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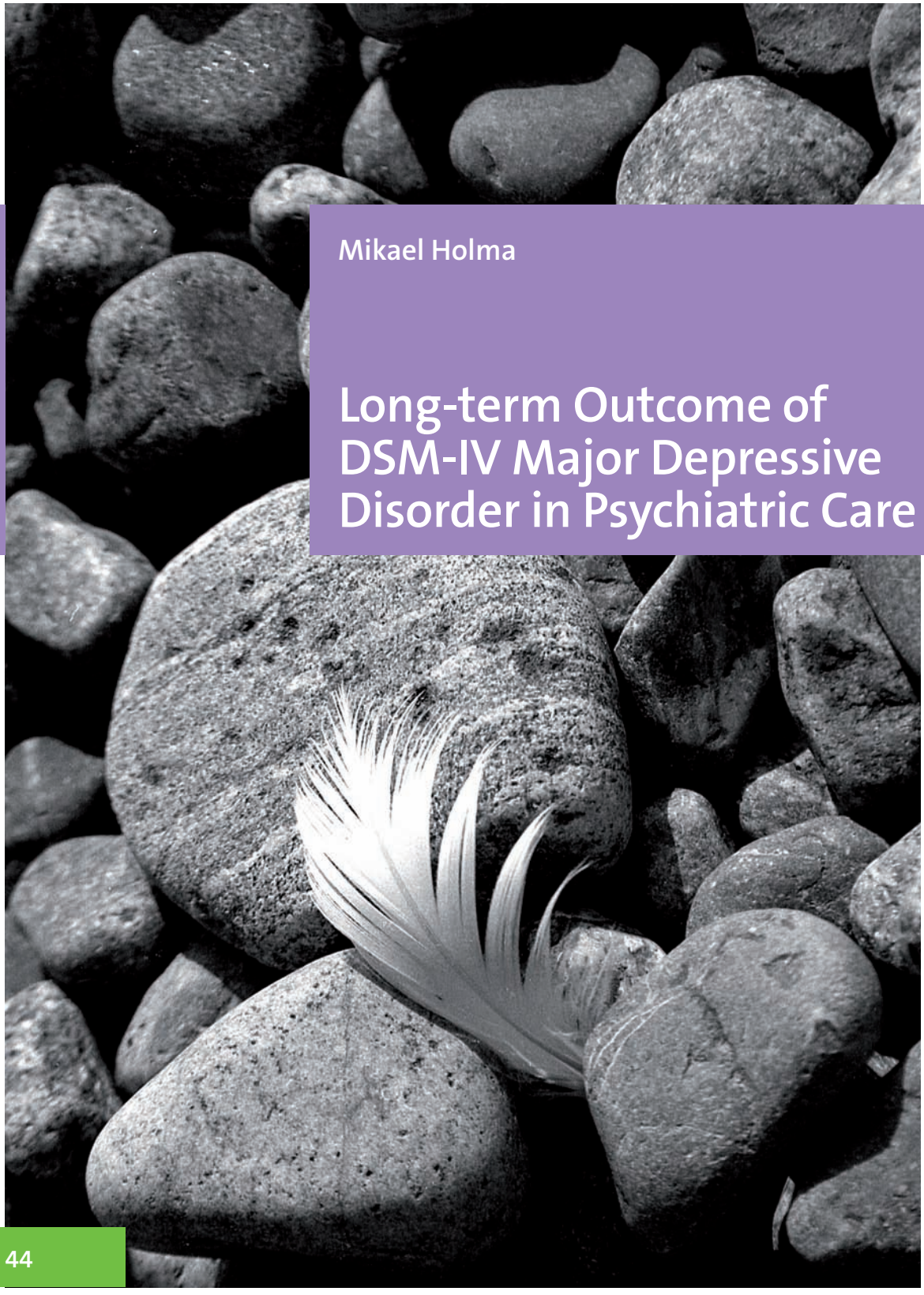

RESEARCH

Mikael Holma

Long-term Outcome of DSM-IV Major Depressive Disorder in Psychiatric Care

44

National Institute for Health and Welfare
Department of Mental Health and Substance Abuse Services
Helsinki, Finland
and
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Helsinki, Finland

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Long-term Outcome of DSM-IV Major Depressive Disorder in Psychiatric Care

ACADEMIC DISSERTATION

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Svanvingar lågt över träden
Klagande vita trumpeter mot havet
Ljuset tänds över en björkstam
Mönstret i nävern kunde vara chiffert
i en dagbok som jag inte får tyda
Någonting sträcker halsen
Någon pekar och vill bli räddad
för att bära oss

(Birgit Holma: Vägen till eremiten, 1987)

To my family

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Tiivistelmä

Mikael Holma, Long-term Outcome of DSM-IV Major Depressive Disorder in Psychiatric Care
[DSM-IV vakavan masennustilan pitkäaikaisennuste psykiatrisessa hoidossa]
Terveyden ja hyvinvoinnin laitos (THL), Tutkimus 44. Helsinki 2010.
ISBN 978-952-245-369-3 (painettu), ISBN 978-952-245-370-9 (pdf)

Tämä tutkimus on osa Vantaan Depressioprojektia (VDS), joka on toteutettu yhteistyössä Terveyden ja Hyvinvoinnin Laitoksen Mielenterveyden- ja päihdepalvelujen – osaston (entinen Kansanterveyslaitoksen Mielenterveyden ja Alkoholitutkimuksen osasto) ja Helsingin Yliopistollisen Keskussairaalan (HYKS) psykiatrian klinikan, Peijaksen sairaalan psykiatrisen tulosyksikön kanssa. VDS on etenevä ja naturalistinen seurantatutkimus, jossa on tutkittu 269 uutta DSM-IV vakavaa masennustilaa sairastavaa psykiatrista potilasta. Tutkimuksen alussa seulottiin 806 aikuista potilasta (ikä 20-59 vuotta) masennusoireiden suhteen alkaen 1.2.1997, jonka jälkeen haastateltiin puolistrukturoidun haastattelun (SCAN, versio 2.0) avulla 542 tutkimukseen suostunutta potilasta. Haastattelujen perusteella otettiin mukaan tutkimukseen 269 vakavaa masennustilaa sairastavaa potilasta, jotka tutkittiin puolistrukturoiduin haastatteluin myös muiden psykiatristen oheissairauksien osalta. Poissulkemiskriteereinä olivat DSM-IV kaksisuuntaisen mielialahäiriön tyyppi I ja II, skitsoaffektiivinen häiriö, skitsofrenia tai muu psykoosi, sekä orgaaninen tai päihteen aiheuttama mielialahäiriö.

Vakavan masennustilan ja oheissairauksien kulkua ja ennustetta tutkittiin seurantahaastatteluin kuuden, 18 kuukauden ja viiden vuoden kohdalla toistetuilla puolistrukturoiduilla haastatteluilla. Indeksiepisodin kesto ja mahdollisten sairauden pahenemisvaiheet ja uusiutumiset ajoitettiin ja sijoitettiin graafiseen aikajanaan, joka perustui DSM-IV-tautiluokituksen määritelmiin. Aika lähtötilanteen jälkeen jaettiin kolmeen jaksoon: (1) täysi remissio (0 vakavan masennustilan oiretta), (2) osittainen remissio (1-4/9 oiretta), (3) vakava masennusjakso (≥5/9 oiretta). Aikajanaan sijoitettiin myös potilaiden saama lääkitys, psykososiaalinen hoito, sairauslomat, myönnetyt työkyvyttömyyseläkkeet, itsemurhayritykset ja mahdolliset diagnoosimuutokset

Viisivuotisseurantahaastattelut suoritettiin 12.4.2002 – 27.4.2004 Vantaan psykiatrisilla poliklinikoilla ja HYKS psykiatrian poliklinikalla, 182 potilasta osallistui haastatteluihin. Haastatteluajankohtana lähes puolet (50%) potilaista olivat täydessä remissiossa, lähes neljäsosa (24%) sairastivat ajankohtaisesti masennusta ja loput (26%) olivat masennuksen suhteen osittaisessa remissiossa. Viiden vuoden seuranta-ajasta potilaat olivat viettäneet keskimäärin puolet (49%) ilman masennusoireilua, viidesosan (20%) vakavassa masennustilassa ja kolmasosan (31%) osittaisessa remissiossa. Lisäksi

seitsemäsosa (15%) potilaista oli yrittänyt itsemurhaa ainakin kerran, ja 29 (12%) potilasta sairastui seurannan aikana kaksisuuuntaiseen mielialahäiriöön. Lähes kaikki potilaat (99%) toipuivat ainakin osittain vakavasta masennustilasta ja enemmistö (88%) saavutti täydellisen remission 11 kuukauden mediaaniajan kuluessa. Suurin osa, lähes kolme neljäsosaa (71%) sairastui seurannan aikana uudestaan masennukseen 21 kuukauden mediaaniajan kuluessa indeksiepisodin lopusta. Masennuksen vaikeusaste ennusti merkittävästi masennustilan uusiutumista ja uusiutumisjaksojen lukumäärää sekä pidensi masentuneena vietettyä aikaa. Tunnettujen ennustetekijöiden kuten masennuksen kesto ja samanaikainen dystymia lisäksi, myös samanaikainen sosiaalinen fobia ja cluster C persoonallisuushäiriö huononsivat ennustetta.

Itsemurhayritysten esiintyvyys vaihteli voimakkaasti masennustilan mukaan ollen lähes 21-kertainen vakavien masennusjaksojen aikana ja nelinkertainen osittaisen remission aikana verrattuina oireettomiin tiloihin. Vaikka aikaisemmat itsemurhayritykset ja vähäinen koettu sosiaalinen tuki lisäsivät myös riskiä, oli masentuneena vietetty aika keskeisin riskitekijä.

Runsas kymmenesosa (12%) masennuspotilaista sairastui seurannan aikana kaksisuuntaiseen mielialahäiriöön (lähinnä tyyppiin II), joka on jonkin verran enemmän verrattuna aikaisempiin tutkimuksiin. Sairastuminen tyypin I häiriöön tapahtui seurannan alkuvaiheessa ja tyypin II tasaisemmin seurannan kuluessa. Aikaisemmin tunnettujen riskitekijöiden lisäksi diagnoosin muutosta ennustivat masennustilan vaikeusaste, samanaikainen sosiaalinen fobia, pakko-oireinen häiriö ja ryhmän B persoonal-lisuushäiriöiden piirteet.

Suurimmalla osalla seuratuista potilaista oli sukuhistoriaa ei vain mielialahäiriöiden (61%), vaan myös muiden vakavien häiriöiden suhteen (yhteensä 75%). Sukuhistoria oli yhteydessä huonompaan ennusteeseen, johon liittyi kohonnut itsemurhayritysten riski, kroonisempi sairaudenkulku ja samanaikaiset persoonallisuushäiriöt. Mielialahäiriöiden sukuhistoriaan liittyi naisten keskuudessa vallitsevaa neurotisismiä ja miesten keskuudessa suvun alkoholismi lisäsi tutkimuspotilaiden alkoholiriippuvuuden riskiä.

Kaiken kaikkiaan vakavan masennustilan pitkäaikaisennuste oli tämän modernin, keskiasteen psykiatrisen hoidon enimmistöltään avohoitopotilaiden seurantatutkimuksen mukaan vaihtelevampi verrattuna aikaisempiin, usein vanhempiin, yliopistoklinikoiden suorittamiin ja sairaalapotilailla tehtyihin tutkimuksiin. Vakavan masennustila oli hyvin toistuva myös tässä tutkimuksessa, mutta toistuvat jaksot näyttivät olevan lyhyempiä, masennuksen kulku oli vähemmän krooninen.

Avainsanat: masennus, psykiatriset potilaat, ennuste, itsemurhayritykset, kaksisuuntainen mielialahäiriö, sukuhistoria.

