suicide attempts, N (%)	25(33)	34(44)	26(67)	11.7	0.003
Previous suicidal ideation, N (%)	36(48)	60(78)	34(87)	24.3	<0.001
Early age at onset (before 18 years of age)	15(20)	27(35)	16(41)	6.9	0.03
BDI score, mean \pm SD ^{b,c}	14.9 \pm 9.6	25.1 \pm 8.9	25.3 \pm 11.5	F=24.0	<0.001
BAI score, mean \pm SD ^b	17.6 \pm 11.9	25.3 \pm 10.8	26.7 \pm 14.7	F=9.9	<0.001
HAM-D score, mean \pm SD ^{b,d}	13.8 \pm 6.6	19.3 \pm 6.2	18.7 \pm 7.6	F=13.8	<0.001
YMRS score, mean \pm SD	9.9 \pm 11.2	5.9 \pm 6.5	5.4 \pm 5.9		
BHS score, mean \pm SD ^b	7.4 \pm 4.3	11.1 \pm 4.7	11.8 \pm 5.4	F=14.8	<0.001
SSI score, mean \pm SD ^a	0.6 \pm 1.3	9.2 \pm 7.4	13.2 \pm 9.6	72.7	<0.001
PSSS-R score, mean \pm SD	43.9 \pm 11.7	40.4 \pm 13.1	41.1 \pm 12.2		
SOFAS score, mean \pm SD	50.8 \pm 13.1	47.1 \pm 10.3	48.0 \pm 13.5		
Anxiety disorder/ any current	21(28)	40(52)	24(62)	14.9	0.001
Eating disorder/ any current	2(3)	7(9)	6(15)	6.3	0.04
Alcohol dependence/ abuse current	13(17)	13(17)	7(18)		
Personality disorder	24(32)	29(38)	29(74)	20.5	<0.001
Smoking ^e	35(47)	42(56)	20(54)		

a Kruskal-Wallis test

b ANOVA = analysis of variance

c BDI items 2 and 9 are omitted

d HAM-D item 3 is omitted

e missing information 4/191; 2%

7.1.3 Suicidal behaviour before index episode

Only 39 of 191 (20%) patients reported no suicidal behaviour during their lifetime. Either during the index or preceding episodes, 147 patients (77%) had had suicidal ideation, or 98 patients (51%) had attempted suicide. Before the index episode 130 patients (68 %) had had serious suicidal ideation, mainly (114; 88%) during a previous depressive episode. Of the 85 patients (45%) with attempted suicide before the index episode, the majority (66; 78%) had occurred during a depressive episode, eight (9%) during a mixed episode and six (7%) between illness episodes. The total lifetime number of suicide attempts was one in 34 (18%), two in 23 (12%) and three or more in 41 (21%) of cases.

7.1.4 Prevalence of suicidal behaviour in bipolar I and bipolar II disorders

There were no statistically significant differences in the prevalence of suicidal behaviour - attempts or ideation - between bipolar I and bipolar II patients before or during the index episode. Moreover, there were no significant differences between bipolar I and bipolar II patients regarding the number of suicide attempts. Bipolar II patients had higher levels of hopelessness (bipolar I patients [mean 9.0 ± 4.9] vs. bipolar II patients [mean 10.5 ± 5.1]; $t=-2.1$, $df=177$, $p=0.04$). There were no significant differences with regard to endorsed items on the SSI between bipolar I and II disorders.

7.1.5 Risk factors for suicidal ideation and suicide attempts

The nominal regression models predicting various types of suicidal behaviour during the index episode are presented in Table 8. The factors most strongly independently associated with suicidal ideation were severe depressive episode and hopelessness. Suicide attempt was associated with hopelessness, comorbid personality disorder and a previous suicide attempt. Since a previous suicide attempt is not a plausible causal risk factor for current suicide attempt, this was omitted from an alternative model. This had no effect on the significance of the remaining risk factors; no new variable emerged as significant.

7.2 Suicidal behaviour during different phases of bipolar disorder (study II)

7.2.1 Prevalence of suicidal behaviour during different phases

There were no suicide attempts during hypomanic/manic phases, whereas suicide attempts took place during depressive, mixed and depressive mixed phases. Furthermore, there were marked differences regarding level of suicidal ideation during different phases, with the highest levels during the mixed phases of the illness (Table 9).

7.2.2 Risk factors of suicidal behaviour during different phases

During the depressive phase of BD, severity of current phase (BDI score), Axis II comorbidity, cluster C comorbidity and previous suicide attempts were related to suicidal behaviour, whereas hopelessness independently predicted suicide attempts and suicidal ideation. During the hypomanic/manic phase there were no suicide attempts, whereas any current anxiety disorder, Axis II comorbidity and cluster B comorbidity, were associated with suicidal ideation in the relatively rare instances when this occurred. A subjective rating of severity of depression (BDI) and younger age predicted suicide attempts during mixed phases (Table 10). Interactions between risk factors did not reach statistical significance.

Table 8. Nominal Regression Models for Different Suicidal Behaviours

Variable	Non-suicidal OR ^a	Suicidal Ideation				Suicide Attempt			
		OR	95% CI	Wald	p	OR	95% CI	Wald	p
Female	1.0	0.81	0.39 to 1.68	0.32	0.57	0.50	0.19 to 1.28	2.10	0.15
Age, y	1.0	1.00	0.97 to 1.03	0.10	0.75	1.00	0.94 to 1.02	1.29	0.26
HAM-D score	1.0	1.10	1.04 to 1.17	11.01	0.001	1.05	0.97 to 1.13	1.59	0.21
BHS score	1.0	1.12	1.04 to 1.22	7.94	0.005	1.16	1.04 to 1.28	7.75	0.005
Previous suicide attempt	1.0	1.40	0.67 to 2.93	0.79	0.38	3.35	1.09 to 7.58	6.40	0.01
Personality Disorder	1.0	0.80	0.37 to 1.72	0.33	0.56	2.99	1.14 to 7.86	4.58	0.03
Subpopulation of BD I									
Female	1.0	2.76	0.80 to 9.60	2.56	0.11	0.84	0.17 to 4.27	0.04	0.84
Age, y	1.0	0.98	0.93 to 1.04	0.41	0.52	0.99	0.92 to 1.06	0.17	0.68
HAM-D score	1.0	1.17	1.05 to 1.31	8.20	0.004	1.13	0.98 to 1.30	2.78	0.10
BHS score	1.0	1.20	1.03 to 1.40	5.52	0.02	1.31	1.08 to 1.60	7.56	0.006
Previous Suicide Attempt	1.0	2.55	0.76 to 8.51	2.31	0.13	5.44	1.10 to 26.85	4.32	0.04
Subpopulation of BDII									
Female	1.0	0.43	0.17 to 1.13	2.90	0.09	0.42	0.13 to 1.37	2.07	0.15
Age, y	1.0	1.00	0.96 to 1.04	0.01	0.92	0.98	0.94 to 1.04	0.38	0.54
HAM-D score	1.0	1.08	1.00 to 1.15	4.33	0.04	1.04	0.96 to 1.13	0.79	0.38
Personality Disorder	1.0	1.06	0.37 to 3.04	0.01	0.92	7.85	2.18 to 28.21	9.96	0.002

a Reference group
HAM-D = Hamilton Rating Scale; item 3 is omitted

Table 9. Prevalence of suicidal behaviour during different phases

	Suicide attempts, N (%) ^a	SSI Percentiles ^b		
		25th	50th	75th
Current Phase Depression (N=105) ^c	24(23)	0.0	5.0	14.5
Current Phase Depressive Mixed (N=24) ^d	5 (21)	0.0	6.5	12.8
Current Phase Mixed (N=15)	3 (20)	0.0	12.0	17.0
Current Phase Hypomanic/Manic (N=33)	0	0.0	0.0	0.0

a $\chi^2=9.1$, df = 3, p=0.03

b (Kruskal-Wallis test) $\chi^2=20.0$, df = 3, p<0.001

c Post-hoc comparisons between depressive and mixed phase Z=-3.9, p<0.001

Post-hoc comparisons between depressive and depressive mixed phase Z=-4.0, p<0.001

Post-hoc comparisons between depressive and hypomanic/manic phase Z=-4.4, p<0.001

d Post-hoc comparisons between mixed and depressive mixed phase Z=-2.4, p=0.02

Table 10. Multinomial Regression Model for Different Suicidal Behaviours during Different Phases

Variable	Non-suicidal OR ^a	Suicidal Ideation				Suicide Attempt				
		OR	95% CI	Wald	p	OR	95% CI	Wald	p	
During Depressive Phase										
Male	1.0	0.70	0.27 to 1.82	0.53	0.47	0.36	0.12 to 1.10	3.24	0.07	
Age, y	1.0	1.00	0.95 to 1.02	0.68	0.41	0.99	0.95 to 1.04	0.18	0.67	
BHS score	1.0	1.18	1.05 to 1.32	7.22	0.007	1.16	1.01 to 1.32	4.70	0.03	
During Mixed Phases										
Male	1.0	1.61	0.30 to 8.71	0.31	0.58	2.45	0.11 to 56.51	0.31	0.58	
Age, y	1.0	0.94	0.87 to 1.03	1.67	0.20	0.81	0.67 to 0.97	5.09	0.02	
BDI score	1.0	1.16	1.00 to 1.35	3.91	0.05	1.30	1.06 to 1.59	6.44	0.01	

a Reference group

BDI = Beck Depression Inventory (items 2 and 9 omitted)

7.3 Prospective study of risk factors for attempted suicide among bipolar disorder patients (study III)

7.3.1 Suicide attempts during the follow-up

At some point during the follow-up, 20% of all patients (35/176) attempted suicide, of whom eventually two (1%) died by suicide between the 6- and the 18-month follow-ups. Of those who attempted suicide, two thirds 69% (24/35) were referred to an emergency room. Of the suicide attempters not referred to an emergency room, almost half 45% (5/11) had not communicated with mental health professionals about their suicide attempts. Three patients (2%) had only aborted suicide attempts during the follow-up. There were no statistically significant differences in the prevalence of suicide attempters between bipolar I and bipolar II patients during the 6-month or the 18-month follow-up.

7.3.2 Differences between suicide attempters and non-attempters during 6-month follow-up

During the 6-month follow-up 15% of patients (27/176) attempted suicide, with overdose being the most commonly used method (21/27 [78%]). During the 6-month follow-up 6% of patients (11/176) made aborted suicide attempts; three of those who had an aborted suicide attempt had made no suicide attempts during the 6-month follow-up. The characteristics of the patients with and without suicide attempts during the 6-month follow-up are presented in Table 11. Significant differences were found between attempters and non-attempters in terms of severity of index episode, depression (objective and subjective ratings), amount of suicidal ideation, amount of anxiety, hopelessness, prevalence of comorbid personality disorder and prevalence of previous suicide attempts. Suicide attempters were also associated with early age at first mood episode, fewer episodes of bipolar disorder, female gender, depressive phase at index episode and younger age at intake.

7.3.3 Differences between suicide attempters and non-attempters during 18-month follow-up

During the 18-month follow-up 18% of patients (29/160) attempted suicide, most (21/29 [72%]) with overdose. Of the 27 patients who had attempted suicide between the baseline and the 6-month follow-up, two patients (7%) completed suicide, and seven (26%) made another attempt before the 18-month follow-up. Eight patients who had not attempted suicide between the baseline and the 6-month follow-up attempted suicide between the 6- and 18-months follow up. Two percent of patients (3/160) made aborted suicide attempts. Two of those with an aborted suicide attempt had no previous suicide attempts. The characteristics of patients with and without suicide attempts during the 18-month follow-up are presented in Table 12. Significant differences were found between attempters

and non-attempters in terms of severity of index episode, depression (objective and subjective ratings), amount of suicidal ideation, amount of anxiety, hopelessness, prevalence of comorbid personality disorder and prevalence of previous suicide attempts. Suicide attempters were also associated with fewer episodes of BD, shorter duration of BD, female gender and younger age at intake.