Sammandrag

Mikael Holma, Long-term Outcome of DSM-IV Major Depressive Disorder in Psychiatric Care
[Långtidsprognosen av DSM-IV svår depression inom psykiatrisk vård]
Institutet för hälsa och välfärd (THL), Forskning 44. Helsingfors 2010.
ISBN 978-952-245-369-3 (trykt), ISBN 978-952-245-370-9 (pdf)

Denna studie är en del av "Vanda Depressionsprojekt" (VDS), genomfört i samarbete med Institutet för Hälsa och Välfärd (THL), avdelningen för psykisk hälsa och missbrukarvård (före detta Folkhälsoinsitutets avdelning för mental hälsa och alkoholforskning) och Helsingfors Universitets Centralsjukhus (HUCS), Psykiatriska kliniken, Peijas sjukhus, Vanda. VDS är en progressiv och naturalistisk kohortstudie med 269 öppenvårds- och sjukhusvårdspatienter insjuknade i ny DSM-IV svår depressiv störning. Studien inleddes med screening av 806 vuxna patienter (i åldern 20-59) för symptom på depression från och med 1.2.1997, de 542 patienter som gav sitt medgivande intervjuades med en semistrukturell diagnostisk metod (SCAN, version 2.0). På basen av intervjuerna, blev 269 diagnostiserade med DSM-IV svår depressiv störning och inkluderades i studien, och intervjuades vidare med semistrukturella metoder för tilläggsdiagnoser. Uteslutningsdiagnoser bestod av DSM-IV bipolär störning typ I och II, schizoaffektiv störning, schizofreni eller annan psykos, samt affektiva störningar inducerade av någon organisk sjukdom eller av rusmedel.

Sjukdomsförlopp med en svår depressiv episod och komorbida tilläggsstörningar undersöktes med hjälp av upprepade semistrukturella intervjuer 6 månader, 18 månader och 5 år efter det studiens inletts. Den första depressiva episodens (index episod) varaktighet och datering av återfall och relapser undersöktes prognostiskt med hjälp av en grafisk livslinje, som byggde på DSM-IV definitioner. Tiden efter början av studien indelades i tre perioder: (1) fullständig remission (inga symtom på svår depressiv störning), (2) partiell remission (1-4/9 symtom), (3) svår depressiv episod (≥5/9 symtom). Förutom symtom, värderingar och besök på mottagningarna, antecknades på livslinjen tidpunkter för förändrat psykopatologiskt tillstånd med hjälp av betydelsefulla livshändelser och därtill information om medicinering, psykosocial behandling, sjuklediheter, beviljade invaliditetspensioner, självmordsförsök och eventuella förändringar i diagnos.

Fem-års uppföljningsintervjuer ägde rum 12.4.2002 – 27.4.2004 i Vanda psykiatriska polikliniker och psykiatriska polikliniken vid Helsingfors Universitets centralsjukhus; 182 patienter (67.7%) deltog i intervjuerna. Vid tiden för intervjun, var hälften av patienterna (50%) i fullständig remission, nästan en fjärdedel (24%) led av aktuell svår depression och resten (26%) var i partiell remission. Av patienterna hade i genomsnitt hälften (49%) tillbringat av tiden utan symtom på depression, en femtedel (20%) svårt

deprimerade och en tredjedel (31%) i partiell remission. Dessutom hade en sjundedel (15%) av patienterna försökt begå självmord minst en gång, och 29 (12%) hade insjuknat i bipolär störning. Nästan alla patienter (99%) hade tillfrisknat åtminstone delvis från den första depressiva episoden och majoriteten (88%) hade uppnått fullständig remission under en median tid på 11 månader. De flesta, nästan tre fjärdedelar (71%) insjuknade på nytt i svår depression under uppföljningstiden efter en median tid på 21 månader efter slutet på indexepisoden. Svårighetsgraden av en depression förutspådde betydligt depressiva återfall och antalet cykler av återfall samt förlängde tiden spenderad deprimerad. Kända prognostiska faktorer, såsom varaktigheten av en depression och samtidig dystymi, samt social fobi och cluster C personlighetsstörning försämrade prognosen.

Förekomsten av självmordsförsök varierade avsevärt beroende på det depressiva tillståndet och var nästan 21-faldig under svåra depressiva episoder, och fyrfaldig under perioder av partiell remission jämfört med perioder av fullständig remission. Även om tidigare självmordsförsök och som lågt uppfattat socialt stöd också ökade risken, var tiden spenderad i svår depression den viktigaste riskfaktorn.

Drygt en tiondedel (12%) av patienterna insjuknade under uppföljningstiden i bipolär störning (främst typ II), vilket är en något högre andel jämfört med tidigare studier. Insjuknande i typ I bipolär störning skedde i början av uppföljningstiden och i typ II bipolär störning jämnt distribuerad under den tiden. Förutom tidigare kända riskfaktorer förutspåddes diagnosförändringen av depressionens svårighetsgrad, samtidig social fobi, obsessiv-kompulsiv störning och symtom på cluster B personlighetsstörning.

Majoriteten av uppföljda patienter hade en släkthistoria av inte bara affektiva störningar (61%), utan även av andra allvarliga psykiska störningar (sammanlagt 75%). En sådan släkthistoria var förknippad med sämre prognos med ökad risk för självmordsförsök, kroniskt sjukdomsförlopp och samtida personlighetsstörningar. Hos kvinnor var en släkthistoria av affektiva störningar förknippad med rådande neuroticism och hos män var en släkthistoria av alkoholism förknippad med alkoholberoende hos forskningspatienter.

Allt som allt var långtidsprognosen för en svår depressiv störning på basen av denna studie med mest öppenvårdspatienter inom modern psykiatrisk vård mera varierad än den i tidigare, vanligen äldre studier utförda i Universitetskliniker och med sjukhuspatienter. Återfallsrisken för svår depression var stor även i denna studie, men nya episoder verkade vara kortare och sjukdomsförloppet vid en depression var mindre kroniskt.

Nyckelord: depression, psykiatriska patienter, prognos, självmordsförsök, bipolär störning, släkthistoria.

Abbreviations

APA	American Psychiatric Association
BAI	Beck Anxiety Inventory
BD	Bipolar Disorder
BDI	Beck Depression Inventory
BDNF	Brain-derived Neurotrophic Factor
CBT	Cognitive Behavioral Therapy
CDS	Collaborative Depression Study
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CLPS	Collaborative Longitudinal Personality Disorders Study
COALA	Comprehensive Assessment List for Affective Disorders
CRF	Corticotrophin Releasing Factor
CORE	Consortium for Research of ECT
DBS	Deep Brain Stimulation
DIS	Diagnostic Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
DTI	Diffusion Tensor Imaging
ECA	Epidemiological Catchment Area Study
ECT	Electroconvulsive Therapy
EPI	Eysenck Personality Inventory
ESEMeD	European Study of the Epidemiology of Mental Disorders
EU	European Union
FH	Family history
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-amonobutyric Acid
GAD	Generalized Anxiety Disorder
GLADS	The Group for Longitudinal Affective Disorders Study
GRIK4	Glutamate Receptor, ionotropic, kainate 4
HAM-D	Hamilton Rating Scale for Depression
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal
HR	Hazard Ratio
HS	Beck Hopelessness Scale

5-HT	5-Hydroxytryptamine (Serotonin)
5-HTR2A	5-Hydroxytryptamine Receptor 2A
5-HTT	5-Hydroxytryptamine Transporter
5-HTTLPR	5-Hydroxytryptamine Transporter Gene Polymorphism in the Promoter Region
HUCS	Helsinki University Central Hospital
HYKS	Helsingin Yliopistollinen Keskussaiaala
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases, 10th edition
IL	Interleukin
IMSR	Interview Measure of Social Relationships
IPT	Interpersonal Therapy
IRLE	Interview for Recent Life Events
JoBS	Jorvi Bipolar Study
LIFE	Longitudinal Interval Follow-up Evaluation
MAOI	Monoamine Oxidase Inhibitor
MIDAS	Rhode Island Methods to Improve Diagnostic Assessment and Services
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
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 Clinical Excellence
NIMH	National Institute of Mental Health
NIMH-CDS	National Institute of Mental Health Collaborative Depression Study
NMDA	N-methyl-D-aspartate
NOS	Not Otherwise Specified
NS	Nonsignificant
OCD	Obcessive Compulsive Disorder
ODIN	European Outcome of Depression International Network
OR	Odds Ratio
PAF	Population Attributable Fraction
PC-VDS	Vantaa Primary Care Depression Study
PET	Positron Emission Tomography
PIF	Psychoses in Finland
PMCD	Peijas Medical Care District
PSSS-R	Perceived Social Support Scale - Revised
PTSD	Postraumatic Stress Disorder
RDC	Research Diagnostic Criteria
RIMA	Reversible Inhibitors of Monoamine Oxidase

SA	Suicide Attempt
SAD	Seasonal Affective Disease
SAS-SR	Social Adjustment Scale-Self Report
SCAN	Schedules for Clinical Assessment of Neuropsychiatry
SCMHP	Suffolk County Mental Health Project
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-II	Structured Clinical Interview for DSM-III-R Personality Disorders
SD	Standard Deviation
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
SOFAS	Social and Occupational Functioning Assessment Scale for DSM-IV
SPECT	Single-photon Emission Computed Tomography
SPSS	Statistical Package for the Social Sciences for Windows
SSI	Scale for Suicidal Ideation
SSRI	Serotonin-Selective Reuptake Inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression Study
TADEP	Tampere Depression Study
TCA	Tricyclic Antidepressant
TERVA	Finnish Health Care Survey
THL	Terveyden ja Hyvinvoinnin Laitos
TNFalpha	Tumor Necrosis Factor-alpha
rTMS	Repetitive Transcranial Magnetic Stimulation
U.K.	United Kingdom
U.S.	United States of America
VDS	Vantaa Depression Study
VNS	Vagus Nerve Stimulation
WHO	World Health Organization

1 Abstract

Mikael Holma, Long-term Outcome of DSM-IV Major Depressive Disorder in Psychiatric Care
National Institute for Health and Welfare (THL), Research 44. Helsinki 2010.
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This study forms a part of the Vantaa Depression Study (VDS), a collaborative depression research project between the Mood, Depression, and Suicidal Behaviour Unit of the National Institute for Health and Welfare, Helsinki (former Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki), and the Department of Psychiatry of Helsinki University Central Hospital (HUCH), Peijas Hospital, Vantaa. The VDS is a prospective, naturalistic cohort study of 269 secondary-level care psychiatric out- and inpatients with a new episode of DSM-IV major depressive disorder (MDD). The VDS involved screening 806 adult patients (aged 20-59 years) in Peijas Hospital for depressive symptoms beginning February 1, 1997, and interviewing the 542 consenting patients with a semistructured interview (SCAN, version 2.0). On the basis of the interviews, 269 patients were diagnosed with DSM-IV MDD and included in the study, and further interviewed with semistructured methods to assess all additional psychiatric diagnoses. The exclusion criteria were DSM-IV bipolar I and II, schizoaffective disorder, schizophrenia or another psychosis, organic and substance-induced mood disorders.

The outcomes of major depressive episode (MDE) and the comorbid disorders were investigated at six and 18 months, and 5 years after the baseline using repeated semistructured interviews. The exact duration of the index episode and the timing of possible relapses and recurrences were prospectively examined using a graphic life chart based on DSM-IV criteria and definitions. Time after baseline was divided into three periods: (1) state of full remission (none of the 9 MDE criteria symptoms), (2) state of partial remission (1-4 of the 9 symptoms), or (3) state of MDE (5+ of the 9 symptoms). In addition to symptom ratings and visits to attending personnel, change points in the psychopathologic states using probes related to important life-events were inquired after. In addition, received medications, psychosocial treatments, sick leaves, granted disability pensions, suicide attempts, and possible changes of diagnoses were timed and placed in the life chart.

The 5-year follow-up interviews took place in the psychiatric outpatient units in Vantaa and Helsinki University Central Hospital (HUCH), between April 12, 2002 and April 27, 2004; 182 patients participated. At 5 years, nearly one-half (50%) of the patients were currently in full remission, nearly one-fourth (24%) in major depressive episode (MDE),

and the rest (26%) in partial remission. During 5 years the patients had spent on average spent nearly half (49%) of the follow-up period in full remission, one-fifth (20%) of the time in MDE, and one-third (31%) of the time in partial remission. Moreover, one-seventh (15%) of patients had attempted suicide at least once, and 29 patients (12%) switched to bipolar disorder. Over the 5-year follow-up, nearly all (99%) of patients achieved a symptom state below major depressive episode (MDE) criteria, and the majority (88%) reached full remission, within a median time of 11 months. The majority, nearly three-fourths (71%) of the patients experienced a recurrence after a medium time of 21 months from the end of the index episode. Higher severity of MDD significantly predicted the risk of recurrence, the number of recurrences and time spent ill. Besides known predictors, such as longer episode duration and preceding dysthymic disorder, also comorbid cluster C personality disorders and social phobia predicted a worse outcome.

The incidence rate of suicide attempts varied robustly depending on the level of depression, being nearly 21-fold during MDEs, and 4-fold during periods of partial remission compared to full remission. Although a history of previous attempts and poor social support also indicated risk, time spent depressed was the central factor determining overall long-term risk.

The overall switch rate (12%) from unipolar MDD to bipolar disorder (BD) (mostly to type II) was to some extent higher than in previous studies. The switch to BD type I usually occurred early, whereas the switch to type II took place more gradually over time. Besides previously known predictors, a higher severity of MDD, comorbid social phobia, OCD, and cluster B features predicted diagnostic switch.

The majority of the followed up patients had positive family histories not exclusively of mood (61%), but also of other mental disorders (in all 75%). Having a positive family of severe mental disorders was likely to be clinically associated with a significantly more adverse outcome with an elevated risk for suicide attempts, more chronic courses, and comorbid personality disorders. More specifically, a family history of mood disorders appeared to be independently associated with high neuroticism among female, and that of alcoholism with alcohol dependence among male patients.

According to the findings of the 5-year follow-up, long-term outcome of MDE appeared to be more variable when outcome was investigated among modern, community-treated, secondary-care mostly outpatients compared to previous older and mostly inpatient tertiary-care studies. MDD was highly recurrent also in the current study, but the recurrent episodes seemed shorter, and the outcome was unlikely to be uniformly chronic.

Keywords: depression, psychiatric care, outcome, suicide attempts, bipolar disorder, family history

2 List of original publications

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

I Holma M, Holma I, Melartin T, Rytsälä H, Isometsä E. Long-term outcome of major depressive disorder in psychiatric patients is variable. Journal of Clinical Psychiatry 2008;69(2):196-205.

II Holma M, Melartin T, Haukka J, Holma I, Sokero P, Isometsä E. Incidence and predictors of suicide attempts in DSM-IV major depressive disorder – a five-year prospective study. American Journal of Psychiatry 2010; 167:801-808.

III Holma M, Melartin T, Holma I, Isometsä E. Predictors for switch from unipolar major depressive disorder to bipolar disorder type I or II: a 5-year prospective study. Journal of Clinical Psychiatry 2008;69(8):1267-1275.

IV Holma M, Melartin T, Paunio T, Holma I, Isometsä E. Family history of psychiatric disorders and the outcome of psychiatric patients with DSM-IV major depressive disorder. (Submitted in Journal of Affective Disorders)

3 Introduction

Depression as a syndrome (Major Depressive Disorder, MDD) is related to the normal emotions of sadness and bereavement, but it does not remit when the external cause of these emotions dissipates, and it is disproportionate to their cause (Belmaker and Agam, 2008). Melancholia which resembles the present term depression, was one of the earliest human diseases described, having been recognized as an illness since ancient times as Hippocrates (ca. 460 - 370 BC) was the first to systematically describe the patterns of this illness. As defined in the Hippocratic writings, melancholia produced certain symptoms that are very similar to those associated with depressive disorder today i.e. persistent sleeplessness, lack of appetite, and despair, as well as suicidal behaviour and seasonal variation. Although Hippocrates attributed melancholia to a chemical excess of black bile, he also noted that symptoms of melancholia could be produced by lingering grief and fear, suggesting that situational problems could also cause depression. The founder of contemporary psychiatry Emil Kraepelin (1856 – 1926) described an illness called manic depression which is now seen as comprising a range of mood disorders such as recurrent major depression and bipolar disorder. He also believed the chief origin of psychiatric illness to be biological and genetic malfunction. Thus, surprisingly many features of contemporary psychiatry have been attributed to a major depressive disorder for a long time.

MDD is a severe illness with high prevalence, multifactorial aetiology, and heterogenic clinical picture characterized by a sad mood and an inability to experience pleasure, often including serious abnormalities in cognition and physiological function. It imposes a substantial burden by inflicting recurrent pain and suffering on individuals and their families. MDD is also one of the most important mental disorders in terms of public health impact. About a fifth of the population (Kessler et al., 1994; Kessler et al., 2003), women more often than men, will experience a clinically significant episode of MDD at some point in their lives. MDD involves a marked risk of functional disability (López et al., 2006), self-destructive behaviour and premature death (Harris and Barraclough, 1997; Sokero et al., 2005). MDD was in the year 2004 considered to be the third leading illness in terms of global disease burden, and by the year 2030 it has been predicted it will be the major disease or injury burden followed by ischaemic heart disease and road traffic accidents (WHO, 2008).

The high disease burden is also understandable from considerations of the nature and course of depression. Previously viewed as an acute and self-limiting illness, it is now clear that depression is not only highly prevalent but also a chronic, recurrent and comorbid illness. Following this paradigm shift in the concept of depression, studies of the natural history of MDE have come to be seen as essential for further understanding the nature of the disorder and developing more effective treatment strategies (Judd, 1997).

Although the comorbid form of MDD is highly prevalent, there is a lack of studies investigating the comprehensive importance of comorbid axis I and II disorders to the outcome of MDD. Furthermore, much of what we now accept regarding the course of depression and its comorbidity is derived from studies based on selected samples, e.g. inpatients, patients of tertiary level university clinics, and samples predating the era of the current new antidepressants and the now widespread use of maintenance therapies. Despite this, it is known from epidemiological studies that most depressive persons in the general population receive inadequate treatment or none at all (Kessler et al., 2003; Hämäläinen et al., 2004).

The Vantaa Depression Study (VDS) is a prospective, naturalistic cohort study of 269 secondary-level care psychiatric out- and inpatients with a new episode of DSM-IV MDD. In the VDS the predictors of outcome, recurrences, suicide attempts as well as functional and work disability are investigated, and the adequacy of treatments evaluated. The present thesis focuses on the outcome of depressive patients followed up for 5 years.

4 Review of the literature

4.1 Depression as an emotion

The term depression is in everyday language used in a wide context ranging from limited time of unhappiness and sorrow in ordinary life to a longer-lasting, incapacitating and even life-threatening illness. Sadness is considered to be one of the seven basic emotions together with fear, anger, joy, surprise, disgust, and contempt, which are thought to constitute evolved functions that are shared between all human beings, both in terms of phenomenology and communicative signals (Ekman, 1992; Sauter et al., 2010). Social or moral emotions, such as guilt, shame, pride, or embarrassment, differ from basic emotions in their external triggers, and their perception and expression differ culturally between individualistic and collectivistic nations (Eid and Diener, 2001; Hari and Kujala, 2009). Neuroimaging studies with positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) have been able to describe the functional neuroanatomy of emotions, and according to them, different aspects of emotion, basic and social emotions involve partly separate brain regions and neuronal circuits (Phan et al., 2002; Hari and Kujala, 2009). Sadness is the core emotion accompanied with depressive affect. Transient depressive feelings are normal reactions to experiences of loss and disappointment, and may be even useful as they may motivate us to solve a problem, help us to give up on hopeless goals, and to detach psychologically from an object of affection, admiration, or identification. In some situations depressive affect might even be evolutionary useful in adaptation to unpropitious situations, redefinition of goals, reallocation of efforts, and by inhibiting potentially disruptive actions (Nesse, 2000). Depression as a syndrome is related to the normal emotions of sadness and bereavement, but it does not remit when the external cause of these emotions dissipates, and it is disproportionate to their cause (Belmaker and Agam, 2008). In this thesis, depression refers to an entity including not only mood, but also physical, mental and behavioral experiences that are associated with more prolonged, impairing and severe conditions that may be clinically diagnosable as a syndrome of depression.

4.2 Classification of mental disorders

The majority of psychiatric diagnoses consist of syndromes where several symptoms exist simultaneously indicating a likely course and outcome. The current psychiatric classifications are categorical systems that divide mental disorders into different types based on sets of criteria with defining characteristics. Classification and subtyping of disorders, serve three purposes: prediction of treatment response, prognosis, and etiologic research. The introduction of operationalized classification systems for mental disorders, such as DSM-III, DSM-III-R, DSM-IV and DSM-IV-TR (APA, 1980; APA, 1987; APA, 1994; APA, 2000a) by the American Psychiatric Association, and ICD-10 (WHO, 1992; WHO, 1993; WHO, 2007) by the World Health Organization, have made a significant contribution to the scientific development of psychiatry by exploiting objective criteria of psychiatric diagnoses with specific thresholds and thus improving the diagnostic reliability (Kendell and Jablensky, 2003). In addition, categorical diagnoses have helped with improving treatment recommendations and clinicicians with treatment decisions, and statements about prognosis (Kendell and Jablensky, 2003; Kraemer et al., 2004).

Strictly speaking, diagnostic categories defined by their syndromes should be regarded as valid only if they have been shown to be discrete entities with natural boundaries that separate them from other disorders (Kendell and Jablensky, 2003). Thus, one could argue, that no psychiatric diagnosis is currently valid. However, if validity and utility of a diagnosis are differentiated, it can be said that most current psychiatrc diagnoses have substantial utility for clinicians (Kendell and Jablensky, 2003). In psychiatry, some characteristic features of diagnostics challenge the definitions of diagnostic criteria. Diagnoses are based mostly on interview and thus the patients' abilities to observe and describe their symptoms. Factors endangering the reliability, and thereupon the validity of psychiatric diagnostics can be described as follows: 1) information variance (different sources of information), 2) observation variance (patients are observed differently), 3) interpretation variance (observations are interpreted differently), 4) criteria variance (the use of different definitions of symptoms and disorders), 5) case variance (variation due to the individual characteristics of the patient), and 6) state variance (variation due to fluctuations of the symptom state over time) (Spitzer and Williams, 1985). In their recent essay, Kendler et al. discussed four different kinds of approaches to psychiatric disorders: 1) essentialist kinds sharing an essence from which their defining features arise; 2) socially constructed kinds being defined by the cultural context in which they arise; 3) practical kinds focusing on useful definitions; and 4) mechanistic property cluster kinds being defined in terms of complex, mutually reinforcing networks of causal mechanisms (Kendler et al., 2010). They considered the latter approach to be the most promising with a view of psychiatric disorders as sets of symptoms that are connected through a system of causal relations.

The classifications currently in use are the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2000a) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (WHO, 2007). In research, DSM-IV rather than ICD-10 is usually used as it provides more detailed guidelines for case definition. The concordance for any mental disorder for ICD-10 and DSM-IV has been found to be 68%, and the concordance for major depressive episodes 83%, with the diagnostic threshold for ICD-10 being lower than for DSM-IV disorders (Andrews et al., 1999). Categorical diagnostic classifications have been criticized as they are likely to represent a heterogeneous set of disorders that are derived from a wide range of etiological and genetic factors (Charney and Manji, 2004). In attempting to solve this problem, some researchers have suggested new, narrower or broader borders for mood disorders. Others have suggested dimensional measuring of narrow symptoms instead of syndromes (Angst and Merikangas, 1997). Developing the next generation of psychiatric classifications of DSM-V and ICD-11 has for long been in progress, and DSM-V is to be published in May, 2013. The aim has been to create more uniform classifications as well as to develop a more dimensional approach, which would enable clinicians to access the severity of a patient's condition by rating factors such as subjective distress and degree of impairment in addition to symptoms. Dimensions would also allow disorders to be deconstructed into components that could be addressed separately (Miller and Holden, 2010). Along the development, a more contemporary validation process have been created including building a behavioural phenotype of clinical description and course, creating a neurobiological profile, identifying genetic and familial patterns, considering the interaction between biology and the environment, and emphasizing treatment response and follow-up studies (Kupfer et al., 2008).

4.3 Diagnosis of mood disorders

Mood disorders are generally defined as illnesses in which the fundamental disturbance is a change in affect or mood to depression (with or without associated anxiety) or to elation characterized by different combinations of several co-occurring symptoms for a defined period of time contributing to significant psychosocial impairment or marked distress (APA, 2000a; WHO, 2007). In DSM-IV, mood disorders are divided into three groups: depressive disorders, bipolar disorders, and other mood disorders. Unipolar forms of primary mood disorders are further divided into three groups: major depressive disorder (MDD), dysthymic disorder, and depression not otherwise specified (APA, 2000a). In ICD-10, mood disorders are divided into manic episode, bipolar affective disorder, depressive episode, recurrent depressive disorder, persistent mood (affective) disorders, and other mood (affective) disorders (WHO, 2007).