7.3.4 Predictors of suicide attempts during follow-up

The Cox's regression model for predicting suicide attempts during follow-up is presented in Table 13. The factors most strongly independently associated with suicide attempts during follow-up were: baseline previous suicide attempts, hopelessness, depressive phase at index episode and younger age at intake. Since a previous suicide attempt is not a plausible causal risk factor for a current suicide attempt, it was omitted from an alternative model. This had, however, little effect on the significance of the remaining risk factors; depressive phase at index episode lost significance, but no new variable emerged as significant.

7.4 Differences in incidence of suicide attempts during phases of bipolar I and II disorders (study IV)

7.4.1 Incidence of suicide attempts

During the follow-up, 20% of patients (35/176) reported at least one suicide attempt, and altogether there were 53 suicide attempts which all could be timed. There were no suicide attempts during manic/hypomanic phases, nor during euthymic phases. Of the 53 suicide attempts, 39 (74%) occurred during a major depressive phase, seven (13%) during depressive mixed phase, three (6%) during mixed phase and four (7%) during depressive symptoms (Figure 2). Of the 176 patients included in the 6-month follow-up, 3 patients (2%) died between the 6-month and the 18-month follow-up (2 [1%] by suicide), and 10 patients dropped out. During the 18-month follow-up; the mean following time was 1.6 person-years.

The incidence of suicide attempts was higher among bipolar II than bipolar I patients in depressive phase (0.5 vs. 0.3; respectively 27 suicide attempts/56.55 person-years vs. 12 suicide attempts/36.06 person years) and in combined mixed phases (mixed and depressive mixed) (1.1 vs. 0.6 respectively 7 suicide attempts/6.66 person-years vs. 3 suicide attempts/4.77 person-years). Bipolar II patients spent more time in risk phases than bipolar I patients. No interaction was found between these factors.

Table 11. Baseline characteristics of 176 bipolar disorder patients with and without suicide attempts during a 6-month follow-up

	Suicide Attempters N=27	Non-Attempters N=149	Total N=176	χ^2	p
Sociodemographic features					
Bipolar disorder I/II					
I	11(41)	70(47)	81(46)		
II	16(59)	79(53)	95(54)		
Gender				5.4	0.02
Male	7(26)	78(52)	85(48)		
Female	20(74)	71(48)	91(52)		
Married or cohabiting	12(44)	62(42)	74(42)		
Age, mean \pm SD, y ^a	32.1 \pm 11.2	38.9 \pm 12.0	37.9 \pm 12.1	t=2.7	0.007
PSSS-R score, mean \pm SD	40.4 \pm 12.2	42.6 \pm 12.4	42.2 \pm 12.4		
History of suicidal behaviour					
Suicide attempt before/during index episode	22(82)	67(45)	89(51)	10.8	0.001
Suicide attempt during index episode	13(48)	21(14)	34(19)	14.9	<0.001
Suicide attempt before index episode	19(70)	60(40)	79(45)	7.2	0.007
First degree relative who completed suicide ^b	1(6)	7(6)	8(6)		
First degree relative who attempted suicide ^b	4(21)	18(15)	22(16)		
Symptom scores					
BDI score, mean \pm SD ^{a,c}	27.2 \pm 9.3	19.8 \pm 10.7	21.0 \pm 10.8	t=-3.3	0.001
BAI score, mean \pm SD ^d	30.2 \pm 12.8	21.4 \pm 12.5	22.8 \pm 12.9	t=-3.3	0.001
HAM-D score, mean \pm SD ^{a,d}	20.8 \pm 5.2	16.2 \pm 7.2	16.9 \pm 7.1	t=-3.1	0.002
YMRS score, mean \pm SD	6.4 \pm 6.2	7.7 \pm 9.3	7.5 \pm 8.9		
BHS score, mean \pm SD ^d	14.0 \pm 4.1	9.1 \pm 4.8	9.8 \pm 5.0	t=-4.8	<0.001
SSI score, mean \pm SD ^e	14.5 \pm 9.3	5.3 \pm 7.1	6.7 \pm 8.2	Z=-4.8	<0.001
SOFAS score, mean \pm SD	45.7 \pm 14.0	48.9 \pm 11.9	48.4 \pm 12.2		
Psychiatric comorbidity					
Anxiety disorder / any lifetime	18(67)	77(52)	95(54)		
Eating disorder / any lifetime	5(19)	21(14)	26(15)		
Psychotic features / lifetime	15(56)	72(48)	87(49)		
Alcohol dependence / abuse lifetime	9(33)	75(50)	84(48)		
Smoking ^f	13(50)	74(50)	87(50)		
Personality disorder	20(74)	59(40)	79(45)	9.6	0.002
Cluster A	7(26)	12(8)	19(11)	5.8	0.02
Cluster B	12(44)	39(26)	51(29)		
Cluster C	13(48)	31(21)	44(25)	7.7	0.005
Course of illness					
Last phase				10.9	0.03
Major depressive phase	17(63)	80(54)	97(55)		
Manic phase	0	22(15)	22(13)		
Hypomanic phase	0	18(12)	18(10)		
Mixed phase (Depressive and manic)	3(11)	10(7)	13(7)		
Mixed phase (Depressive and hypomanic)	7(26)	19(13)	26(15)		
Polyphasic episode	15(56)	75(50)	90(51)		
Rapid cycling	10(37)	43(29)	53(30)		
Early age at onset (before 18 years of age)	14(52)	40(27)	54(31)	5.6	0.02
Total number of mood episodes, mean \pm SD ^e	4.6 \pm 3.4	10.0 \pm 23.0	8.9 \pm 20.8	Z=-2.1	0.03
Duration of illness, mean \pm SD, y	10.7 \pm 7.4	14.8 \pm 10.9	14.2 \pm 10.5		
Adequate pharmacotherapy for the index phase	13(48)	63(42)	76(43)		

a Student's t-test

b 23% missing information

c BDI items 2 and 9 are omitted

d HAM-D item 3 is omitted

e Mann-Whitney test

f 2 % missing information

Table 12. Baseline characteristics of 160 bipolar disorder patients with and without suicide attempts during an 18-month follow-up

	Suicide Attempters N=29	Non-Attempters N=131	Total N=160		
	N (%)	N (%)	N (%)	χ^2	p
Sociodemographic features					
Bipolar disorder I/II					
I	11(38)	64(49)	75(47)		
II	18(62)	67(51)	85(53)		
Gender				4.2	0.04
Male	9(31)	71(54)	80(50)		
Female	20(69)	60(46)	80(50)		
Married or cohabiting	13(45)	54(41)	67(42)		
Age, mean \pm SD, y ^a	32.6 \pm 10.1	39.9 \pm 11.7	38.6 \pm 11.8	t=3.1	0.002
PSSS-R score, mean \pm SD	40.4 \pm 12.4	42.7 \pm 12.2	42.3 \pm 12.3		
History of suicidal behaviour					
Suicide attempt before/during index episode or during 6-month follow-up	26(90)	55(42)	81(51)	19.7	<0.001
Suicide attempt during index episode	11(38)	16(12)	27(17)	9.4	0.002
Suicide attempt before index episode	19(66)	50(38)	69(43)	6.2	0.01
First degree relative who completed suicide ^b	1(4)	7(6)	8(6)		
First degree relative who attempted suicide ^b	6(22)	16(15)	22(16)		
Symptom scores					
BDI score, mean \pm SD ^{a,c}	26.4 \pm 9.7	19.2 \pm 10.7	20.5 \pm 10.9	t=-3.3	0.001
BAI score, mean \pm SD ^d	29.8 \pm 13.1	20.7 \pm 12.0	22.3 \pm 12.7	t=-3.6	<0.001
HAM-D score, mean \pm SD ^{a,d}	20.7 \pm 6.9	16.0 \pm 7.1	16.8 \pm 7.3	t=-3.2	0.002
YMRS score, mean \pm SD	6.0 \pm 5.2	8.0 \pm 9.7	7.7 \pm 9.1		
BHS score, mean \pm SD ^d	13.3 \pm 4.4	8.7 \pm 4.9	9.5 \pm 5.1	t=-4.6	<0.001
SSI score, mean \pm SD ^e	13.1 \pm 9.5	4.6 \pm 6.6	6.2 \pm 7.9	Z=-4.7	<0.001
SOFAS score, mean \pm SD	46.0 \pm 14.4	48.8 \pm 12.1	48.3 \pm 12.5		
Psychiatric comorbidity					
Anxiety disorder / any lifetime	20(69)	65(50)	85(53)		
Eating disorder / any lifetime	7(24)	16(12)	23(14)		
Psychotic features / lifetime	14(48)	65(50)	79(49)		
Alcohol dependence / abuse lifetime	13(45)	65(50)	78(49)		
Smoking ^f	13(46)	67(52)	80(51)		
Personality disorder	19(66)	48(37)	67(42)	7.0	0.008
Cluster A	7(24)	11(8)	18(11)	4.4	0.04
Cluster B	12(41)	29(22)	41(26)		
Cluster C	11(38)	30(23)	41(26)	7.7	0.005
Course of illness					
Last phase during index episode				10.9	0.03
Major depressive phase	20(69)	67(51)	87(54)		
Manic phase	0	21(16)	21(13)		
Hypomanic phase	1(3)	16(12)	17(11)		
Mixed phase (Depressive and manic)	3(10)	10(8)	13(8)		
Mixed phase (Depressive and hypomanic)	5(17)	17(13)	22(14)		
Polyphasic episode	18(62)	62(47)	80(50)		
Rapid cycling	13(45)	34(26)	47(29)		
Early age at onset (before 18 years of age)	13(45)	33(25)	46(29)		
Total number of mood episodes, mean \pm SD ^c	4.3 \pm 3.5	10.4 \pm 23.8	9.3 \pm 21.8	Z=-2.7	0.007
Duration of illness, mean \pm SD, y	10.9 \pm 7.8	15.5 \pm 11.0	14.7 \pm 10.6	t=2.1	0.03
Adequate pharmacotherapy for the index phase	10(35)	58(44)	68(43)		

a Student's t-test

b 15% missing information

c BDI items 2 and 9 are omitted

d HAM-D item 3 is omitted

e Mann-Whitney test

f 1 % missing information

Table 13. Cox's regression model for predicting suicide attempters during follow-up

Variable	Suicide Attempt			
	OR	95% CI	Wald	p
Bipolar I disorder	1.20	0.58 to 2.47	0.24	0.62
Male	1.52	0.72 to 3.18	1.20	0.27
Age, y	0.94	0.91 to 0.97	12.45	<0.001
BHS score	1.19	1.10 to 1.29	17.30	<0.001
Previous suicide attempts	3.85	1.69 to 8.78	10.27	0.001
Depressive phase at the index episode	2.43	1.11 to 5.35	4.89	0.027

7.4.2 Factors associated with high incidence of suicide attempts during follow-up

The incidence of suicide attempts was higher among females than males and also among bipolar II than bipolar I patients (Table 14). However, when other risk factors were taken into account, subtype of bipolar disorder nor gender independently predicted suicide attempts. Lifetime comorbid anxiety disorders and comorbid personality disorders were related to a higher incidence of suicide attempts, whereas lifetime comorbid substance abuse/dependence was not. None of these comorbidities independently predicted suicide attempts. The higher the values of Hamilton Rating Scale for Depression, as well as Beck Hopelessness Scale, the higher were the risk ratios of incidence of suicide attempts.

The incidence of suicide attempt was 37-fold during combined mixed and depressive mixed states and 18-fold during major depressive phase as compared with the other phases (mania, hypomania, hypomanic symptoms, euthymia, depressive symptoms, cyclothymia and substance induced phase). The Cox's proportional hazard model predicting suicide attempts during follow-up, the predetermined covariates comprised of gender, age, subtype of bipolar disorder, lifetime comorbid substance dependence/abuse, lifetime any comorbid anxiety disorder, suicide attempts before follow-up, comorbid personality disorders, lifetime psychotic features, the highest value of Beck Hopelessness Scale, the highest value of Hamilton Rating Scale for Depression and the time spent in risk phases, both in combined mixed phases (mixed and depressive mixed) and depressive phases. In this model suicide attempts before follow-up increased the risk almost 4-fold, whereas the major depressive phase increased the risk 11-fold and combined mixed phases (mixed and depressive mixed) increased the risk almost 28-fold (Figure 3). No interaction between either of the high-risk phases and the static risk factors modifying the effect was detected, i.e. there was no evidence for any of the static risk factors modifying the effect of the high-risk phases.