4.3.1 Diagnosis of major depressive disorder (MDD)

According to DSM-IV MDD is characterized by one or more major depressive episodes lasting at least two weeks. In order to warrant a diagnosis of MDD, persistent (1) depressive mood or (2) significant loss of interest or pleasure are the required core symptoms, which must be accompanied by at least four associated symptoms (total of 5 or more symptoms) during most of the day or nearly every day, e.g. (3) significant weight or appetite change, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or extreme or inappropriate guilt, (8) a diminished ability to think or to concentrate or indecisiveness, and (9) recurrent thoughts of death or suicidal ideation, or a suicide attempt or a specific plan for committing suicide (APA, 2000a). In addition, these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; are not due to the direct effects of a substance or a general medical condition; are not better accounted for by bereavement. DSM-IV also lists three levels of severity of MDD. Based on the number of criteria symptoms, the severity of the symptoms and the degree of functional disability and distress, MDD can be mild, moderate or severe (with or without psychotic features). The symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, and symptoms that are due to a general medical condition, direct physiological effects of a substance, mood-incongruent delusions or hallucinations, bipolar mixed episode, or bereavement must be ruled out. The terms and codes in DSM-IV are mostly comparable with ICD-10 (WHO, 2007), and diagnosis of MDD is basically similar in both classifications. However, compared with DSM-IV, ICD-10 splits one criterion (feelings of worthlessness and unreasonable guilt), requires one symptom less for diagnosis, and also includes fatigue or loss of energy among the core symptoms.

A simpler definition of MDD has been suggested, as studies have shown that treatment providers have difficulties recalling all nine symptoms, and the somatic symptoms (weight change, insomnia, loss of energy and psychomotor retardation) are difficult to apply in patients with medical illnesses (Zimmerman and Galione, 2010). A recent study found, after eliminating the four somatic criteria from the DSM-IV definition of MDD, a high level of concordance between this simpler definition and the original DSM-IV classification (Zimmerman et al., 2010). According to DSM-IV, periods of sadness are aspects of the human experience, which should not be diagnosed as a MDE unless criteria are met for severity, duration, and clinically significant distress or impairment (Maj, 2008). This clinical significane criterion has also been criticized. Kendler et al. found similarities between bereavement-related depression and depression related to other stressful life events questioning the validity of the bereavement exclusion for the diagnosis of major depression (Kendler et al., 2008), whereas Wakefield et al. recommended based on their findings to extend the bereavement exclusion to even other uncomplicated loss-events triggering depression (Wakefield et al., 2007; Wakefield et al., 2009). The proposed

version of DSM-V emphasizes three basic dimensions of depression: depression with anxiety, with substance abuse, and with suicidal behavior. In addition, a new diagnosis of *mixed anxiety depression* has been introduced (www.dsm5.org) (Miller and Holden, 2010). In this thesis, unless otherwise specified, depression refers to unipolar DSM-IV MDD.

4.3.1.1 Subgroups of MDD

DSM-IV describes important distinctive features of an depressive episode for the purposes of research or treatment choice (APA, 2000a). *Psychotic* features may be present in a severe MDE, and include the presence of either hallucinations or delusions. Psychotic symptoms appear to repeat over recurrent episodes (Coryell et al., 1994). *Melancholic* features of DSM-IV MDE include (a) loss of pleasure in all, or almost all, activities, (b) lack of reactivity to usually pleasurable stimuli, (c) a distinct quality of the depressive mood, (d) depression regularly worse in the morning, (d) early morning awakening, (e) marked psychomotor change, either retardation or agitation, (f) significant loss of appetite or weight loss, and (e) excessive or inappropriate guilt (APA, 2000a). Melancholic features and psychotic features may represent a distinctive form of severe depression arising from a different pathophysiology than other forms of depression (Parker and Manicavasagar, 2005). It has also been reported that patients with melancholic depression respond better to biological therapies (e.g. tricyclic antidepressants [TCAs] and/or eletroconvulsive therapy [ECT]) (Perry, 1996). The validity of the DSM-IV criteria in differentiating melancholic and non-melancholic depression has been criticized with the suggestion that observable psychomotor disturbances are the only necessary and sufficient feature of the definition of melancholia, whereas the other features are prevalent in both types and are thus non-specific (Parker, 2003). A previous report from the Vantaa Depression Study (VDS) discovered no major differences in current co-morbidity, or course of depression between melancholic and non-melancholic patients, and the consistency of DSM-IV melancholic features across episodes appeared weak (Melartin et al., 2004a). *Atypical* depressive features include (1) mood reactivity and (2) two or more of the following features: (a) significant weight gain or increased appetite, (b) hypersomnia, (c) leaden paralysis, and (d) a long-standing pattern of interpersonal rejection sensitivity (APA, 2000b). It was previously recognized that patients with atypical depression responded better to the monoamine oxidase inhibitors (MAOI) in contrast to patients with melancholic depression (Stewart and Thase, 2007). The current definition of atypical features appears problematic as interpersonal rejection sensitivity and leaden paralysis may have their phenomenological base in anxiety rather than depression (Parker et al., 2002). Rejection sensibility is in addition a prominent feature of borderline personality (APA, 2000a). *Seasonal* pattern depressions have an apparent regular onset and disappearance during certain times of the year. In the Northern hemisphere the most common pattern is autumn or winter depression (SAD or seasonal affective disease). *Postpartum* onset specifier can be taken to a MDE if the onset is within 4 weeks after the delivery (APA, 2000a).

4.3.2 Diagnosis of other depressive disorders

According to DSM-IV (APA, 2000a) depressive disorders include in addition to MDD two other forms: dysthymic disorder and depression not otherwise specified (NOS), which includes several forms of briefer or milder periods of depression. *Dysthymic disorder* in DSM-IV consists of chronic but milder symptoms than MDE. The diagnostic criteria include (A) a depressed mood for most of the day or for more days than not for at least two years, (B) the presence, while depressed at least two of the following: (1) poor appetite or overeating, (2) insomnia or hypersomnia, (3) low energy or fatigue, (4) low self-esteem, (5) poor concentration or difficulty in making decisions, or (6) feelings of hopelessness. The symptoms cause clinically significant distress or impairment in important areas of functioning. In addition, no major depressive episode (MDE) should have been present during the first two years, i.e., the disturbance cannot be better accounted for as chronic MDD or MDD in partial remission. A number of subjects with disabling depressive symptoms fail to meet the diagnostic criteria for MDD or dysthymia, some of these subsyndromal conditions are included in the category *depression not otherwise specified* (APA, 2000a). Appendix B in DSM-IV (APA, 2000a) defines diagnostic criteria for *recurrent brief depressive disorder*, where the episodes are identical to MDE in the number and severity of symptoms but do not meet the 2-week duration requirement lasting at least 2 days but less than two weeks. Episodes must recur at a minimum of once a month for a period of 12 consecutive months (APA, 2000a). For *minor depression*, although not considered an official clinical diagnosis, the American Psychiatric Association defined research diagnostic criteria in Appendix B of DSM-IV (APA, 2000a). The essential features are identical to MDE in duration, but involve fewer symptoms and less impairment. An episode involves either a sad or depressed mood or loss of interest or pleasure in nearly all activities. In total, at least two but less than five additional symptoms must be present. *Subsyndromal depressive symptoms* were included to a clinical condition proposed by Judd et al. in order to further analyse the pleomorphism of the depressive spectrum in the National Institute of Mental Health (NIMH) Epidemiological Catchment Area (ECA) Program (Judd et al., 1997). It was there defined as at least two current depressive symptoms, present every day for most of the time, for at least two weeks, in persons not meeting the criteria for MDD, minor depression or dysthymic disorder. Thus it could refer to residual symptoms of a past MDE or a prodromal of a future MDE (Judd et al., 1997).

4.3.3 Diagnosis of bipolar disorder

Bipolar disorder, or manic-depressive illness as it was previously named, is a mental disorder characterized by recurrent episodes of mania, hypomania, mixed states and depression. Bipolar disorder is divided into bipolar I and bipolar II disorders, and bipolar disorder not otherwise specified (NOS). *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 at least by one hypomanic episode and one or more major depressive episodes (APA, 2000a). There are no differences in DSM-IV criteria regarding unipolar depression or major depressive episode of bipolar disorder.

The criteria of a *manic* episode include nearly every day over at least a 1-week period (or any period if hospitalization is necessary) (A) a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least for 1 week (or any duration if hospitalization is necessary) and (B) during the period of mood disturbance, three (or more) of the following symptoms persisting (four if the mood is irritable) to a significant degree: (1) inflated self-esteem or grandiosity, (2) decreased need for sleep, (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or a subjective experience that subject's thoughts are racing, (5) distractibility, (6) increase in goal-directed activity or psychomotor agitation, or (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (APA, 2000a). The disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning, or to require hospitalization, or it is characterized by the presence of psychotic features.

A *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. In addition, the disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning, or to require hospitalization, or to include psychotic features.

A *hypomanic* episode is characterized by a persistently elevated, expansive or irritable mood lasting for at least four days. 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. A hypomanic episode must be clearly different from the individual's usual non-depressed mood, and there must be a clear change in functioning that is not characteristic for the individual, and changes in mood and functioning must be observable by others. The DSM-IV hypomania-specific criteria for a hypomanic phase (APA, 2000) differ from the criteria for a manic phase in that the expression "abnormally changed" is omitted from criterion (A), and a duration of only 4 days is required. Also, hypomania is differentiated from mania in that the phase must not be severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and no psychotic features are present.

Bipolar disorder NOS is a coverall category, diagnosed when the disorder does not fall within a specific subtype (APA, 2000a). Especially, when an individual aged over 50 years has his/her first manic or hypomanic episode the possibility of an organic aetiology must

be ruled out. Potential hypomanic and manic episodes must be evaluated when treating depressive patients. The proposed DSM-V somewhat lowers the threshold for bipolar diagnosis by allowing a bipolar episode diagnosis during antidepressant treatment if the symptoms persist beyond the physiological effect of that treatment (www.dsm5.org).

4.4 Prevalence of mood disorders

The prevalence of depressive symptoms varies depending on the population studied and criterion used, the variations in time frames, age ranges, diagnostic criteria and interview schedules (DIS, CIDI) complicate the synthesis of findings. In addition, the generalizability of diagnostic criteria across countries requires further confirmation (Patten, 2003). Efforts to eliminate these problems have been made in order to unify different study methods. WHO has created a large research consortium (WHO World Mental Health Survey Initiative, 2004), where a wordwide survey has reported the prevalence and severity of mental disorders and use of mental health services (Demyttenaere et al., 2004; Wang et al., 2007).

4.4.1 Prevalence of MDD

It has been estimated that about a fifth of the population (Kessler et al., 1994; Kessler et al., 2003), will experience a clinically significant MDE at some point in their lives. The prevalence for females is about twice as high as for males (Paykel et al., 2005); it is fairly low until the early teens, when it begins to rise in roughly linear fashion (Kessler et al., 1994), the median age of onset being approximately 30 years (Kessler et al., 2003).

General population studies have generally reported a 12-month prevalence of 4% to 9%, and a lifetime prevalence of 13% to 18% of MDD. The National Comorbidity Survey Replication (NCS-R), conducted in 2001-2002, found a 12-month prevalence of 6.6% and lifetime prevalence of MDD of 16.2% among U.S. adults (Kessler et al., 2003). In Europe, The European Study of the Epidemiology of Mental Disorders/ Mental Health Disability (ESEMeD/MHDEA 2000) reported from six countries a 12-month prevalence of 4% and lifetime prevalence of 13% (Alonso et al., 2004). In Finland, the Health 2000 project reported a 12-month prevalence of 4.9% and lifetime prevalence of 17.7% (Pirkola et al., 2005a; Suvisaari et al., 2009), while the 12-month prevalence was 9.3% in the Finnish Health Care Survey (TERVA) (Lindeman et al., 2000). The use of a diagnostic interview with strict exclusion criteria probably explains the lower prevalence in the more recent Health 2000 project. The Tampere Depression (TADEP) Study found clinical depression in a tenth of primary care patients, and in one-half of patients in community mental heath centres (Salokangas et al., 1996).

There have been opposing views on whether the prevalence of MDD has increased or not (Compton et al., 2006; Hawthorne et al., 2008). The increasing usage of antidepressant medications, granted disability pensions, and depressions diagnosed younger than before, have led to the common interpretation that the prevalence of depression has also increased. Those with a contrary view have argued with easier prescription and usage of medications, higher alertness among clinicians to diagnose depression, changes in society towards more open discussion about depressive feelings and false diagnoses among patients with burn-out (Karlsson, 2009; Lönnqvist, 2009).

4.4.2 Prevalence of bipolar disorder

The lifetime prevalence of bipolar disorder (BD) type I is commonly estimated to be about 1%, but in more recent general population studies it has varied from 1.9% to 3.3% (ten Have et al., 2002; Grant et al., 2005; Kessler et al., 2005b; Pini et al., 2005). The 12-month prevalence of BD has been reported to be from 0.1 to 2.0% (ten Have et al., 2002; Mitchell et al., 2004; Kessler et al., 2005b; Pini et al., 2005). The differences in prevalence have depended on the diagnostic instrument used.

In epidemiological studies BD II has been even more difficult to diagnose with certainty and studies investigating lifetime prevalences separating BD I and II, which have been few (Szadoczky et al., 1998; Scully et al., 2004), reported the lifetime prevalence of BD II to be 0.1 and 2.0%, and of BD I 0.3 and 1.5%. The prevalence of hypomania in the Epidemiological Catchment Area Study (ECA) was 0.5%, lower than the 0.8% for mania (Weissman et al., 1988). In Finnish studies, the prevalence of BD has been estimated to be lower than the international prevalences (Lehtinen et al., 1990b; Veijola et al., 1996; Räsänen et al., 1998; Kieseppä et al., 2004). The most recent Finnish general population study, Psychoses in Finland (PIF) (Perala et al., 2007), used several screening methods and structured interviews by psychiatrists to confirm the diagnosis of patients screening positive for psychotic symptoms. The study reported a lifetime prevalence of 0.24% for BD I, and 0.42% with the inclusion of register diagnoses of BD I. The Tampere Depression Project used the Present State Examination as a diagnostic instrument to evaluate the prevalence of BD and MDD in primary care (N=437) and secondary care (N=435). In community health centers, the 12 month prevalence of BD was 2.1%, and in community mental health centres, 7.6% (Sorvaniemi and Salokangas, 2005).

4.5 Aetiology and pathogenesis of MDD

4.5.1 Multifactorial aetiology

The aetiology of MDD is understood as a multifactorial longitudinal process, where genetic factors, temperament, early traumatic experiences, current stress and their interactive and cumulative effects act as predisposing factors (Melartin and Isometsä, 2009). Furthermore, MDD is a clinically heterogeneous disorder with a highly variable course increasing the likelihood of a wide range of individual risk factors (Kendler et al., 2002; Kendler et al., 2006a; Belmaker and Agam, 2008). Many levels of scientific explanation, from molecular to sociological are needed; until now, despite many efforts an integrative and pervasive model remains to be uncovered. The concept of depression has shifted from one where genetic, biological, developmental and environmental risk factors were thought to be unrelated to one where these risk factors are believed to be related and interacting (Kendler et al., 2002; Caspi et al., 2003; Charney and Manji, 2004; Kendler et al., 2006a). However, aetiological risk factors for MDD are not necessarily similar to factors affecting the outcome and course of the disorder. Integrating the tools of genomics and neural science is needed to reveal the causes of neuropsychiatric illnesses and to suggest new strategies for treatment and prevention (Akil et al., 2010).

4.5.2 Heritability and genetic risk factors

Heritability is a concept that refers to the proportion of total variation in a trait that can be attributed to variation in genetic factors. Heritability is estimated in relation to a population, and can vary from one population to another depending on the relative impact of heritable and environmental factors. Family-, twin- and adoption studies have shown that psychiatric disorders exist often within families, and liability to depression is at least partly inheritable (Oates, 1997; Rutter et al., 1999). According to them, the offspring of depressed parents have a 3-fold risk of a mental disorder by the age of 35 (Weissman et al., 2006), and a 3- to 4-fold risk to MDD compared to those without a family history (Sullivan et al., 2000); the risk of maternal depression is transmitted even across generations (Weissman et al., 2005). When one of monozygotic twins suffers from depression, the likelihood of depression in the other twin is about 50%, and among dizygotic twins approximately 20% (Sullivan et al., 2000). In representative studies investigating normal populations, the estimates of heritability have varied between 35 to 40%, and have been on an average somewhat higher in women (40-45%) compared to men (25-30%) (Sullivan et al., 2000; Kendler et al., 2006c). The heritability of liability to major depression can be even up to 75% in clinical cohorts of subjects with more recurrent, difficult depressive episodes, and early age at onset (Uher, 2008). The

heritability of liability to bipolar disorder is estimated to be as high as 85-90% (McGuffin et al., 2003; Kieseppä et al., 2004). However, a more recent Swedish study estimated a lower heritability of 59% for bipolar disorder (Lichtenstein et al., 2009).

A combination of genetic factors, early life stress and ongoing stress may ultimately determine individual responsiveness to stress and vulnerability to depression (Caspi et al., 2003; Uher and McGuffin, 2008; Caspi et al., 2010). According to several reports, allelic variation of 5-HTT expression and function (length polymorphism in the promoter region of human serotonin transporter gene [5-HTTLPR]) together with modelling life-events may predispose to depression, and also predict the response to antidepressant treatment (Caspi et al., 2003; Caspi et al., 2010). Genetic differences seem to affect the serotonergic system, and the development of neural circuits already in childhood, and the vulneralibity to stress in subjects with a short allele of this gene (S) can be observed already in childhood (Jacobs et al., 2006). The potential mechanisms include a heightened reactivity to emotional and stressful stimuli mediated by the serotonergic nerve system (Canli and Lesch, 2007), and the regulation of hypothalamus-pituitary-adrenal (HPA) axis (Gotlib et al., 2008; Chen et al., 2009; El Hage et al., 2009).

However, also evidence against these findings has emerged questioning the interpretations of the findings by investigation methods, and effects of gender and age (Monroe and Reid, 2008), whereas a recent meta-analysis found no associations between 5-HTTLPR, stressful life events, and risk of depression (Risch et al., 2009). The authors reasoned that the prior probability of a positive finding would be extremely small. Therefore they excluded studies that others have considered as best evidence. Animal models, for instance, would justify a prior probability of the conventional 0.05. As vulnerability to early and adult stress is also associated with disturbances in the regulation of the HPA-axis, candidate genes affecting the corticotropin releasing hormone (CRH) system and glucocorticoid receptors have also been investigated (Heim et al., 2008; McGowan et al., 2009). Different candidate genes seem to have also significant interactions. Human serotonin transporter and brain-derived neurotrophic factor (BDNF) genes likely regulate the functions of some neural circuits, and may modulate the propensity to depression related to early stress (Heim et al., 2008).

However, the heritability of liability can be estimated for groups, not individuals, and the causation of major depression is probabilistic, not deterministic (Sullivan et al., 2000). Genetic linkage studies in unipolar MDD suggest a number of candidate regions on different chromosomes (Abkevich et al., 2003; Zubenko et al., 2003; Holmans et al., 2004), but to date, no study has found a gene-variation that would directly explain the occurrence of depression (El Hage et al., 2009). The liability of depression is affected probably by several genes, which are of limited importance at the population level,

despite their significance in individual families (Akil et al., 2010). Genes that predispose to MDD are not specific to depression, for example, the genetic correlation between depression and generalized anxiety disorder (GAD) is very high, and also significant between other anxiety disorders (Kendler et al., 2007; Hettema, 2008).

4.5.3 Psychosocial risk factors

A majority of MDE's emerge after a significant negative life event which includes typically experiences of loss, separations, and other situations of humiliation, shame, or entrapment (Kendler et al., 2003a). Psychosocial risk factors for depression can be divided into early and recent risk factors. The former include experiences from childhood and adolescence and the latter risk factors, such as stressful life events and poor social support, preceed the occurrence of MDE (Kendler et al., 2002; Kendler et al., 2006a). It has been hypothesized that high levels of early life trauma lead to illness through the developmental interaction of genetic variants with neural circuits that regulate emotion, mediating together risk and resilience in adults (Gillespie et al., 2009).

4.5.3.1 Early psychosocial factors

Several studies have demonstrated the relationship of serious negative life events and difficult circumstances in childhood and the development of depression, and other mental disorders in the adulthood. Such life events have ranged from physical or sexual abuse (Heim et al., 2000; Gladstone et al., 2004; Kendler and Prescott, 2006), to a disturbed family environment, such as poor parenting, parental loss or separation, and depression of parents (Lyons-Ruth et al., 1986; Tennant, 1988; Kessler et al., 1997; Veijola et al., 2004; Kendler and Prescott, 2006). It has been hypothesized that poor parenting increases the risk for MDD through individual specific environment, i.e. individuals react to parenting in different ways guided in part by genetically influenced characteristics e.g. temperament (Kendler and Prescott, 2006).

Within the Health 2000 study in Finland, the impact of adverse environmental factors during childhood seemed to include a wide range of factors from direct causal associations to complex interacting environmental effects (Pirkola et al., 2005). Evidence has been found to support the vulnerability hypothesis, i.e. the consequences of an unfavourable childhood background might be worse if combined with adult adverse life-events (Korkeila et al., 2005). Futhermore childhood adverse life-events have been found to associate with adult depression-prone personality characteristics (Korkeila et al., 2004), and with an increased likelihood of experiencing a high number of life events in adulthood and their perceived burdensomeness (Korkeila et al., 2010). Early trauma can induce long-term neuroendocrinological and biological effects, which in turn increase the emotional sensitivity and risk of depression during stress (Korkeila et al., 2005; Danese et al.,

2008; Heim et al., 2008). However, every individual with depression has not experienced early trauma, and everyone with traumatic experiences does not become depressed. Individuals may react to childhood experiences in different ways guided by genetically influenced characteristics e.g. temperament, nurture, age, duration of stress and later mending experiences (Karlsson et al., 2007; Kendler and Baker, 2007).

4.5.3.2 Recent psychosocial factors

Together with genetic vulnerability and temperamental factors, adverse life events are likely to form one of the key domains of liability to MDD (Kendler et al., 2002; Kendler et al., 2006a). The relative risk of depression within 6 months after a significant negative life event is estimated to be up to sixfold (Paykel, 1978; Kendler et al., 2006a). Loss and humiliating events have been particularly demoralizing among depressives (Farmer and McGuffin, 2003) and in epidemiologic twin studies (Kendler et al., 2003a). Men have been more sensitive to divorce and work difficulties, and women to their social network events (Kendler and Prescott, 2006). Different types of difficulties may lead to different profiles of depressive symptoms (Keller et al., 2007). The role of psychosocial stress may vary over time being largest at the beginning and diminishing over recurrent depressive episodes, and may be less important in precipitating in melancholic or psychotic subtypes of MDD (Kendler et al., 2000; Mitchell et al., 2003). Low social support appears to increase the risk of recurrent MDE (Kendler et al., 2006a), and depression may in term have significant negative consequences on the social support available (Coryell et al., 1993; Leskelä et al., 2008).

In addition, the ability to receive and respond to support may be influenced by early negative experiences and relationships to significant others. In gene-environment interaction studies genetic risk has been found to influence overall liability to illness and alterer an individual's sensitivity to the pathogenic effects of the environment (Kendler and Prescott, 2006). Genetic mediation by 5-HTTLPR of vulnerability to an adverse environment has been reported in several studies (Caspi et al., 2010). Also, other gene-environment interactions have been reported, e.g. serotonin receptor 2A gene may be involved in the development of depression by influencing the ability of individuals to use environmental support (Jokela et al., 2007) and the dopamine transporter gene, genotype A2/A2, may be involved in the development of depressive symptoms in individuals with adverse life-events (Elovainio et al., 2007). Other possible interactions are e.g. an interaction between life-events and neuroticism, where neuroticism has a greater impact on the risk of MDD at high rather than low levels of stressful life-events (Kendler et al., 2004). According to a bidirectional model, partly genetically determined individual differences in personality, influence world-view and the likelihood of experiencing stressful life events, and the quality of interpersonal relationships, which in turn influence the risk of depression (Kendler et al., 2003b). In the VDS, the majority of patients attributed the onset of MDE to some adverse event, although no clustering of live events appeared to associate with the time of onset (Leskelä et al., 2004).