Figure 2. Incidence per one year with 95% confidence interval of suicide attempt in respect to phases of bipolar disorder

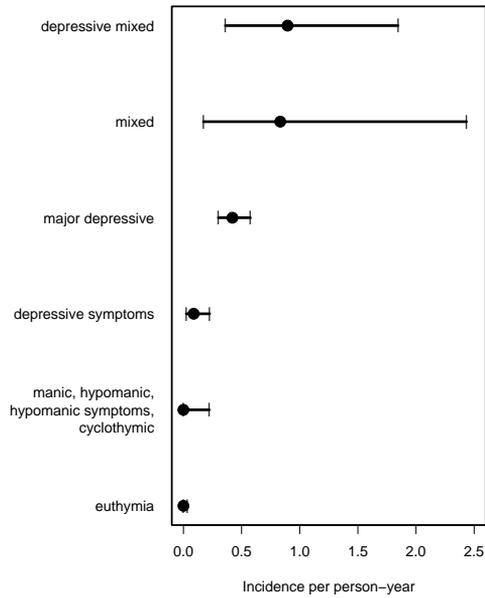


Figure 3. Risk factors of suicide attempts. Hazard ratios with 95% confidence interval based on multivariate Cox's proportional hazards model (logarithmic x-axis scale)

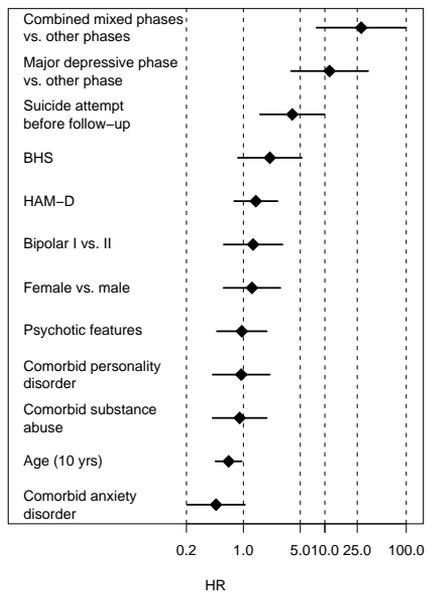


Table 14. Risk factors for suicide attempts. Relative risk (RR) from univariate Poisson model, and hazard ratio (HR) from multivariate Cox's model.

Variable	Number of suicide attempts	Person-years	Incidence	RR	CI 95%	HR	CI 95%
Static variables							
Age at baseline ^a						0.96	0.92 to 1.00
<i>Gender</i>							
Male	15	137.28	0.11	1.00	1.00 to 1.00		
Female	38	139.03	0.27	2.50	1.38 to 4.55	1.27	0.57 to 2.84
<i>Subtype of bipolar disorder</i>							
Bipolar I	16	129.47	0.12	1.00	1.00 to 1.00		
Bipolar II	37	146.84	0.25	2.04	1.13 to 3.67	1.32	0.58 to 3.02
<i>Suicide attempt before follow-up</i>							
No	9	141.05	0.06	1.00	1.00 to 1.00		
Yes	44	135.25	0.33	5.10	2.49 to 10.44	3.98	1.60 to 9.90
<i>Lifetime comorbid substance dependence/abuse</i>							
No	29	140.08	0.21	1.00	1.00 to 1.00		
Yes	24	136.23	0.18	0.85	0.50 to 1.46	0.90	0.42 to 1.93
<i>Any lifetime comorbid anxiety disorder</i>							
No	16	128.32	0.12	1.00	1.00 to 1.00		
Yes	37	147.99	0.25	2.01	1.12 to 3.60	0.46	0.20 to 1.05
<i>Comorbid personality disorder</i>							
No	18	160.15	0.11	1.00	1.00 to 1.00		
Yes	35	116.16	0.30	2.68	1.52 to 4.73	0.94	0.42 to 2.11
<i>Lifetime psychotic features</i>							
No	28	140.08	0.20	1.00	1.00 to 1.00		
Yes	25	136.23	0.18	0.92	0.54 to 1.57	0.96	0.47 to 1.94
HAM-D max ^{a, b} [2-18]	10	125.68	0.08	1.00	1.00 to 1.00		
HAM-D max ^{a, b} [19-23]	14	66.61	0.21	2.64	1.17 to 5.95		
HAM-D max ^{a, b} [24-38]	29	84.03	0.35	4.34	2.11 to 8.90	1.04	0.97 to 1.10
BHS max ^{a, b, c} [1-9]	5	112.17	0.04	1.00	1.00 to 1.00		
BHS max ^{a, b, c} [10-14]	16	77.53	0.21	4.63	1.70 to 12.64		
BHS max ^{a, b, c} [15-20]	31	85.20	0.36	8.16	3.17 to 21.99	1.08	0.99 to 1.18
Time-varying variables							
Time spent in other phases ^d	4	172.29	0.02	1.00	1.00 to 1.00		
Time spent in mixed phases ^e	10	11.42	0.88	37.73	11.83 to 120.29	27.98	7.89 to 99.20
Time spent in major depressive phases	39	92.61	0.42	18.14	6.48 to 50.76	11.43	3.85 to 34.01

a For continuous variables (age, HAM-D, and BHS) HR are calculated for increment of 10 units.

b HAM-D max is defined as the maximum score of Hamilton Rating Scale for Depression (HAM-D) and BHS max is defined as the maximum score of Beck Hopelessness Scale (BHS). Both HAM-D and BHS were divided into tertiles.

c There was one Beck Hopelessness Scale missing.

d Other phases include manic and hypomanic phases, hypomanic symptoms, euthymic, cyclothymic, substance induced mood phases.

e Mixed phase include both mixed and depressive mixed phases.

8. DISCUSSION

8.1 Main findings

The Jorvi Bipolar Study (JoBS) is a prospective, naturalistic cohort study of 191 secondary-level care psychiatric out- and inpatients with a new episode of DSM-IV BD. One-fifth of patients attempted suicide and over half of the patients had suicidal ideation during index episode. In a cross-sectional study, it was shown that 51% of cohort of patients had attempted suicide either before or during the index episode. In addition to these patients, eight subjects with no preceding suicide attempts attempted suicide at some point during the follow-up. Taken together, more than half of the patients (55%; 103/188) who were initially included in the study and remain alive have attempted suicide during their lifetime. Previous studies have not investigated the variation in the incidence of suicide attempts during different phases of bipolar disorder. The incidence of suicide attempts varies remarkably depending on the type of illness phase during 18-month follow-up; it increased 37-fold during mixed phases and 18-fold during major depressive phase.

At the baseline numerous factors were associated with suicidal behaviour in univariate analyses. In the multivariate models hopelessness, comorbid personality disorder, severe depression and a previous suicide attempt, with minor differences between ideation and attempts, were the main independent risk factors. There were no differences in suicidal behaviour prevalence between bipolar I and II disorders. However, the risk factors for suicidal behaviour in bipolar I and II disorders were not identical.

There were no suicide attempts during hypomanic/manic phases of the index episode, whereas suicide attempts took place during depressive, mixed and depressive mixed phases of the index episode. The highest levels of suicidal ideation were associated with the mixed phases of the illness. A subjective rating of severity of depression (BDI) and younger age predicted suicide attempts during mixed phases, whereas hopelessness was independently associated with suicidal behaviour during the depressive phase of the index episode.

During an 18-month follow-up one-fifth of patients with BD attempted suicide. However, not all of these attempts led to an emergency room, and a minority of attempters did not even communicate them to the attending professionals, which suggests that the problem of suicidal behaviour and, as a consequence, risk of completed suicide among patients with BD could often be underestimated. Baseline previous suicide attempts, hopelessness, depressive phase at index episode and younger age at intake independently predicted suicide attempts during follow-up, whereas having bipolar I or II, or psychiatric Axis I or II comorbidity did not predict suicide attempts.

Incidence of suicide attempts varies remarkably depending on the type of illness phase, with mixed and depressive phases involving highest risk. However, there were many factors associated with the elevated incidence of suicide attempts, so time spent in risk phases both in combined mixed phases (mixed and depressive mixed), depressive phases and suicide attempt before follow-up were the most robust predictors of suicide attempts during follow-up.

8.2 Results

8.2.1 Suicidal ideation and attempts in bipolar I and II disorders (study I)

Numerous factors were found to be associated with suicide attempts. Many single risk factors for attempted suicide have been investigated in previous studies, but a comprehensive view of risk factors related to suicide attempts in bipolar disorder, particularly bipolar II, is still emerging. In accordance with previous studies anxiety disorders (Leverich et al., 2003), personality disorders (Leverich et al., 2003; Vieta et al., 1999; Uçok et al., 1998), eating disorders (Leverich et al., 2003), severity of depressive episode (Leverich et al., 2003; Lopez et al., 2001; Oquendo et al., 2000; Uçok et al., 1998), earlier age at onset (Perlis et al., 2004; Slama et al., 2004; Leverich et al., 2003; Tsai et al., 1999) and suicidal ideation (Oquendo et al., 2000) were significant predictors of suicide attempts in univariate analyses. Rapid cycling was related to suicide attempts in univariate analyses convergent with some (Coryell et al., 2003; MacKinnon et al., 2003) but not all studies (Serretti et al., 2002; Tsai et al., 1999; Wu and Dunner, 1993). Females attempted suicide more often than males, unlike in recent studies (Leverich et al., 2003; Lopez et al., 2001; Oquendo et al., 2000). However, in multivariate models level of hopelessness, comorbid personality disorder and a history of preceding suicide attempts were the major independent risk factors for suicide attempts. Thus, the factors most effectively indicating risk for suicide attempts in bipolar disorder are not much different from those in unipolar depression.

Contrary to expectations, alcohol or substance abuse or dependence were found to be unrelated to suicide attempts during the index episode. Comorbid alcohol dependence or abuse is associated with suicide attempts in many (Tondo et al., 1999; Potash et al., 2000; Goldberg et al., 2001b; Lopez et al., 2001; Slama et al., 2004), but not all studies (Galfalvy et al., 2006; Oquendo et al., 2000; Leverich et al., 2003). The literature regarding alcohol or substance abuse or dependence and its association to suicide attempts among bipolar patients is conflicting.

Suicidal ideation is highly prevalent in bipolar disorder. Over three-fourths of patients with BD reported suicidal ideation during their lifetime. All suicide attempters also reported suicidal ideation: so suicidal ideation appears to be a precondition and a highly sensitive indicator of risk of suicide attempt. Suicide attempters had a significantly

higher level of suicidal ideation than the mere ideators, which supports a continuum view of non-fatal suicidal behaviour. Ideators and attempters are an overlapping population in a lifetime perspective, as nearly half of those with suicidal ideation during the current episode had attempted suicide during previous episodes. Furthermore, in psychological autopsy studies, a significant proportion of suicide victims were found to have died at their first suicide attempt, but having had communicated about suicidal ideation (Isometsä et al., 1994). Unexpectedly, despite the higher level of ideation, the overall level of psychopathology was otherwise not different between the two groups. In univariate analyses comorbid anxiety disorders were related to suicidal ideation, whereas in contrast to previous studies psychotic symptoms (Bottlender et al., 2000), past suicide attempts (Bottlender et al., 2000; Goldberg et al., 1999) and personality disorders (Vieta et al., 1999) were not associated. However in multivariate models, hopelessness and severity of depressive episode were independent predictors of suicidal ideation. Thus, suicidal ideation appears largely a reflection of depressive aspects of the illness, with few other factors besides hopelessness being important.

8.2.2 Suicidal behaviour during different phases of bipolar disorder (study II)

There are no previous studies on the prevalence of suicidal behaviour (both suicidal ideation and suicide attempts) during different phases. The highest levels of suicidal ideation were found during the mixed phases of the illness. There were no suicide attempts during hypomanic/manic phases, whereas suicide attempts took place during depressive, mixed and depressive mixed phases. Hopelessness was independently associated with suicidal behaviour during the depressive phase. A subjective rating of severity of depression (BDI) and younger age predicted suicide attempts during mixed phases.