4.5.3.3 Personality and temperamental factors

Temperament has been seen as the early appearing core of later personality. It manifests early in life remains relatively stable, is inherited and is based on biological processes. Cloninger has described four dimensions of temperament, i.e. novelty seeking, harm avoidance, reward dependence, persistence, and dimensions of character associated with different aspects of self-concept, i.e. self-directedness, co-operativeness, and self-transcendence (Cloninger et al., 1993). *Personality* can be conceptualized as a large entity of individual differences including values, motives, attitudes, needs, coping mechanisms, capabilities, attainments and self-esteem. Personality develops from temperament through experiences, maturation and interaction with the environment (Pervin et al., 2005). Two widely studied personality dimensions describing negative and positive trait entities, neuroticism, and extraversion have been included in the largely supported Big Five model or Five Factor Model together with agreeableness, conscientiousness and openness to new experience (Goldberg, 1993). Personality dimensions have been found to influence the risk for depression. High neuroticism has been considered a risk factor for depression in prospective epidemiological twin (Kendler et al., 1993b; Kendler et al., 2006b; Fanous et al., 2007), general population (Ormel et al., 2004) and clinical studies (Angst and Clayton, 1986; Hirschfeld et al., 1989; Boyce et al., 1991). Moreover, low extraversion has been suggested to be a vulnerability factor for depression (Hirschfeld et al., 1989; Kendler et al., 2006b) and high extraversion to even exert some protective effects against depression (Farmer et al., 2002). However, the role of extraversion as a risk factor for depression is more obscure than that of neuroticism, as prospective studies (Angst and Clayton, 1986; Hirschfeld et al., 1989; Boyce et al., 1991; Kendler et al., 1993b; Fanous et al., 2007) have not proved low extraversion to be a risk factor. The relationship between personality and affective disorders is complex. Personality features may 1) have a common aetiology with affective disorders, 2) predispose an individual to affective disorders, 3) be shaped by repeated episodes of the illness, 4) modify the clinical picture of the illness, 5) be an attenuated expression of the disorder, or 6) be state-dependent concomitants of affective disorders (Shea and Yen, 2003; Brandes and Bienvenu, 2006).

4.5.4 Structural and functional brain imaging findings

In general, the structure of the brain is normal in patients with depression, but mild abnormalities may exist. Magnetic resonance imaging (MRI) studies have demonstrated that small hippocampal volumes associate with recurrent or severe MDD (Sheline et al., 1999), and when compared with control subjects, MDD patients have had smaller volumes of the orbital frontal cortex and anterior cingulated cortex (Videbech and Ravnkilde, 2004; Campbell and MacQueen, 2006). MRI studies have also revealed decreased white matter

volumes in the left anterior cingulated gyrus and right middle frontal gyrus among elderly MDD patients (Bell-McGinty et al., 2002), whereas patients with familial MDD have shown an enlarged middle genu area of corpus callosum (Lacerda et al., 2005). The increased rate of white matter hyperintensities, possibly implicating impairment of white matter tracts connecting the cortex with the limbic areas, has been found in the frontal lobes and basal ganglia in elderly MDD patients (Videbech, 1997; MacFall et al., 2001). More recently, white matter abnormalities have been revealed also in first-episode, treatment-naïve young adults in the frontal, temporal and parietal lobes with a modern MRI technique, diffusion tensor imaging (DTI) (Ma et al., 2007). Postmortem studies have also revealed a decrease in gliacells (astrocytes and oligodendrocytes) especially in the amygdala and prefrontal regions of the brain (Rajkowska and Miguel-Hidalgo, 2007). It seems these changes can sometimes be found already in the early stage of illness, and in young adolescents with a familial risk of depression. Treatment likely modifies the effects of illness, e.g. the previously decreased volume of amygdala increases with treatment for depression (Fu et al., 2004). In addition, antidepressant medication may prevent the reduction of hippocampal volume among patients with major depression (Sheline et al., 2003).

A general picture of disturbed brain functioning is that during depression the metabolism in frontal cortex is diminished and the metabolism of limbic system is increased; thus, the enhanced activity in the regions central to emotions are beyond the control of the central cortical regions. Functional neuroimaging techniques i.e. functional magnetic imaging (fMRI), positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) have shown changes among MDD patients in several brain areas, including the orbital and medial prefrontal cortex, the amygdala and related parts of the striatum and thalamus (Drevets, 2000). Functional imaging studies of the brain report that serotonin transporter polymorphism also associates with reduced hippocampal volume (Frodl et al., 2004), or with greater amygdala neuronal activity (Hariri et al., 2002). The normalization of the overactivity of the anterior part (Brodmanns area 25) of the gyrus cingularis situated in the medial prefrontal cortex correlates strongly with a good response to antidepressant medication, and has been the neuroanatomical target of the experimental neuromodulation treatment (deep brain stimulation [DPS]) (Mayberg, 2009). However, the clinical picture of depressive patients is very heterogenous and substantial individual variations exist also in the findings of functional brain imaging studies. Different brain regions probably correlate with discrete symptom domains of major depression and together make up the MDD syndrome (Milak et al., 2005).

4.5.5 Neurochemical, neurotrophic and neuroendocrinological findings

Noradrenergic and serotonergic systems originate deep in the brain and fan out over almost the entire brain, suggesting a system capable of modulating many areas of feeling, thinking, and behaving (Belmaker and Agam, 2008). The monoamine hypothesis of depression developed while investigating antidepressants and their mechanism of action postulating that a central illness mechanism is a deficiency in the brain monoamine (serotonin, norepinephrine or dopamine) neurotransmission (Thase et al., 2002). However, in its original form the hypothesis seems inadequate, and has evolved to include e.g. adaptive changes in receptors to explain the delay in onset of the antidepressant effect (Hirschfeld, 2000). Moreover, monoamine depletion has induced depressed mood in subjects with a family history of MDD and in drug-free patients with MDD in remission, but in healthy subjects only if they have a family history of depression, and have thus failed to demonstrate a causal relation between dysfunction in the monoamine systems of serotonin and noradrenalin (Ruhe et al., 2007). Therefore, disturbance in monoamine neural transmission is related to the illness mechanisms of depression, but only as one factor (Belmaker and Agam, 2008). The monoamine hypothesis has evolved into the direction of a chemical or molecular hypothesis of depression, which presumes that mood disorders are produced by long-term changes in the production or activity of molecules e.g. neuropeptides, growth factors and their receptors and intracellular signalling molecules in the brain (Manji et al., 2001; Castren, 2005). The network hypothesis proposes that problems in information processing within neural networks, rather than changes in chemical balance, might underlie depression, and that antidepressant drugs induce plastic changes in neuronal connectivity e.g. by increasing the expression and signalling of BDNF, which gradually lead to improvements in neuronal information processing and the recovery of mood (Castren, 2005).

Stress promotes adaptation, but a disturbed diurnal rhythm or failed shut-off of mediators e.g. glucocorticoids and growth hormone after stress leads over time to allostatic load (wear and tear on the body) (McEwen, 2003). Abnormal, excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis is observed in approximately half of individuals with depression. Hypercortisolism has been observed in subjects with severe and psychotic depression, and hypocortisolism in subjects with atypical depression (Gold et al., 2002). In addition to directly causing neuronal atrophy and hippocampal volume reduction, life stress and glucocorticoids also reduce cellular resilience and neurogenesis (Sapolsky, 2000; Manji et al., 2001; Heim et al., 2008; McKinnon et al., 2009). An excessive amount of glucocorticoids may also be partly responsible for the decreased level of BDNF and thus the deficiency in neutotrophic support (Nestler et al., 2002). It has been observed that not only the overall production of cortisol, but also enhanced corticotrophin releasing factor (CRF) carry the responsibility for HPA-axis hyperactivity (Nestler et al., 2002).

CRH predominantly acts through CRH-1 receptors to produce a number of anxiety- and depression-like symptoms. Impaired corticosteroid receptor signaling has been suggested to be a key mechanism in the pathogenesis of depression, and is a target of future antidepressant development (Holsboer, 2000; Refojo and Holsboer, 2009).

The BDNF-hypothesis of depression postulates that loss of BDNF is directly involved in the pathophysiology of depression, and its restoration may underlie the therapeutic efficacy of antidepressant treatment. However, critical views have been presented for reassessing this hypothesis and it is suggested that maybe the role of BDNF lies more in the development of depressive symptoms than at the core of disease pathology (Groves, 2007).

Since the beginning of the 1990's there have been findings that depression is characterized by cell-mediated immune activation and inflammation (Maes, 1994). More recently, it has been reported that, depression is an inflammatory disorder because the plasma levels of cytokines are increased, i.e. interleukin-(IL)-6 and tumour necrosis factor-alpha (TNFalpha) (Dowlati et al., 2010). These cytokines are stress-sensitive and may cause depressive behaviours, which may be induced by an increased catabolism of tryptophan, the precursor of serotonin, to neurotoxic agents. Most antidepressants have also specific anti-inflammatory effects (Maes, 2010).

There is also growing evidence that, far from being a disorder with purely psychological manifestations, MDD is a systemic illness with damaging effects on multiple organ systems (Manji et al., 2001). It has been associated with alterations in endocrine, cardiovascular and immune systems, as well as in bone metabolism (Michelson et al., 1996; Musselman et al., 1998; Jiang et al., 2002), and appears to have adverse effects on comorbid medical diagnoses, such as coronary artery disease, stroke, diabetes and osteoporosis (Frasure-Smith et al., 1993; Michelson et al., 1996; Vataja et al., 2001; Lustman and Clouse, 2002; Carney et al., 2003; Frasure-Smith and Lesperance, 2003). Generally, evidence from research indicates that depression and vascular disease have a bi-directional association, especially in the elderly (Thomas et al., 2004). Depression has also been linked to memory deficits (impairments in verbal declarative memory) associating with a hippocampal dysfunction (Bremner et al., 2004).

4.6 Comorbidity of MDD

4.6.1 Definition of the concept

Comorbidity refers to the occurrence of two or more distinct disorders in a person in a defined period of time (Klerman, 1990). The comorbidity concept originates in the literature for the epidemiology of medical diseases. After that, it has been increasingly applied in psychiatry, largely as a consequence of the introduction of the definite descriptive, operational criteria for mental disorders (Feighner et al., 1972; Spitzer et al., 1978; APA, 1980). In particular, DSM-III-R of the American Psychiatric Association introduced the use of multiple diagnoses within a multiaxial classification system (APA, 1987). It has been discussed whether the concept of comorbidity refers to co-occurrence, covariation (Lilienfeld, 2003), or multimorbidity (Kessler et al., 1994).

Different models of comorbidity have been described (Klein and Riso, 1993; Neale and Kendler, 1995; Krueger and Markon, 2006). These include 1) the associated liabilities model (each disorder is influenced by a latent liability factor, and these factors are correlated), 2) the multiformity model (multiple pathways from the same liability lead to different manifestations), 3) the causation model (one disorder directly causes another disorder), 4) the independence model (comorbid disorders are independent conditions, separate from other disorder), and 5) the spurious association model (some external variable or set of variables creates spurious associations between disorders) (Krueger and Markon, 2006). The associated liabilities model has been further developed converging for comorbidity and common forms of psychopathology in a hierachical model. This includes two superordinate liabilities: 1) internalizing (general liability toward negative-affect such as mood and anxiety disorders), and 2) externalizing (general liability toward disinhibitory disorders such as substance use disorders and antisocial behaviour disorders) (Krueger, 1999; Vollebergh et al., 2001). The internalizing liability often bifurcates into two subordinate liabilities, distress and fear (Watson, 2005).

Comorbidity has also been criticised for being an artefact produced by the categorical diagnostic classification systems (Maj, 2005). Non-comprehensive definitions of comorbidity, variations in diagnostic assessments, timing of diagnosing, time-frame (e.g. lifetime or current), and different health care settings have led to substantial discrepancies in the reported prevalence of comorbid disorders, producing a rather complex picture of their significance (Weiss et al., 1992; Zimmerman, 1994; Wittchen, 1996; Bogenschutz and Nurnberg, 2000; Vella et al., 2000). Arguments for a dimensional approach have been made especially regarding personality disorders (Watson, 2005) where also subsyndromal disorders would be of importance (Melartin et al., 2010). In this thesis, unless otherwise specified, however, comorbidity refers to current categorical (DSM-IV) diagnostic comorbidity.

4.6.2 Comorbidity of MDD in general populations

A number of epidemiological studies have reported a high comorbidity of depression (Regier et al., 1990; Angst, 1996; Kessler et al., 1996a; Kessler et al., 1996b; Kessler et al., 2003; Hasin et al., 2005; Pirkola et al., 2005c), and comorbid depression is more of a rule than an exception. In the National Comorbidity Survey Replication (NCS-R) study (Kessler et al., 2003), about 80% of respondents with 12-month DSM-IV MDD had at least one *axis I comorbid disorder*, anxiety disorders being the most common (67.8%), followed by substance use disorders (27.1%). In the Finnish Health 2000 study, 32% of respondents with 12-month DSM-IV MDD had at least one comorbid disorder, anxiety disorder being the most common (25%), followed by alcohol use disorder (9%) (Pirkola et al., 2005c). In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study (Hasin et al., 2005) in subjects with lifetime DSM-IV MDD, the most common comorbid axis I disorders was any anxiety disorder (41.4%), followed by any alcohol use disorder (40.3%).

The assessment of comorbid personality disorders is more difficult especially in cross sectional studies. A current depressive episode may for instance accentuate symptoms of personality disorder. There is only a little information on the prevalence of MDD with comorbid *axis II disorders* in the general population. Calculating from the figures of the Baltimore site of the Epidemiological Catchment Area (ECA) study (Samuels et al., 1994), a prevalence of 8% for comorbid axis II disorders was obtained. In the European Outcome of Depression International Network (ODIN) study (Casey et al., 2004), conducted in five European countries, and in the NESARC study (Hasin et al., 2005), 22% and 38% of individuals with MDD respectively, had personality disorders. The most common comorbid personality disorders in the ODIN study were cluster C personality disorders, whereas in the NESARC study obsessive-compulsive personality disorder (18.3%), followed by paranoid (15.1%), schizoid (10.2%), avoidant (9.6%), antisocial (8.1%), histrionic (5.3%), and dependent (2.2%) personality disorders (borderline, schizotypal and narcissistic were not included in the study). In a representative study from Norway (Torgersen et al., 2001), the prevalence of personality disorders was 13.4% with avoidant (5.0%), obcessive-compulsive (2.0%), paranoid (2.4%), schizoid (1.7%), dependent (1.5%) being common, and borderline personality disorder being less common (0.7%) than usually reported.

4.6.3 Comorbidity of MDD in clinical cohorts

Comorbid disorders tend to be more common in clinical compared to epidemiological studies, probably due to the more serious course of illness (Kessler et al., 1994). In psychiatric settings, the reported prevalences of current comorbid disorders among patients with MDD have varied widely. The reported prevalences of comorbid disorders appear too low in a number of studies (Keller et al., 1983; Mueller et al., 1999; Kanai et al., 2003) as compared with the prevalences reported more from the current perspective (Zimmerman et al., 2000; Melartin et al., 2002). Many of the early studies focused on a single type of comorbid disorder which may well inflate the prevalence of comorbidity found. The prevalence of axis I disorders in MDD patients in psychiatric settings have varied widely, but all in all approximately half of the patients have had a current anxiety disorder and about one-fifth a current substance use disorder (Melartin et al., 2002). In the VDS, 70% of patients with current MDD had at least one current axis I comorbid disorder, of which 57% had anxiety disorders, and 25% substance use disorders (Melartin et al., 2002). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al., 2005), investigating 1376 outpatients with DSM-IV MDD assessessed the concurrent comorbidity of MDD with the Psychiatric Diagnostic Screening Questionnaire, found 61.8% of cases having at least one comorbid disorder, social anxiety disorder (20.8%) being the most common, followed by GAD (18.8%), OCD (13.4%), PTSD (12.4%), bulimia (11.9%), any alcohol use disorder (11.9%), panic disorder (11.1%) and agoraphobia (9.4%). There are only a few studies of psychiatric comorbidity among primary care patients. MDD patients in primary care or psychiatric out-patient settings have not been found to differ markedly in current axis I comorbidity (Vuorilehto et al., 2007). In Primary Care-VDS (PC-VDS) of 137 patients with DSM-IV MDD, 59% had at least one current comorbid axis I disorder, anxiety disorders being the most common, 50% (GAD 20%, social phobia 16%, panic disorder 9% and simple phobia 9%), followed by substance use disorder (16%) and somatoform disorder (14%) (Vuorilehto et al., 2005).

The reported prevalence of comorbid personality disorders of MDD patients in psychiatric settings has varied widely (18%-86%): overall, about half of the patients have had a current personality disorder (Melartin et al., 2002). In the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) study of 859 outpatients, 51.3% with a current DSM-IV MDD had at least one personality disorder, cluster C disorders being the most common (27.3%), especially avoidant personality disorder (20.3%), followed by cluster B (14.1%) and cluster A (7.3%) (Zimmerman et al., 2005). In VDS, 44% of patients with current MDD had at least one personality disorder, cluster C personality disorders being the most common (32%), followed by cluster A (19%) and B (14%) personality disorders (Melartin et al., 2002). There have been some differences in the prevalences of personality disorders between primary care and psychiatric care patients. In PC-VDS, 58%

of DSM-IV MDD patients had a comorbid axis II disorder, cluster B (35%) and C (35%) personality disorders being the most common, followed by cluster A (7%) personality disorder (Vuorilehto et al. 2005). There are a few studies of the long-term stability of personality disorders. In a study of 142 outpatients with MDD, the 10-year stability of categorical personality disorder diagnosis was found to be relatively poor and not higher than that for anxiety disorders (Durbin and Klein, 2006). However, the relative stability of personality disorder dimensional scores was greater than that for categorical diagnosis, generally reaching a moderate level, and approached the long-term stability of normal-range personality traits. The findings from the VDS (Melartin et al., 2010) have been similar: the categorical stability of concurrent personality disorder diagnoses assigned when depressed was relatively poor, but the dimensional stability was moderate.

4.7 Course and outcome of major depressive episode (MDE)

4.7.1 Methodological aspects in defining outcome

The lack of a standard and valid set of outcome definitions has affected the study of the naturalistic course of depressive disorders (Frank et al., 1991; Prien et al., 1991; Keller, 2003; Keller, 2004). Descriptors for the clinical course of depressive illness, concepts such as remission, relapse and recurrence have been incoherently used as measures of outcome. The inconsistencies in definitions of outcome make the comparison and interpretation of the findings difficult. The first effort to achieve a terminology consensus was made by Frank et al., who suggested conceptual definitions for MDD outcome (Frank et al., 1991). Unfortunately, partly because of incompatible and changing lengths of duration used for remission and recovery in these criteria, they somewhat failed to achieve consistency (Keller, 2003). Clinical experience indicates that remission is the optimal outcome of treatment (Keller, 2003; Keller, 2004), and it has been proposed that remission should optimally be a completely asymptomatic state, with absence of both symptoms and functional impairment (Keller, 2003).

This standard for remission seems essential because the presence of residual symptoms is considered a strong predictor of relapse or recurrence (Ramana et al., 1995; Judd et al., 1998; Judd et al., 1999; Pintor et al., 2004), a more chronic course of depression (Judd et al., 2000), shorter time between episodes (Judd et al., 1998), decreased likelihood of recovery (Keller et al., 1992), and impaired social functioning (Kennedy and Paykel, 2004). Thus, the presence of even minimal residual symptoms may warrant continuation of treatment. By some standards, however, patients may be considered to be in remission despite one or two minor symptoms (Keller et al., 1982; Keller et al., 1983; Keller et al., 1992). A broadening of the concept of remission beyond symptom levels to include assessments of functioning and quality of life has been suggested (Zimmerman et al., 2008).

Many studies have reported only a cross-sectional outcome of depression i.e. reported the status of the patient at the end of the follow-up period, thus ignoring relapses and recurrences during the follow-up. This limitation has been overcome in some studies on psychiatric patient populations, such as the NIMH-CDS (Keller et al., 1987) with the use of life-chart methodology, based on multiple assessments during the longitudinal course of psychiatric disorders in sufficient detail to provide the basis for calculating length of episodes and time to remission. In this thesis the criteria of DSM-IV are used: in *full remission*, during the past 2 months, no significant signs or symptoms of MDD are present, in *partial remission* symptoms of MDD are present but the full criteria are not met, or there is a period without any significant symptoms of MDD lasting less than 2 months from the end of MDE, *relapse* refers to the return of symptoms fulfilling MDE criteria after a period of more than two weeks but less than two months with symptoms below the MDE threshold, and *recurrence* refers to the return of MDE after at least two consecutive months of partial or full remission.

4.7.2 Duration of MDE in general populations

Kraepelin speculated that left untreated, major depressive episodes would tend to last about 6 to 8 months in most cases (Kraepelin, 1921). Subsequent reports have generally supported this assertion (Shobe and Brion, 1971; Angst, 1986; Posternak et al., 2006). Studies on general populations (Sargeant et al., 1990; Angst and Merikangas, 1997; Eaton et al., 1997; Spijker et al., 2002) show a somewhat better prognosis than in psychiatric care. In population surveys (ECA, NEMESIS, NCS-R) half of all MDEs resolved rapidly in two to four months (Eaton et al., 1997; Spijker et al., 2002; Kessler et al., 2003) or even faster (Hämäläinen et al., 2008), but in about one-fifth of all subjects with MDD, the course was chronic (Spijker et al., 2002). On the other hand, among incident cases of MDD in a twin study, Kendler found that 98% of episodes resolved within one year (Kendler et al., 1997). The duration of MDEs has been in clinical studies mostly closer to the top of the range (Keller et al., 1982; Keller et al., 1992; Coryell et al., 1994a; Angst and Preisig, 1995; Solomon et al., 1997; Furukawa et al., 2000; Kennedy et al., 2003).

4.7.3 Outcome of MDD

The outcome of MDD can be examined from different indicators: recovery or achieving full remission, recurrence, or time spent in symptom states of major depressive episode (MDE) or partial remission. On the basis of available studies of its outcome, MDD appears to be a chronic illness with a high risk of recurrence over an individual's lifetime. The long-term rates of achieving full remission have been found to vary between 80% and 92% (Keller et al., 1992; Thornicroft and Sartorius, 1993; Eaton et al., 1997; Kanai et al., 2003; Kennedy et al., 2003) and the long-term risk of recurrence between 58% and 95% (Lee and Murray, 1988; Maj et al., 1992; Surtees and Barkley, 1994; Mueller et al., 1999; Kanai

et al., 2003; Kennedy et al., 2003). It seems that approximately 80% (between 58% and 95%) of people experiencing MDE will have at least one more episode during their lifetime (Angst, 1986; Lee and Murray, 1988; Maj et al., 1992; Surtees and Barkley, 1994; Mueller et al., 1999; Kanai et al., 2003; Kennedy et al., 2003), and about 20% will have a chronic course of MDE lasting over 2 years (Keller et al., 1992). Moreover, previous long-term studies have shown that symptoms at subsyndromal level are common and persist for many years after an episode of MDD (Angst et al., 1997; Judd et al., 1998), even with antidepressant treatment (Kennedy and Paykel, 2004). According to a recent review of subtreshold depression among older adults, subtreshold depression was at least 2-3 times more prevalent than major depression, was associated with significant adverse health outcomes, and approximately 8-10% developed to major depression per year (Meeks et al., 2010). However, the long-term rates of achieving full remission of an individual depressive episode have been high, between 80% and 92% (Keller et al., 1992; Thornicroft and Sartorius, 1993; Eaton et al., 1997; Kanai et al., 2003; Kennedy et al., 2003), and even after lengthy periods of illness, a significant proportion of patients have been observed to approach remission (Mueller et al., 1996; Brodaty et al., 2001). The risk of recurrence seems to increase with each successive recurrence and to decrease with longer durations of recovery (Keller et al., 1992). A recent review of prevalence of recurrence in clinical settings, concluded as recurrence rates of MDD after 5 years 60%, after 10 years 67% and after 15 years 85% which were much higher than in the general population (35% after 15 years) (Hardeveld et al., 2010).