During the depressive phase of BD, severity of current phase (BDI score), Axis II comorbidity, cluster C comorbidity and previous suicide attempts were related to suicidal behaviour, whereas hopelessness independently predicted suicide attempts and suicidal ideation. During the hypomanic/manic phase there were no suicide attempts, whereas any current anxiety disorder, Axis II comorbidity and cluster B comorbidity were associated with suicidal ideation in the relatively rare instances when this occurred.

Mixed phases of the illness were related to the highest level of suicidal ideation; there was a clear gradient in mixed states proper involving more high SSI scores than the depressive mixed, and which, in turn, had a greater number of high scores than the depressive phases. It is noteworthy that despite the highest levels of anxiety in the mixed phases, anxiety itself was not a predictor for suicidal behaviour. Also, it appears that a subjective rating (BDI) rather than an objective rating (HAM-D) of the severity of depression was related to suicidal behaviour in accordance with a prospective study by Oquendo and colleagues (2004). During the mixed phases hopelessness, subjective severity of depression, suicidal ideation before index episode, Axis II comorbidity, comorbid cluster C were associated with suicidal behaviour, whereas subjective severity of depression and age independently predicted suicide attempts.

8.2.3 Prospective study of risk factors for attempted suicide among bipolar disorder patients (study III)

During the 18-month follow-up 20% of patients attempted suicide. Previous prospective studies have often investigated mixed patient populations; including subjects with both unipolar and bipolar affective disorders (Fawcett et al., 1990; Nordström et al., 1995; Oquendo et al., 2004). These studies have suggested that BD may carry a higher risk for attempted suicide than major depressive disorder (Chen and Dilsaver, 1996; Bottlender et al., 2000; Sokero et al., 2005). In the Vantaa Depression Study (Sokero et al., 2005), a comparable study of unipolar patients, 8% of unipolar major depressive patients attempted suicide during an 18-month follow-up. Thus, findings are concordant with the view that patients with BD are at particularly high risk for suicidal behaviour.

The prevalence of suicide attempters during the follow-up (20%) was almost same as in study by Galfalvy et al. (2006), higher than in three other reports; recent study by Marangell et al. (2006), one with a mixed population (Oquendo et al., 2004) and one with a mixed inpatient population (Nordström et al., 1995), but lower than in one study (Coryell et al., 2003). Findings reveal that while suicide attempts among unselected bipolar patients are carefully investigated every fifth BD patient attempts suicide during a medium-term (18-month) follow-up. Many studies may have underestimated suicidal behaviour among bipolar patients, because previous studies have assessed neither aborted suicide attempts, nor suicide attempts which, despite intent to die, were not communicated to professionals.

The risk of suicide attempt was predicted by four independent factors: previous suicide attempts, hopelessness, depressive phase at index episode and younger age at intake. Whereas having bipolar I or II, or psychiatric Axis I or II comorbidity did not predict suicide attempts. Hopelessness, which has been researched widely as a risk factor for suicide attempts in suicidology in general, has seldom been studied among BD patients (Fawcett et al., 1990; Oquendo et al., 2004; Galfalvy et al., 2006). Hopelessness independently predicted suicide attempts in both cross-sectional study and the prospective study of risk factors for suicide attempters.

The findings regarding alcohol and substance dependence or abuse, smoking and rapid cycling, by contrast, have been much less consistent in the few previous prospective studies. These factors were not associated with suicide attempters in the study.

8.2.4 Differences in incidence of suicide attempts during phases of bipolar I and II disorders (study IV)

No previous study has investigated the variation in the incidence of suicide attempts during different phases of bipolar disorder. Incidence of suicide attempts varies remarkably depending on the type of illness phase; it was 37-fold during mixed phases and 18-fold during major depressive phase. Combined mixed (mixed or depressive mixed) or depressive phases (with risk not significantly modified by any other factor) and prior suicide attempts independently predicted suicide attempts. Given a population attributable fraction of 86%, it is obvious that the risk factors which best independently predicted suicide attempts were the high-risk phases, not the individual characteristics of the patient.

The prevalence of suicide attempts between bipolar I and II disorders is a controversial issue (Lester, 1993; Vieta et al., 1997; Rihmer and Pestalicy, 1999). Some studies (Stallone et al., 1980; Bulik et al., 1990; Tondo et al., 1999; Balazs et al., 2003) have reported higher rates of suicide attempts for bipolar II disorder, whereas the Stanley Foundation Bipolar Network Study (Leverich et al., 2003) and some other studies (Endicott et al., 1985; Coryell et al., 1987; Dalton et al., 2003) found no difference. Some studies (Judd et al., 2003a), but not all (Post et al., 2003; Joffe et al., 2004) have reported the longitudinal symptomatic course of BD II is more dominated by the depressive phase of illness. Overall, differences in risk for suicide attempts between bipolar I and II patients are more likely to be largely a consequence of differences in distribution of time spent at risk, and thus vary depending on the longitudinal course of illness, not by type of disorder per se. Spending more time depressed or in the mixed illness phases would readily explain why bipolar II is often associated with more frequent suicidal behaviour than bipolar I.

Research on suicidology has shown that time-varying risk factors are important (Kraemer et al., 1997). Kapur et al. (2006) found in their recent multicentre cohort study that repetition of suicidal behaviour tended to occur quickly - almost half of individuals who did so repeated within one year within the first two months after the index episode. Regarding bipolar patients, Ösby et al. (2001) found standardized mortality ratios to be especially high during the first years after the first diagnosis. Likewise, Høyer et al. (2002) reported that the risk of suicide was high immediately after admission and immediately following discharge among hospitalised affective disorder patients. Even if these studies have emphasized the importance on time aspects of suicidal behaviour, there are no previous studies which would take into account any aspect of time spent in different phases of bipolar disorder, when investigating the risk factors of attempted suicide.

8.3 Methods

8.3.1 Sample and diagnostic measures

The Jorvi Bipolar Study (JoBS) is the first clinical cohort study based on systematic screening for bipolar disorder within a geographically defined catchment area. The study involved a relatively large (N=191) and unselected sample of both in- and outpatients with a new phase of bipolar I and II disorder from three Finnish cities (Espoo, Kauniainen, Kirkkonummi).

Patients entering the study were carefully diagnosed using semi-structured SCID-I interviews with excellent reliability for diagnosing bipolar I and II disorders ($\kappa=1.0$ and 1.0, respectively). Furthermore, both Axis I and Axis II comorbidities were evaluated and patients' symptomatic status and other characteristics were assessed, with a number of standardized observer scales and questionnaires (Mantere et al., 2004).

8.3.2 Life-chart methodology

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 the other prospective studies including and reporting on BD types I and II separately (Judd et al., 2003b; 2003c; Post et al., 2003; Dittman et al., 2002; Nolen et al., 2004; Joffe et al., 2004). This kind of graphic life-chart was planned and used in the Vantaa Depression Study (Melartin et al., 2004). As with the LIFE, change points in the psychopathologic state using probes related to important events were investigated. Unlike the LIFE, in the interview the life-chart was made directly comparable with the DSM-IV criteria, and classified the patients' follow-up time into periods of 4 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 all other information when needed. Time after the baseline interview was divided into 10 time periods: euthymia, manic, hypomanic, major depressive, mixed, depressive mixed (according to Benazzi and Akiskal, 2001), cyclothymic, substance induced mood phase, depressive and hypomanic symptoms (Mantere et al., in press).

8.3.3 Evaluation of suicidal behaviour

8.3.3.1 Strengths of the evaluation of suicidal behaviour

The present study is also among the few (Oquendo et al., 2000; 2004; Galfalvy et al., 2006) using a psychometric scale to measure current suicidal ideation, as well as suicidal ideation during the whole current episode. There are no previous studies on the prevalence of suicidal behaviour (both suicidal ideation and suicide attempts) during different phases. Furthermore, previous studies have not assessed the risk factors of the many domains for attempted suicide during depressive and mixed phases. Previous studies have not reported the prevalence of suicidal behaviour during the depressive mixed phase (depressive mixed phase defined according to Benazzi and Akiskal, 2001). Previous studies have not reported aborted suicide attempts among bipolar patients, nor to actively investigate suicide attempts that otherwise often remain hidden due to lack of contact with services or communication with professionals (study III). There are no previous studies which have examined the differences in incidence during different phases of bipolar disorder. Moreover, previous studies have not estimated the relative importance of static vs. time-varying risk factors for overall risk for suicide attempts nor importance of time at risk for overall risk (study IV). Neither are there studies regarding suicidal behaviour among bipolar patients which would estimate the population attributable fraction (study IV).

8.3.3.2 Limitations of evaluation of suicidal behaviour

Suicidal ideation based on an aggregate variable (either current SSI ≥ 6 or had seriously considered suicide earlier during the index episode) was reported (study I). However, the findings were essentially the same when analyses were conducted separately, based on only the SSI or ideation during the episode. The temporal association between suicidal ideation and attempts is complex. The fact that suicide attempts could occur at any time during the whole index episode, but that the symptoms were measured at the time of the first interview (Mantere et al., 2004), may have caused an underestimation of psychopathology at the time of attempt (study I). The most important limitation of study II was the small number of suicide attempters during mixed and depressive mixed phases. Because of multiple comparisons and small sample sizes, risk of spurious findings may exist in the descriptive univariate analyses. The multinomial models constitute main findings. Although they are statistically robust, some degree of type II error may have also occurred (study II).

While this study is among the few prospective studies assessing risk factors for attempted suicide in persons with BD, patients were only followed for up to 18 months. Fawcett and co-workers (1990) found that short-term (follow-up of less than one year) predictors of death by suicide or serious suicide attempts differed from long-term (two to ten years) predictors. Therefore, a longer follow-up period is likely needed to examine the differences between short- and long-term predictors for attempted suicide (study III).

Although 92% and 85% of patients were followed at 6 and 18 months, respectively, there was a somewhat higher drop-out rate of suicidal patients after the 6-month follow-up visit. Therefore the single risk factors of suicide attempters among those who were followed up after 6 and 18 months were analyzed separately. Since the findings remained consistent, it is unlikely that attrition biased the results with regard to predictors. However, the possibility of undetected suicide attempters among those dropping out of the follow-up cannot be excluded (study III). Since the aim was to investigate risk factors predicting future suicide attempts, the potential preventive effect of maintenance treatment or longitudinal course of illness on outcome was not examined (study III). One weakness was that information on lifetime aggression and impulsivity, which were linked to suicidal behaviour in a recent prospective study by Oquendo and co-workers (2004), was not gathered. However, aggression and impulsive behaviour are commonly related to comorbid cluster B personality disorders (Oquendo et al., 2004) and substance or alcohol abuse or dependence, neither of which independently predicted suicide attempts in prospective study (study III and study IV). In theory there could be circularity between suicide attempts and major depressive phase. However, suicidal ideation, not suicide attempt, is one of nine major depressive phase criteria symptoms (study IV). Only average time spent in risk phases was investigated. It is possible that the risk of suicide attempts varies more than could be measured during the separate phase depending on the severity of depression. This relatively crude classification is, despite observed marked contrast between phases, unlikely to reveal fully the true variations in risk that likely depend on the severity of symptoms.

9. CONCLUSIONS AND FUTURE IMPLICATIONS

9.1 Conclusions and clinical implications

Suicidal behaviour is markedly prevalent among bipolar patients. Over their lifetime, more than half of the patients with bipolar disorder attempt suicide. Suicidal behaviour varies markedly between different phases. Furthermore, the incidence of suicide attempts varies remarkably depending on the type of illness phase, with mixed and depressive phases involving the highest risk per time. Time spent at high-risk illness phases is most likely the major determinant of overall risk for suicide attempts among patients with BD.

During the index episode, suicide attempts and suicidal ideation are related to phases which are associated with depressive aspects of the illness. Hopelessness and severity of depression are key indicators of risk in all phases. Preceding suicidal behaviour, hopelessness, depression and comorbidity are all key indicators of risk. Based on the cross-sectional study, the prevalence of suicidal behaviour in bipolar I and II disorders are similar, but the risk factors for it may differ somewhat between the two. However, based on the prospective study it seems that spending more time depressed or in the mixed illness phases would readily explain why bipolar II is often associated with more frequent suicidal behaviour than bipolar I.

More than half of the patients have attempted suicide during their lifetime, a finding which highlights the public health importance of suicidal behaviour in bipolar disorder. Suicidal behaviour is associated with depressive aspects of illness. Clinically, it is crucial to recognize BD and manage the mixed and depressive phases of bipolar patients fast and effectively as time spent in depressive and mixed phases involves a remarkably high risk of suicide attempts. Reducing time spent in risk phases is probably an important preventive measure. It is important to evaluate suicidal behaviour of BD patients and try to prevent it by intensive treatment.

9.2 Implications for future research

Many single risk factors for suicidal behaviour have been investigated in previous cross-sectional and retrospective studies, but a comprehensive view of risk factors related to suicidal behaviour in bipolar disorder is still emerging. Furthermore, there are only few prospective studies regarding suicidal behaviour in bipolar disorder. Although hopelessness is an essential risk factor for suicidology overall, it's role has been rarely investigated in bipolar disorder. There is a need for prospective studies to investigate the wide range of risk factors of suicidal behaviour and use of multivariate statistics, which is needed to differentiate independent risk factors from confounding associations.

Furthermore, future suicide studies should investigate not only static but also time-varying risk factors, and include time at risk estimations when estimating overall suicide risk. Future studies based on daily prospective mood ratings should investigate if the risk of suicide attempt is identical during the whole phase. Challenges for future studies will be to investigate whether there are modifying risk factors during different phases, when more risk factors are taken into account and in a larger sample of bipolar patients. In addition, future studies should examine the effect of both interventions - effective acute phase treatment of high-risk phases and effective maintenance treatment to prevent recurrences of high-risk phases - to prevent suicidal behaviour in bipolar disorder.

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11. REFERENCES

1. Ahrens B, Müller-Oerlinghausen B, Schou M, Wolf T, Alda M, Grof E, Grof P, Lenz G, Simhandl C, Thau K, Vestergaard P, Wolf R, Möller HJ. Excess cardiovascular and suicide mortality of affective disorders may be reduced by lithium prophylaxis. *J Affect Disord* 1995;33:67-75.
2. Akiskal HS, Benazzi F: Optimizing the Detection of Bipolar II Disorder in Outpatient Private Practice. Toward a Systematization of Clinical Diagnostic Wisdom. *J Clin Psychiatry* 2005;66:914-921.
3. Akiskal HS, Akiskal KK, Lancrenon S, Hantouche EG, Fraud JP, Gury C, Allilaire JF. Validating the bipolar spectrum in the French National EPIDEP Study: overview of the phenomenology and relative prevalence of its clinical prototypes. *J Affect Disord* 2006;96:197-205.
4. Altman S, Haeri S, Cohen LJ, Ten A, Barron E, Galynker II, Duhamel KN. Predictors of relapse in bipolar disorder: A review. *J Psychiatr Pract* 2006;12:269-282.
5. Altshuler LL, Gitlin MJ, Mintz J, Leight KL, Frye MA. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. *J Clin Psychiatry* 2002;63:807-811.
6. American Psychiatric Association: Diagnostic and statistical manual of mental disorders, Fourth Edition, Text Revision, Washington, DC, American Psychiatric Association, 2000.
7. American Psychiatric Association: Practice guideline for the treatment of patients with Bipolar disorder. *Am J Psychiatry* 2002;159 (April suppl).
8. American Psychiatric Association: Practice guideline for the assessment and treatment of patients with suicidal behaviours. *Am J Psychiatry* 2003;160 (November suppl).
9. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord* 1998;50:143-151.

10. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34-38 years. *J Affect Disord* 2002;68:167-181.
11. Angst J, Sellaro H, Stassen A, Gamma A. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord* 2005;84:149-157.
12. Arsenault-Lapierre G, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. *BMC Psychiatry* 2004;4:37.
13. Barber ME, Marzuk PM, Leon AC, Portera L. Aborted suicide attempts: a new classification of suicidal behavior. *Am J Psychiatry* 1998;155:385-389.
14. Balazs J, Lecrubier Y, Csiszer N, Kosztak J, Bitter L. Prevalence and comorbidity of affective disorders in persons making suicide attempts in Hungary: importance of the first depressive episodes and of bipolar II diagnoses. *J Affect Disord* 2003;76:113-119.
15. Baldessarini RJ, Tondo L, Hennen J. Treatment delays in bipolar disorders. *Am J Psychiatry* 1999;156:811-812.
16. Baldessarini RJ, Tondo L, Hennen J. Lithium treatment and suicide risk in major affective disorders: update and new findings. *J Clin Psychiatry* 2003;64(Suppl 5):44-52.
17. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord* 2006a;8:625-639.
18. Baldessarini RJ, Pompili M, Tondo L. Suicide in bipolar disorder: Risks and management. *CNS Spectr* 2006b;11:465-471.
19. Beautrais AL, Joyce PR, Mulder RT, Fergusson DM, Deavoll BJ, Nightingale SK. Prevalence and comorbidity of mental disorders in persons making serious suicide attempts: a case-control study. *Am J Psychiatry* 1996;153:1009-1014.
20. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-571.
21. Beck AT, Weissman A, Lester D, Trexler L. The measure of pessimism: The hopelessness scale. *J Consult Clin Psychol* 1974;42:861-865.
22. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol* 1979;47:343-352.

23. Beck AT, Steer RA, Kovacs M, Garrison B. Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. *Am J Psychiatry* 1985;142:559-563.
24. Beck AT. Hopelessness as a predictor of eventual suicide. *Ann N Y Acad Sci* 1986;487:90-96.
25. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;56:893-897.
26. Beck AT, Brown G, Steer RA. Prediction of eventual suicide in psychiatric inpatients by clinical ratings of hopelessness. *J Consult Clin Psychol* 1989;57:309-310.
27. Beck AT, Brown G, Berchick RJ, Stewart BL, Steer RA. Relationship between hopelessness and ultimate suicide: a replication with psychiatric outpatients. *Am J Psychiatry* 1990;147:190-195.
28. Benazzi F, Akiskal HS. Delineating bipolar II mixed states in the Ravenna-San Diego collaborative study: the relative prevalence and diagnostic significance of hypomanic features during major depressive episodes. *J Affect Disord* 2001;67:115-122.
29. Bernal M, Haro JM, Bernert S, Brugha T, de Graaf R, Bruffaerts R, Lepine JP, de Girolamo G, Vilagut G, Gasquet I, Torres JV, Kovess V, Heider D, Neeleman J, Kessler R, Alonso J and the ESEMED/MHEDEA Investigators. Risk factors for suicidality in Europe: Results from the ESEMED study. *J Affect Disord* 2006 Oct 27; [Epub ahead of print].
30. Bertolote JM, Fleischmann A, De Leo D, Bolhari J, Botega N, De Silva D, Tran Thi Thanh H, Phillips M, Schlebusch L, Varnik A, Vijayakumar L, Wasserman D. Suicide attempts, plans, and ideation in culturally diverse sites: the WHO SUPRE-MISS community survey. *Psychol Medicine* 2005;35:1457-1465.
31. Blumenthal JA, Burg MM, Braefoot J, Williams RB, Haney T, Zimet G. Social support, type A behavior, and coronary artery disease. *Psychosom Med* 1987;49:331-340.
32. Borges G, Angst J, Nock MK, Ruscio AM, Walters EE, Kessler RC. A risk index for 12-month suicide attempts in the National Comorbidity Survey Replication (NCS-R). *Psychol Med* 2006;36:1747-1757.
33. Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. *Am J Psychiatry* 2000;157:1925-1932.
34. Bottlender R, Jäger M, Strauß A, Möller HJ. Suicidality in bipolar compared to unipolar depressed inpatients. *Eur Arch Psychiatry Clin Neurosci* 2000;250:257-261.

35. Brown GK, Beck AT, Steer RA, Grisham JR. Risk factors for suicide in psychiatric outpatients: a 20-year prospective study. *J Consult Clin Psychol* 2000;68:371-377.
36. Bulik CM, Carpenter LL, Kupfer DJ, Frank E. Features associated with suicide attempts in recurrent major depression. *J Affect Disord* 1990;18:29-37.
37. Cannon DM, Ichise M, Fromm SJ, Nugent AC, Rollis D, Gandhi SK, Klaver JM, Charney DS, Manji HK, Drevets WC. Serotonin transporter binding in bipolar disorder assessed using [¹¹C] DASB and positron emission tomography. *Biol Psychiatry* 2006;60:207-217.
38. Cavanagh JT, Carson AJ, Sharpe M, Lawrie SM. Psychological autopsy studies of suicide: a systematic review. *Psychol Med* 2003;33:395-405.
39. Carter TD, Mundo E, Parikh SV, Kennedy JL. Early age at onset as a risk factor for poor outcome of bipolar disorder. *J Psychiatr Res* 2003;37:297-303.
40. Casey PR, Dunn G, Kelly BD, Birkbeck G, Dalgard OS, Lehtinen V, Britta S, Ayuso-Mateos JL, Dowrick C; ODIN Group. Factors associated with suicidal ideation in the general population: Five-centre analysis from the ODIN study. *Br J Psychiatry* 2006;189:410-415.
41. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biol Psychiatry* 1996;39:896-899.
42. Chengappa KN, Levine J, Gershon S, Kupfer DJ. Lifetime prevalence of substance or alcohol abuse and dependence among subjects with bipolar I and II disorders in a voluntary registry. *Bipolar Disord* 2000;2:191-195.
43. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry* 2005;162:1805-1819.
44. Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, Torrent C, Comes M, Corbella B, Parramon G, Corominas J. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Arch Gen Psychiatry* 2003;60:402-407.
45. Coryell W, Andreasen NC, Endicott J, Keller M. The significance of past mania or hypomania in the course and outcome of major depression. *Am J Psychiatry* 1987;144:309-315.
46. Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL. The enduring psychosocial consequences of mania and depression. *Am J Psychiatry* 1993;150:720-727.

- 47.** Coryell W, Salomon D, Turvey C, Keller M, Leon AC, Endicott J, Schettler P, Judd L, Mueller T. The long-term course of rapid-cycling bipolar disorder. *Arch Gen Psychiatry* 2003;60:914-920.
- 48.** Dalton EJ, Cate-Carter TD, Mundo E, Parikh SV, Kennedy JL. Suicide risk in bipolar patients: the role of comorbid substance use disorders. *Bipolar Disord* 2003;5:58-63.
- 49.** Dittmann S, Biedermann NC, Grunze H, Hummel B, Scharer LO, Kleindienst N, Forsthoff A, Matzner N, Walser S, Walden J. The Stanley Foundation Bipolar Network: results of the naturalistic follow-up study after 2.5 years of follow-up in the German centres. *Neuropsychobiology* 2002;46(Suppl 1):2-9.
- 50.** Endicott J, Nee J, Andreasen N, Clayton P, Keller M, Coryell W. Bipolar II. Combine or keep separate? *J Affect Disord* 1985;8:17-28.
- 51.** Fagiolini A, Kupfer DJ, Rucci P, Scott JA, Novick DM, Frank E. Suicide attempts and ideation in patients with bipolar I disorder. *J Clin Psychiatry* 2004;65:509-514.
- 52.** Fawcett J, Scheftner W, Clark D, Hedeker D, Gibbons R, Coryell W. Clinical predictors of suicide in patients with major affective disorders: a controlled prospective study. *Am J Psychiatry* 1987;144:35-40.
- 53.** Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, Gibbons R. Time-related predictors of suicide in major affective disorder. *Am J Psychiatry* 1990;147:1189-1194.
- 54.** First MB, Gibbon M, Spitzer RL, Williams JBW. Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II), version 2. New York, New York Psychiatric Institute, Biometrics Research, 1996.
- 55.** First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV). Washington, DC, American Psychiatric Press, 1997.
- 56.** First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen. (SCID-I/P W/ PSY SCREEN) New York. Biometrics Research, New York State Psychiatric Institute, 2/2001 revision.
- 57.** Frank E, Cyranowski JM, Rucci P, Shear MK, Fagiolini A, Thase ME, Cassano GB, Grochocinski VJ, Kostelnik B, Kupfer DJ. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. *Arch Gen Psychiatry* 2002; 59:905-911.

- 58.** Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, Grochocinski V, Houck P, Scott J, Thompson W, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Arch Gen Psychiatry* 2005;62:996-1004.
- 59.** Frye MA, Altshuler LL, McElroy SL, Suppes T, Keck PE, Denicoff K, Nolen WA, Kupka R, Leverich GS, Pollio C, Grunze H, Walden J, Post RM. Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. *Am J Psychiatry* 2003;160:883-889.
- 60.** Galfalvy H, Oquendo MA, Carballo JJ, Sher L, Grunebaum MF, Burke A, Mann JJ. Clinical predictors of suicidal acts after major depression in bipolar disorder: a prospective study. *Bipolar Disord* 2006;8:586-595.
- 61.** Goetzel RZ, Hawkins K, Ozminkowski RJ, Wang S. The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large US employers in 1999. *J Occup Environ Med* 2003;45:5-14.
- 62.** Goldacre M, Seagroatt V, Hawton K. Suicide after discharge from psychiatric inpatient care. *Lancet* 1993;342:283-286.
- 63.** Goldberg JF, Garno JL, Portera L, Leon AC, Kocsis JH, Whiteside JE. Correlates of suicidal ideation in dysphoric mania. *J Affect Disord* 1999;56:75-81.
- 64.** Goldberg JF, Harrow M, Whiteside JE. Risk for bipolar illness in patients initially hospitalized for unipolar depression. *Am J Psychiatry* 2001a;58:1265-1270.
- 65.** Goldberg JF, Singer TM, Garno JL. Suicidality and substance abuse in affective disorders. *J Clin Psychiatry* 2001b;62(suppl 25):35-43.
- 66.** Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. *Am J Psychiatry* 1992;149:1148-1156.
- 67.** Gonzalez-Pinto A, Mosquera F, Alonso M, Lopez P, Ramirez F, Vieta E, Baldessarini RJ. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disord* 2006;8:618-624.
- 68.** Goodwin FK, Jamison KR. *Manic-Depressive illness*. New York, Oxford University Press, 1990.
- 69.** Goodwin GM. Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2003;17:149-173; discussion 7.

- 70.** Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, Huang B. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2005;66:1205-1215.
- 71.** Gray SM, Otto MW. Psychosocial approaches to suicide prevention: applications to patients with bipolar disorder. *J Clin Psychiatry* 2001;62 (Suppl 25):56-64.
- 72.** Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht R, Vieta E, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders. Part I: Treatment of bipolar depression. *World J Biol Psychiatry* 2002;3:115-124.
- 73.** Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht RW, Vieta E, Möller HJ. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, Part II: Treatment of Mania. *World J Biol Psychiatry* 2003;4:5-13.
- 74.** Grunze H, Kasper S, Goodwin G, Bowden C, Möller HJ; WFSBP Task Force on Treatment Guidelines for Bipolar Disorders. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment. *World J Biol Psychiatry* 2004;5:120-135.
- 75.** Guze SB, Robins E. Suicide and primary affective disorders. *Br J Psychiatry* 1970;117:437-438.
- 76.** Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lönnqvist J. Is low dietary intake of omega-3 fatty acids associated with depression? *Am J Psychiatry* 2004;161:567-569.
- 77.** Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
- 78.** Harris EC, Barraclough B. Suicide as an outcome for mental disorders. A meta-analysis. *Br J Psychiatry* 1997;170:205-228.
- 79.** Haw C, Hawton K, Houston. Townsend E. Psychiatric and personality disorders in deliberate self-harm patients. *Br J Psychiatry* 2001;178:48-54.
- 80.** Hawton K, Houston K, Haw C, Townsend E, Harriss L. Comorbidity of axis I and axis II disorders in patients who attempted suicide. *Am J Psychiatry* 2003a;160:1494-1500.

- 81.** Hawton K, Zahl D, Weatherall R. Suicide following deliberate self-harm: long term follow-up study of patients who presented to a general hospital. *Br J Psychiatry* 2003b;182:537-542.
- 82.** Hawton K, Sutton L, Haw C, Sinclair J, Harriss L. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J Clin Psychiatry* 2005;66:693-704.
- 83.** Hawton K, Harriss L, Zahl D. Deaths from all causes in a long-term follow-up study of 11,583 deliberate self-harm patients. *Psychol Med* 2006;36:397-405.
- 84.** Hayden EP, Nurnberger JI Jr. Molecular genetics of bipolar disorder. *Genes Brain Behav* 2006;5:85-95.
- 85.** Hegerl U, Althaus D, Schmidtke A, Niklewski G. The alliance against depression: 2-year evaluation of a community-based intervention to reduce suicidality. *Psychol Med* 2006;36:1225-1233.
- 86.** Henriques G, Wenzel A, Brown GK, Beck AT. Suicide attempters' reaction to survival as a risk factor for eventual suicide. *Am J Psychiatry* 2005;162:2180-2182.
- 87.** Hillegers MH, Burger H, Wals M, Reichart CG, Verhulst FC, Nolen WA, Ormel J. Impact of stressful life events, familial loading and their interaction on the onset of mood disorders: study in a high-risk cohort of adolescent offspring of parents with bipolar disorder. *Br J Psychiatry* 2004;185:97-101.
- 88.** Hintikka J, Viinamäki H, Tanskanen A, Kontula O, Koskela K. Suicidal ideation and parasuicide in the Finnish general population. *Acta Psychiatr Scand* 1998;98:23-27.
- 89.** Hintikka J, Pesonen T, Saarinen P, Tanskanen A, Lehtonen J, Viinamäki H. Suicidal ideation in the Finnish general population. A 12-month follow-up study. *Sos. Psychiatry Psychiatr Epidemiol* 2001;36:590-594.
- 90.** Hirschfeld RMA, Williams JBW, Spitzer RL, Calabrese JR, Flynn L, Keck PE Jr, Lewis L, McElroy SL, Post RM, Rappaport DJ, Russell JM, Sachs GS, Zajecka J. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry* 2000;157:1873-1875.
- 91.** Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 2003;64:161-174.
- 92.** Ho TP. The suicide risk of discharged psychiatric patients. *J Clin Psychiatry* 2003;64:702-707.

- 93.** Høyer EH, Mortensen PB, Olesen AV. Mortality and causes of death in a total national sample of patients with affective disorders admitted for the first time between 1973 and 1993. *Br J Psychiatry* 2000;176:76-82.
- 94.** Ichimiya T, Suhara T, Sudo Y, Okubo Y, Nakayama K, Nankai M, Inoue M, Yasuno F, Takano A, Maeda J, Shibuya H. Serotonin transporter binding in patients with mood disorders: a PET study. *Biol Psychiatry* 2002;51:715-722.
- 95.** Inskip HM, Harris EC, Barraclough B. Lifetime risk of suicide for affective disorder, alcoholism, and schizophrenia. *Br J Psychiatry* 1998;172:35-37.
- 96.** Isometsä ET, Henriksson MM, Aro HM, Lönnqvist JK. Suicide in bipolar disorder in Finland. *Am J Psychiatry* 1994;151:1020-1024.
- 97.** Isometsä E, Heikkinen M, Henriksson M, Aro H, Lönnqvist J. Recent life events and completed suicide in bipolar affective disorder. A comparison with major depressive suicides. *J Affect Disord* 1995;33:99-106.
- 98.** Isometsä ET, Lönnqvist JK. Suicide attempts preceding completed suicide. *Br J Psychiatry* 1998;173:531-535.
- 99.** Isometsä E, Suominen K, Mantere O, Valtonen H, Leppämäki S, Pippingsköld M, Arvilommi P. The mood disorder questionnaire improves recognition of bipolar disorder in psychiatric care. *BMC Psychiatry* 2003;3:8.
- 100.** Isometsä E. Suicide in bipolar I disorder in Finland: psychological autopsy findings from the National Suicide Prevention Project in Finland. *Arch Suicide Res* 2005;9:251-260.
- 101.** Jamison KR. Suicide and bipolar disorder. *J Clin Psychiatry* 2000;61(Suppl.9):47-51.
- 102.** Joffe RT, MacQueen GM, Marriott M, Trevor Young L. A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. *Bipolar Disord* 2004;6:62-66.
- 103.** Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser JD, Solomon DA, Leon AC, Rice JA, Keller MB. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002;59:530-537.
- 104.** Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 2003a;60:261-269.

- 105.** Judd LL, Schettler PJ, Akiskal HS, Maser J, Coryell W, Solomon D, Endicott J, Keller M. Long-term symptomatic status of bipolar I vs bipolar II disorder. *Int J Neuropsychopharmacol* 2003b;6:127-137.
- 106.** Judd LL, Akiskal HS, Schettler PJ, Coryell W, Maser J, Rice JA, Solomon DA, Keller MB. The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? *J Affect Disord* 2003c;73:19-32.
- 107.** Judd LL, Akiskal HS, Schettler PJ, Endicott J, Lean AC, Solomon DA, Coryell W, Maser JD, Keller MB. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch Gen Psychiatry* 2005;62:1322-1330.
- 108.** Kapur N, Cooper J, King-Hele S, Webb R, Lawlor M, Rodway C, Appleby L. The repletion of suicidal behavior: A multicenter cohort study. *J Clin Psychiatry* 2006; 67:1559-1609.
- 109.** Keck PE Jr. Long-term management strategies to achieve optimal function in patients with bipolar disorder. *J Clin Psychiatry* 2006;67(Suppl 9):19-24.
- 110.** Keller F, Wolfersdorf M. Hopelessness and the tendency to commit suicide in the course of depressive disorders. *Crisis* 1993;14:173-177.
- 111.** Kessing LV, Sondergard L, Kvist K, Andersen PK. Suicide risk in patients treated with lithium. *Arch Gen Psychiatry* 2005;62:860-866.
- 112.** Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8-19.
- 113.** Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry* 1999;56:617-626.
- 114.** Kessler RC, Merikangas KR. The National Comorbidity Survey Replication (NCS-R): background and aims. *Int J Methods Psychiatr Res* 2004;13:60-68.
- 115.** Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005a;62:593-602.
- 116.** Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, Severity, and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005b;62:617-627.

- 117.** Kessler RC, Berglund P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *JAMA* 2005c;293:2487-2495.
- 118.** Kiesepä T, Partonen T, Haukka J, Kaprio J, Lönnqvist J. High concordance of bipolar I disorder in a nationwide sample of twins. *Am J Psychiatry* 2004;161:1814-1821.
- 119.** Krishnan KR. Psychiatric and Medical Comorbidities of Bipolar Disorder. *Psychosomatic Medicine* 2005;67:1-8.
- 120.** Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ. Coming to terms with the terms of risk. *Arch Gen Psychiatry* 1997;54:337-343.
- 121.** Lam DH, Hayward P, Watkins ER, Wright K, Sham P. Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. *Am J Psychiatry* 2005;162:324-329.
- 122.** Lee S, Tsang A, Zhang MY, Huang YQ, He YL, Liu ZR, Shen YC, Kessler RC. Lifetime prevalence and inter-cohort variation in DSM-IV disorders in metropolitan China. *Psychol Med* 2006;12:1-13.
- 123.** Lehtinen V, Taipale V. Integrating mental health services: the Finnish experience. *Int J Integr Care* 2001;1:1-7.
- 124.** Lester D. Suicidal behaviour in bipolar and unipolar affective disorders: a meta-analysis. *J Affect Disord* 1993;27:117-121.
- 125.** Leverich GS, McElroy SL, Suppes T, Keck PE Jr, Denicoff KD, Nolen WA, Altshuler LL, Rush AJ, Kupka R, Frye MA, Autio KA, Post RM. Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry* 2002;51:288-297.
- 126.** Leverich GS, Altshuler LL, Frye MA, Suppes T, Keck PE Jr, McElroy SL, Denicoff KD, Obrocea G, Nolen WA, Kupka R, Walden J, Grunze H, Perez S, Luckenbaugh DA, Post RM. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry* 2003;64:506-515.
- 127.** Leverich GS, Post RM. Course of bipolar illness after history of childhood trauma. *The Lancet* 2006;367:1040-1042.
- 128.** Lopez P, Mosquera F, de Leon J, Gutierrez M, Ezcurra J, Ramirez F, Gonzales-Pinto A. Suicide attempts in bipolar patients. *J Clin Psychiatry* 2001;62:963-966.

- 129.** Lönnqvist J, Aro H, Heikkinen M, Heilä H, Henriksson M, Isometsä E, Kuurne K, Marttunen M, Ostamo A, Pelkonen M, Pirkola S, Suokas J, Suominen K. Project plan for studies on suicide, attempted suicide, and suicide prevention. *Crisis* 1995;16:162-175.
- 130.** MacKinnon DF, Zandi PP, Gershon E, Nurnberger JI Jr, Reich T, DePaulo JR. Rapid switching of mood in families with multiple cases of bipolar disorder. *Arch Gen Psychiatry* 2003;60:921-928.
- 131.** MacKinnon DF, Potash JB, McMahon FJ, Simpson SG, Depaulo JR Jr, Zandi PP. Rapid mood switching and suicidality in familial bipolar disorder. *Bipolar Disord* 2005;7:441-448.
- 132.** Mann JJ, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry* 1999;156:181-189.
- 133.** Mann JJ, Huang YY, Underwood MD, Kassir SA, Oppenheim S, Kelly TM, Dwork AJ, Arango V. A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch Gen Psychiatry* 2000;57:729-738.
- 134.** Mann JJ. Neurobiology of suicidal behaviour. *Nat Rev Neurosci* 2003;4:819-828.
- 135.** Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, Hegerl U, Lönnqvist J, Malone K, Marusic A, Mehlum L, Patton G, Phillips M, Rutz W, Rihmer Z, Schmidtke A, Shaffer D, Silverman M, Takahashi Y, Varnik A, Wasserman D, Yip P, Hendin H. Suicide prevention strategies: a systematic review. *JAMA* 2005;294:2064-2074.
- 136.** Mann J, Currier D. Understanding and preventing suicide. Part 6. The American Psychiatric Publishing textbook of mood disorders, edited Stein DJ, Kupfer DJ, Schatzberg AF. The American Psychiatric Publishing, 2005.
- 137.** Manji HK, Quiroz JA, Payne JL, Singh J, Lopes BP, Viegas JS, Zarate CA. The underlying neurobiology of bipolar disorder. *World Psychiatry* 2003;2:136-146.
- 138.** 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 Disord* 2004;6:395-405.
- 139.** Mantere O, Suominen K, Melartin T, Valtonen H, Arvilommi P, Leppämäki S, Rytälä H, Isometsä E. Differences in axis I and II comorbidity between bipolar I and II disorders and major depressive disorder. *J Clin Psychiatry* 2006;67:584-593.
- 140.** Mantere O, Suominen K, Valtonen H, Arvilommi P, Leppämäki S, Isometsä E. Differences in outcome of DSM-IV bipolar I and II disorders. *Bipolar Disord*, in press.

- 141.** Marangell LB, Bauer MS, Dennehy EB, Wisniewski SR, Allen MH, Miklowitz DJ, Oquendo MA, Frank E, Perlis RH, Martinez JM, Fagiolini A, Otto MW, Chessick CA, Zboyan HA, Miyahara S, Sachs G, Thase ME. Prospective predictors of suicide and suicide attempts in 1,556 patients with bipolar disorders followed for up to 2 years. *Bipolar Disord* 2006;8:566-575
- 142.** McDonald C, Zanelli J, Rabe-Hesketh S, Ellison-Wright I, Sham P, Kalidindi S, Murray RM, Kennedy N. Meta-analysis of magnetic resonance imaging brain morphometry studies in bipolar disorder. *Biol Psychiatry* 2004;56:411-417.
- 143.** McElroy SL, Altshuler LL, Suppes T, Keck PE Jr, Frye MA, Denicoff KD, Nolen WA, Kupka RW, Leverich GS, Rochussen JR, Rush AJ, Post RM. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry* 2001;158:420-426.
- 144.** McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry* 2003;60:497-502.
- 145.** McIntyre RS, Soczynska JK, Bottas A, Bordbar K, Konarski JZ, Sidney HK. Anxiety disorders and bipolar disorder: a review. *Bipolar Disord* 2006;8:665-676.
- 146.** Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET. Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. *J Clin Psychiatry* 2004;65:810-819.
- 147.** Miklowitz DJ, Simoneau TL, George EL, Richards JA, Kalbag A, Sachs-Ericsson N, Suddath R. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. *Biol Psychiatry* 2000;48:582-592.
- 148.** Miklowitz DJ. A review of evidence-based psychosocial interventions for bipolar disorder. *J Clin Psychiatry* 2006;67(suppl 11):28-33.
- 149.** Miklowitz DJ, Taylor DO. Family-focused treatment of the suicidal bipolar patient. *Bipolar Disord* 2006;8:640-651.
- 150.** Mitchell PB, Slade T, Andrews G. Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general population survey. *Psychol Med* 2004;34:777-785.
- 151.** Morriss R, Gask L, Battersby L, Francheschini A, Robson M. Teaching front-line health and voluntary workers to assess and manage suicidal patients. *J Affect Disord* 1999;52:77-83.

- 152.** Morriss R, Gask L, Webb R, Dixon C, Appleby L. The effects on suicide rates of an educational intervention for front-line health professionals with suicidal patients (the STORM Project). *Psychol Med* 2005;35:957-960.
- 153.** Mortensen PB, Agerbo E, Erikson T, Qin P, Westergaard-Nielsen N. Psychiatric illness and risk factors for suicide in Denmark. *Lancet* 2000;355:9-12.
- 154.** Müller-Oerlinghausen B, Berghöfer A, Bauer M. Bipolar disorder. *Lancet* 2002;359:241-247.
- 155.** Müller-Oerlinghausen B, Felber W, Berghöfer A, Lauterbach E, Ahrens B. The impact of lithium long-term medication on suicidal behavior and mortality of bipolar patients. *Arch Suicide Res* 2005;9:307-319.
- 156.** Möller HJ. Suicide, suicidality and suicide prevention in affective disorders. *Acta Psychiatr Scand* 2003;(suppl. 418):73-80.
- 157.** National Institute for Health Clinical Excellence (NICE) clinical guideline (2006): The Management of bipolar disorder in adults, children and adolescents, in primary and secondary care, 2006.
- 158.** Nolen WA, Luckenbaugh DA, Altshuler LL, Suppes T, McElroy SL, Frye MA, Kupka RW, Keck PE Jr, Leverich GS, Post RM. Correlates of 1-year prospective outcome in bipolar disorder: results from the Stanley Foundation Bipolar Network. *Am J Psychiatry* 2004;161:1447-1454.
- 159.** Nordentoft M, Breum L, Munck LK, Nordestgaard AG, Hunding A, Bjaeldager PAL. High mortality by natural and unnatural causes: a 10 year follow-up study of patients admitted to a poisoning treatment centre after suicide attempts. *BMJ* 1993;306:1637-1641.
- 160.** Nordström P, Åsberg M, Åberg-Wistedt A, Nordin C. Attempted suicide predicts suicide risk in mood disorders. *Acta Psychiatr Scand* 1995;92:345-350.
- 161.** O'Carroll PW, Berman AL, Maris RW, Moscicki EK, Tanney BL, Silverman MM. Beyond the Tower of Babel: A Nomenclature for Suicidology. *Suicide Life Threat Behav* 1996;26:237-252.
- 162.** Oquendo MA, Waternaux C, Brodsky B, Parsons B, Haas GL, Malone KM, Mann JJ. Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters. *J Affect Disord* 2000;59:107-117.

- 163.** Oquendo MA, Galfalvy H, Russo S, Ellis SP, Grunebaum MF, Burke A, Mann JJ. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *Am J Psychiatry* 2004;161:1433-1441.
- 164.** Oquendo MA, Currier D, Mann JJ. Prospective studies of suicidal behavior in major depressive and bipolar disorders: what is the evidence for predictive risk factors? *Acta Psychiatr Scand* 2006;114:151-158.
- 165.** Owens D, Horrocks J, House A. Fatal and non-fatal repetition of self-harm. Systematic review. *Br J Psychiatry* 2002;181:193-199.
- 166.** Owens D, Wood C, Greenwood DC, Hughes T, Dennis M. Mortality and suicide after non-fatal self-poisoning: 16-year outcome study. *Br J Psychiatry* 2005;187:470-475.
- 167.** Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Bowden CL, Sachs GS, Nierenberg AA. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry* 2004;55:875-881.
- 168.** Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, Ketter TA, Miklowitz DJ, Otto MW, Gyulai L, Reilly-Harrington NA, Nierenberg AA, Sachs GS, Thase ME. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2006;163:217-224.
- 169.** Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kiesepä T, Härkänen T, Koskinen S, Lönnqvist J. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry* 2007;64:19-28.
- 170.** Pini S, de Queiroz V, Pagnin D, Pezawas L, Angst J, Cassano GB, Wittchen HU. Prevalence and burden of bipolar disorders in European countries. *European Neuropsychopharmacology* 2005;15:425-434.
- 171.** Pirkola S, Sohlman B, Wahlbeck K. The characteristics of suicides within a week of discharge after psychiatric hospitalization - a nationwide register study. *BMC Psychiatry* 2005;5:32.
- 172.** Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE, Jr., McElroy SL, Luckenbaugh DA, Pollio C, Kupka R, Nolen WA. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life-chart method. *J Clin Psychiatry* 2003;64:680-690.

- 173.** Post RM, Leverich GS. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. *Dev Psychopathol* 2006;18:1181-1211.
- 174.** Potash JB, Kane HS, Chiu YF, Simpson SG, MacKinnon DF, McInnis MG, McMahon FJ, DePaulo JR Jr. Attempted suicide and alcoholism in bipolar disorder: clinical and familial relationships. *Am J Psychiatry* 2000;157:2048-2050.
- 175.** Qin P, Nordentoft M. Suicide risk in relation to psychiatric hospitalization: evidence based on longitudinal registers. *Arch Gen Psychiatry* 2005;62:427-432.
- 176.** Rihmer Z, Pestalicy P. Bipolar II disorder and suicidal behavior. *Psychiatr Clin North Am* 1999;22:667-673.
- 177.** Rihmer Z, Kiss K. Bipolar disorders and suicidal behaviour. *Bipolar Disord* 2002;4 (Suppl 1):21-25.
- 178.** Rihmer Z and Angst J. Mood Disorders: Epidemiology. In Sadock BJ, Sadock AJ (eds), Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Vol 8. New York: Lippincott Williams & Wilkins, 2005.
- 179.** Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. *Bipolar Disord* 2006;8:103-116.
- 180.** Räsänen P, Tiihonen J, Hakko H. The incidence and onset-age of hospitalized bipolar affective disorder in Finland. *J Affect Disord* 1998;48:63-68.
- 181.** Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. *Postgrad Med* 2000;1-104;SpecNo:1-104.
- 182.** Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, Lavori P, Lebowitz B, Rudorfer M, Frank E, Nierenberg AA, Fava M, Bowden C, Ketter T, Marangell L, Calabrese J, Kupfer D, Rosenbaum JF. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry* 2003; 53:1028-1042.
- 183.** Schmidtke A, Bille-Brahe U, DeLeo D, Kerkhof A, Bjerke T, Crepet P, Haring C, Hawton K, Lönnqvist J, Michel K, Pommereau X, Querejeta I, Phillippe I, Salander-Renberg E, Temesvary B, Wasserman D, Fricke S, Weinacker B, Sampaio-Faria JG. Attempted suicide in Europe: rates, trends and sociodemographic characteristics of suicide attempters during the period 1989-1992. Results of the WHO/EURO Multicentre Study on Parasuicide. *Acta Psychiatr Scand* 1996;5:327-338.

- 184.** Schmidtke A. Perspective: suicide in Europe. *Suicide Life Threat Behav* 1997;27:127-136.
- 185.** Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, Abbott R, Hayhurst H. Cognitive-behavioural therapy for bipolar disorder. *Br J Psychiatry* 2006;188:488-489.
- 186.** Seidman SN. Psychoneuroendocrinology of mood disorders. Part 2. The American Psychiatric Publishing textbook of mood disorders, edited Stein DJ, Kupfer DJ, Schatzberg AF. The American Psychiatric Publishing, 2005.
- 187.** Serretti A, Mandelli L, Lattuada E, Smeraldi E. Rapid cycling mood disorder: clinical and demographic features. *Compr Psychiatry* 2002;43:336-343.
- 188.** Shi L, Thiebaud P, McCombs JS. The impact of unrecognized bipolar disorders for patients treated for depression with antidepressants in the fee-for-services California Medicaid (Medi-Cal) program. *J Affect Disord* 2004;82:373-383.
- 189.** Singh JB, Quiroz JA, Gould TD, Zarate Jr. CA, Manji HK. Molecular and Cellular Neurobiology of severe mood disorders. Part 3. The American Psychiatric Publishing textbook of mood disorders, edited Stein DJ, Kupfer DJ, Schatzberg AF. The American Psychiatric Publishing, 2005.
- 190.** Simon GE. Social and economic burden of mood disorders. *Biol Psychiatry* 2003;54:208-215.
- 191.** Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, Sachs GS, Nierenberg AA, Thase ME, Pollack MH. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2004;161:2222-2229.
- 192.** Simon NM, Zalta AK, Otto MW, Ostacher MJ, Fischmann D, Chow CW, Thompson EH, Stevens JC, Demopulos CM, Nierenberg AA, Pollack MH. The association of comorbid anxiety disorders with suicide attempts and suicidal ideation in outpatients with bipolar disorder. *J Psychiatr Res* 2007;41:255-264.
- 193.** Skegg K. Self-harm. *Lancet* 2005;366:1471-1483.
- 194.** Slama F, Bellivier F, Henry C, Rousseva A, Etain B, Rouillon F, Leboyer M. Bipolar patients with suicidal behavior: toward the identification of a clinical subgroup. *J Clin Psychiatry* 2004;65:1035-1039.
- 195.** Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet C Semin Med Genet* 2003;123:48-58.

- 196.** Soares JC, Mann JJ. The anatomy of mood disorders - review of structural neuroimaging studies. *Biol Psychiatry* 1997;41:86-106.
- 197.** Sokero P, Melartin T, Rytsälä H, Leskelä U, Lestelä-Mielonen P, Isometsä E. A Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *Clin J Psychiatry* 2003;64:1094-1100.
- 198.** Sokero P, Melartin T, Rytsälä H, Leskelä U, Lestelä-Mielonen P, Isometsä E. A prospective study of risk factors for attempted suicide among psychiatric patients with DSM-IV major depressive disorder. *Br J Psychiatry* 2005;186:314-318.
- 199.** Sokero P, Eerola M, Rytsälä H, Melartin T, Leskelä U, Lestelä-Mielonen P, Isometsä E. Decline in suicidal ideation among patients with MDD is preceded by decline in depression and hopelessness. *J Affect Disord* 2006;95:95-102.
- 200.** Sorvaniemi M, Hintikka J. Recorded psychiatric comorbidity with bipolar disorder - a Finnish hospital discharge register study. *Nord J Psychiatry* 2005;5:531-533.
- 201.** Sorvaniemi MP, Salokangas RK. Prevalence of bipolar disorder and major depression among patients seen in primary and secondary care in Finland. *Can J Psychiatry* 2005;50:186-187.
- 202.** Stallone F, Dunner DL, Ahearn J, Fieve RR. Statistical predictions of suicide in depressives. *Compr Psychiatry* 1980;21:381-387.
- 203.** Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry* 2005;10:105-116.
- 204.** Sublette ME, Oquendo MA, Mann JJ. Rational approaches to the neurobiologic study of youth at risk for bipolar disorder and suicide. *Bipolar Disord* 2006;8:526-542.
- 205.** Suokas J, Lönnqvist J. Outcome of attempted suicide and psychiatric consultation: risk factors and suicide mortality during a five-year follow-up. *Acta Psychiatr Scand* 1991; 84:545-549.
- 206.** Suominen K, Henriksson M, Suokas J, Isometsä E, Ostamo A, Lönnqvist J. Mental disorders and comorbidity in attempted suicide. *Acta Psychiatr Scand* 1996;94:234-240.
- 207.** Suominen KH, Isometsä ET, Henriksson MM, Ostamo AI, Lönnqvist JK. Suicide attempts and personality disorder. *Acta Psychiatr Scand* 2000;102:118-125.

- 208.** Suominen K, Isometsä E, Ostamo A, Lönnqvist J. Level of suicidal intent predicts overall mortality and suicide after attempted suicide: a 12-year follow-up study. *BMC Psychiatry* 2004a;20:11.
- 209.** Suominen K, Isometsä E, Suokas J, Haukka J, Achte K, Lönnqvist J. Completed suicide after a suicide attempt: a 37-year follow-up study. *Am J Psychiatry* 2004b;161:562-563.
- 210.** Suppes T, Leverich GS, Keck PE Jr, Nolen WA, Denicoff KD, Altshuler LL, McElroy SL, Rush AJ, Kupka R, Frye MA, Bickel M, Post RM. The Stanley Foundation Bipolar Treatment Outcome Network II. Demographics and illness characteristics of the first 261 patients. *J Affect Disord* 2001;67:45-59.
- 211.** Taylor L, Faraone SV, Tsuang MT. Family, twin, and adoption studies of bipolar disease. *Curr Psychiatry Rep* 2002;4:130-133.
- 212.** ten Have M, Vollenberg W, Bija R, Nolen WA. Bipolar disorder in the general population in the Netherlands (prevalence, consequences and care utilisation): results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *J Affect Disord* 2002;68:203-213.
- 213.** Thompson WK, Kupfer DJ, Fagiolini A, Scott JA, Frank E. Prevalence and Clinical Correlates of Medical Comorbidities in Patients with Bipolar I Disorder: Analysis of Acute-Phase Data from a Randomized Controlled Trial. *J Clin Psychiatry* 2006;67:783-788.
- 214.** Tohen M, Zarate CA Jr, Hennen J, Khalsa H-MK, Strakowski SM, Gebre-Medhin P, Salvatore P, Baldessarini RJ. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. *Am J Psychiatry* 2003;160:2099-2107.
- 215.** Tondo L, Baldessarini RJ, Hennen J, Minnai GP, Salis P, Scamonatti L, Masia M, Ghiani C, Mannu P. Suicide attempts in major affective disorder patients with comorbid substance use disorders. *J Clin Psychiatry* 1999;60 (Suppl.2):63-69.
- 216.** Tondo L, Baldessarini R. Reduced suicide risk during lithium maintenance treatment. *J Clin Psychiatry* 2000;61(suppl 9):97-104.
- 217.** Tondo L, Isacson G, Baldessarini RJ. Suicidal behavior in bipolar disorder: risk and prevention. *CNS Drugs* 2003;17:491-511.
- 218.** Tsai SY, Lee JC, Chen CC. Characteristics and psychosocial problems of patients with bipolar disorder at high risk for suicide attempt. *J Affect Disord* 1999;52:145-152.
- 219.** Tsai SY, Kuo CJ, Chen CC, Lee HC. Risk factors for completed suicide in bipolar disorder. *J Clin Psychiatry* 2002;63:469-476.

- 220.** Uçok A, Karaveli D, Kundakci T, Yazici O. Comorbidity of personality disorders with bipolar mood disorders. *Compr Psychiatry* 1998;39:72-74.
- 221.** Upanne M, Hakanen J, Rautava M. Can Suicide Be Prevented? The Suicide Project in Finland 1992-1996: Goals, Implementation and Evaluation. National Research and Development Centre for Welfare and Health (STAKES), Helsinki, 1999.
- 222.** van Heeringen K, Hawton K, Williams JMG. Pathways to suicide: an integrative approach. In Hawton K, van Heeringen (eds), *The international Handbook of Suicide and Attempted Suicide*. England. Wiley J & Sons Ltd, 2000.
- 223.** van Heeringen K. The neurobiology of suicide and suicidality. *Can J Psychiatry* 2003;48:292-300.
- 224.** Vieta E, Benabarre A, Colom F, Gasto C, Nieto E, Otero A, Vallejo J. Suicidal behavior in bipolar I and bipolar II disorder. *J Nerv Ment Dis* 1997;185:407-409.
- 225.** Vieta E, Colom F, Martinez-Aran A, Benabarre A, Gasto C. Personality disorders in bipolar II patients. *J Nerv Ment Dis* 1999;187:245-248.
- 226.** Vieta E, Colom F, Martinez-Aran A, Benabarre A, Reinares M, Casto C. Bipolar II disorder and comorbidity. *Compr Psychiatry* 2000;41:339-343.
- 227.** Vieta E, Colom F, Corbella B, Martinez-Aran A, Reinares M, Benabarre A, Casto C. Clinical correlates of psychiatric comorbidity in bipolar I patients. *Bipolar Disord* 2001;3:253-258.
- 228.** Weissman MM, Leaf PJ, Tischler GL, Blazer DG, Karno M, Bruce ML, Florio LP. Affective disorders in five United States communities. *Psychol Med* 1988;18:141-153.
- 229.** Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, Lepine JP, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen HU, Yeh EK. Prevalence of suicide ideation and suicide attempts in nine countries. *Psychol Medicine* 1999;29:9-17.
- 230.** Williams JMG and Pollock LR. The psychology of suicidal behaviour. In Hawton K, van Heeringen (eds), *The international Handbook of Suicide and Attempted Suicide*. England. Wiley J & Sons Ltd, 2000.
- 231.** Wittchen H-U, Jacobi F. Size and Burden of Mental Disorders in Europe - a critical review and appraisal of 27 studies. *Eur Neuropsychopharmacol* 2005;15:357-376.

- 232.** World Health Organization, 1986. Working Group on Preventive Practices in Suicide and Attempted Suicide: Summary Report (ICP/PSF 017 (S) 6526 V) Copenhagen: World Health Organization Regional Office for Europe.
- 233.** World Health Organization. The tenth revision of the international statistical classification of diseases and health related problems (ICD-10): Diagnostic criteria for research purpose, Vol 10th. Geneva, Switzerland; World Health Organization, 1993.
- 234.** World Health Organization. Country reports and charts web page.
http://www.who.int/mental_health/prevention/suicide/country_reports/en/index.html
- 235.** World Health Organization. Suicide prevention (SUPRE) web page.
http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/index.html
- 236.** Wu LH, Dunner DL. Suicide attempts in rapid cycling bipolar disorder patients. *J Affect Disord* 1993;29:57-61.
- 237.** Yatham LN, Kennedy SH, O'Donovan C, Parikh S, MacQueen G, McIntyre R, Sharma V, Silverstone P, Alda M, Baruch P, Beaulieu S, Daigneault A, Milev R, Young LT, Ravindran A, Schaffer A, Connolly M, Gorman CP; Canadian Network for Mood and Anxiety Treatments. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. *Bipolar Disord* 2005;7(Suppl3):5-69.
- 238.** Yatham LN, Kennedy SH, O'donovan C, Parikh SV, Macqueen G, McIntyre RS, Sharma V, Beaulieu S; for CANMAT guidelines group. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. *Bipolar Disord* 2006;8:721-739.
- 239.** Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978;133:429-435.
- 240.** Zahl DL, Hawton K. Repetition of deliberate self-harm and subsequent suicide risk: long-term follow-up study of 11 583 patients. *Br J Psychiatry* 2004;185:70-75.
- 241.** Ösby U, Brandt L, Correia N, Ekblom A, Sparen P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry* 2001;58:844-850.