There are many aspects in the previous studies on long-term outcome that make the generalizability more difficult: the majority of studies are mostly among inpatients, from tertiary-level treatment centres or university hospitals, and the patients are likely to have undergone many prior treatments which may produce bias towards more chronic, severe and recurrent illnesses compared with more unselected cohorts of MDD patients. In addition, studies have used different diagnostic criteria, are mostly from an era with availability of only tricyclic antidepressants, lack of recommendations for widespread continuation and maintenance phase treatments, have different definitions of outcome, or have not used semistructured interviews or life-chart. Only a few studies have studied long-term outcome among outpatients. Furthermore, the effect of comorbidity on the long-term outcome of MDD has been studied in a surprisingly smaal number of cases. When investigated, the reported prevalences of comorbid disorders appear too low to be credible from the current perspective (Keller et al., 1992; Kanai et al., 2003). Table 1 lists major studies which have investigated the long-term outcome of MDD in psychiatric patients. Of these six out of thirteen studies have studied exclusively inpatients and four out of thirteen mainly inpatients. Of the 2719 patients included in these cohorts only 31% are outpatients. Of the thirteen studies only six studies (comprising overall 41% of the 2719 patients) have been conducted during the era of SSRIs; in some of the other studies SSRIs became available only after several years of initial follow-up. Thus, the length of depressive episode and rate of recurrence can be expected to vary by the level

of treatment setting and inpatient or outpatient status. Overall, whether the general view of long-term outcome is also true for community psychiatric samples warrants investigation.

Table 1. Long-term outcome studies among psychiatric patients.

Study	Author(s)	Year of intake	Reported follow-up	N at baseline	Outpatients/ inpatients	Semistructured interviews	Comorbid mental disorders systematically diagnosed	Diagnostic criteria	Life chart
Zürich follow-up study	Angst, 1978	1959-63	40 years	203	Inpatients	No	No	ICD-8, DSM-III in follow-up	No
Sydney, Australia	Kiloh, 1972	1966-70	25 years	145	Inpatients	SADS (short form)	No	ICD-8	No
WHO Collaborative Study	Sartorius et al. 1980	1972	11 years	573	62.8% inpatients	WHO/SADD	No	ICD-9	No
Maudsley hospital, England	Lee and Murray, 1988	1965-66	18 years	89	Inpatients	SADS-L	No	ICD-7, RDC in follow-up	No
Edinburgh Study	Surtees and Barkley, 1994	1976	12 years	80	Inpatients	No	No	ICD-8, RDC in follow-up	Yes
NIMH-CDS	Keller et al.,1983	1978-81	20 years	431	77% inpatients	SADS	No	RDC	Yes
Napels/Italy	Maj et al., 1992	1982-83	5.5 years	72	62.5% inpatients	SADS-L	No	RDC	Yes
University of Colorado, USA	Ilardi et al., 1997	1987-1991	7 years	50	Inpatients	DIS, PDE	Axis II	DSM-III-R	Yes
Cambridge study	Ramana et al., Paykel et al., 1995	1990-92	11 years	70	76% inpatients	CID, SADS-L in follow-up	No	RDC, DSM-III-R, ICD-10 in follow-up	Yes
GLADS, Japan	Furukawa et al., 2000	1992-95	10 years	95	85% Outpatients	PISA, COALA	No	DSM-IV	Yes
Suffolk County Mental Health Project (SCMHP)	Naz et al., 2007	1989-1995	4 years	60	Inpatients	SCID	Axis I	DSM-III-R	Yes
Barcelona, Spain	Pintor et al., 2003	1991-96	4 years	183	Outpatients	SCID	No	DSM-III-R	No
Collaborative Longitudinal Personality Disorders Study (CLPS)	Grilo et al., 2010	1996	6 years	668	43% outpatients, 12% inpatients	SCID	Axis I and II	DSM-IV	Yes

4.7.3.1 Clinical factors as predictors of outcome

Preventing chronicity and recurrence of depressive episodes is the central aim of treatment, and information on risk factors for chronicity and recurrences is important for identifying patients at particularly high risk. A longer time to remission or non-recovery have been predicted by severity of MDE, and longer durations of index episode (Keller et al., 1984; Coryell et al., 1992; Keller et al., 1992; Ramana et al., 1995; Mueller et al., 1996) and *relapse or recurrence* by number of prior MDEs, and longer duration of MDE (Coryell et al., 1992; Maj et al., 1992; Surtees and Barkley, 1994; Ilardi et al., 1997; Mueller et al., 1999). Severity of depression has either predicted relapse or recurrence (Ramana et al., 1995; Kennedy et al., 2003; Melartin et al., 2004b) or not (Keller et al., 1983; Sherrington et al., 2001), and has been considered a risk factor for partial remission (Judd et al., 1998; Kanai et al., 2003). Individual studies have identified some additional risk factors for poor outcome, including female gender (Kennedy et al., 2004), younger (Eaton et al., 1997) or older age (Surtees and Barkley, 1994), endogenous or melancholic depression (Kiloh et al., 1988), psychotic symptoms (Lee and Murray, 1988), neuroticism (Grilo et al., 2010), psychosocial impairment (Solomon et al., 2004), and lack of self-confidence (Surtees and Wainwright, 1996). High neuroticism (Surtees and Wainwright, 1996; Gormley et al., 1999; Bock et al., 2010) and low self-esteem (Andrew et al., 1993; Surtees and Wainwright, 1996; Sherrington et al., 2001) have also been related to longer durations of MDE. The presence of residual symptoms or partial remission is further considered a strong predictor of relapse or recurrence (Paykel et al., 1995; Judd et al., 1998; Judd et al., 1999; Nierenberg et al., 2010), a more chronic course of depression (Judd et al., 2000), shorter time between episodes (Judd et al., 1998), a decreased likelihood of recovery (Keller et al., 1992), and impaired social functioning (Kennedy and Paykel, 2004). A recent review of prevalence of recurrence in clinical settings, concluded that the number of previous MDEs and subclinical residual symptoms to be the most important predictors for recurrence (Hardeveld et al., 2010).

4.7.3.2 Comorbidity as a predictor of outcome

Despite comorbid MDD being common (Kessler et al., 1996b; Melartin et al., 2002; Zimmerman et al., 2002), the effect of comorbidity on long-term outcome of MDD has been studied in a surprisingly small number of cases. There is also relatively little information on current axis I comorbidity and the risk of relapse/recurrence in clinical cohorts of depressive patients. In the few studies, comorbid dysthymia (double depression), and Axis I comorbid disorders have been associated with longer time to remission or non-recovery (Keller et al., 1982; Keller et al., 1992; Mueller et al., 1996) and the probability of *relapse or recurrence* with comorbid anxiety syndromes, and axis II disorders (Coryell et al., 1992; Maj et al., 1992; Surtees and Barkley, 1994; Ilardi et al., 1997; Mueller et al., 1999; Grilo et al., 2010). Depressed patients with panic disorder or with higher symptom ratings

of anxiety have shown a longer time to recovery (Coryell et al., 1988; Clayton et al., 1991; Parker et al., 2000). The US National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS) found some anxiety syndromes, but not current alcoholism, to be associated with higher risk of relapse (Coryell et al., 1992; Mueller et al., 1994). CDS is the only study to have investigated the effects of current comorbid alcoholism among patients with MDD, finding those with current alcoholism to be only half as likely to recover from their MDE (Mueller et al., 1994).

In a few naturalistic outcome studies in which semistructured interviews for both MDD and axis II disorders were used, personality disorders predicted longer time to remission (Sato et al., 1993; Greenberg et al., 1995; Ilardi et al., 1997; Viinamäki et al., 2002; Viinamäki et al., 2003; Bock et al., 2010), and risk of relapse (Alnaes and Torgersen, 1997; Ilardi et al., 1997; Grilo et al., 2010). Overall, the available evidence on the effects of current comorbidity on the outcome of MDD in clinical cohorts is somewhat difficult to interpret because of several methodological limitations. These include not using semi/structured interviews for both MDD and comorbid disorders, or not controlling for the effects of additional comorbid disorders, or not using life-chart methodology (and thus reporting only cross-sectional findings). A recent review of personality pathology and outcome in MDD, while pointing out many methodological problems in measurements, suggests that comorbid personality pathology should not be seen as an impediment to good treatment response (Mulder, 2002). Although comorbidity in MDD is prevalent, the effect of overall comorbidity on the length of episode or risk of recurrence has not been systematically and comprehensively investigated.

4.7.3.3 Psychosocial factors as predictors of outcome

The influence of adverse events on the outcome of depression has been unclear, despite evidence on precipitating depressive episodes together with genetic vulnerability and temperament factors (Kendler et al., 1993; Kendler et al., 2002; Kendler et al., 2004). Stressful life events and a lack of social support are associated with worse outcomes of depression in community studies and some clinical studies (Coryell et al., 1988; Paykel, 1994), while most prospective studies of severe and recurrent depression have found little effect on time to remission or subsequent relapse (Andrew et al., 1993; Paykel, 1994; Sherrington et al., 2001). Adverse events before the onset of a depressive episode have also predicted even better outcomes in some studies (Reno and Halaris, 1990; Monroe and Depue, 1991) possibly due to more reactive nature of depression. The role of adverse life events has been less significant among patients with severe depression (Andrew et al., 1993; Paykel et al., 1996; Sherrington et al., 2001). However, different kinds of patient samples, and methods of measurement makes comparison between investigations difficult. Adversities exerting their influence after the onset of depression may predict long-term outcome more effectively. In a long-term study, the presence of stressful circumstances predicted less improvement in depression (Swindle et al., 1989). Poor social support after

the onset of depression has predicted a worse outcome for MDD, and the presence of more supportive social resources has predicted more improvement in depression (Billings and Moos, 1985; Swindle et al., 1989). In addition, being more independent, having less conflicts, and supportive friends and activities, has predicted a more stable remission (Moos et al., 1998), while having fewer closer relationships has predicted partial or non-remission (Cronkite et al., 1998). However, social support has been less significant on outcome among patients with severe depression (Sherrington et al., 2001). In VDS, the medium-term outcome was significantly influenced by adverse life events and social support especially for patients currently in full remission (Leskelä et al., 2006).

4.7.4 Suicidal behaviour

4.7.4.1 Classification of suicidal behaviour

The concept of suicidal behaviour ranges from suicidal ideation to suicide attempts and completed suicide and it may vary with respect to manifestation, performance, seriousness and lethality (Beck, 1986). *Suicidal ideation* is usually defined as thoughts and wishes of suicide in individuals who have not made any overt suicide attempts (Beck, 1986), and 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 of suicide (Brown et al., 2005). *Suicide attempt* is defined by the American Psychiatric Association as a self-injurious behaviour with a non-fatal outcome accompanied by evidence (either explicit or implicit) that the person intended to die, where intent is defined as subjective expectation and desire for a self-destructive act to end in death (APA, 2003). Also other terms have been used instead of suicide attempt, such as deliberate self-harm in the U.K. *Suicide* is defined as a self-inflicted death with evidence (either explicit or implicit) that the person intended to die (APA, 2003). There has been debate on whether those attempting suicide and those completing, present a single or two separate populations (Linehan, 1986; Beautrais, 2001). It seems that they are overlapping populations, and the three types of suicidal behaviour – suicidal ideation, suicide attempt and completed suicide, can be seen as a continuum of self-harming behaviours (Beck et al., 1973).

4.7.4.2 Stress-diathesis model

Although suicidal behaviour is episodic and most likely occurs when a person is in major depressive episode and not when they are in remission, not all people who suffer from recurrent depression become suicidal, and some suicidal behaviour occurs in individuals who are not clinically depressed. Thus, a psychiatric disorder is generally a necessary, but insufficient condition for suicide. Mann et al. (1999) proposed a paradigmatic stress-diathesis model in which the risk for suicidal acts is not determined merely by a psychiatric illness (the stressor) but also by a diathesis. They wanted to develop a model

to help determine who remains vulnerable, despite seeming to have recovered, and to what extent this underlying vulnerability is associated with the acute suicidal state, i.e. conceptualize suicidal acts as the outcome of the balance between trait- and state-related predisposing and protective factors. The diathesis may be reflected in the tendencies to experience more suicidal ideation and to be more impulsive and thus being more likely to act on suicidal feelings. In their study Mann et al. (1999) found that a trait factor, such as aggression or impulsivity, was significant in distinguishing past suicide attempters from non-attempters (Mann et al., 1999). This categorized individuals at risk from suicide attempts regardless of psychiatric diagnosis. Their model showed that subjective depression, hopelessness and suicidal ideation were greater in suicide attempters than in non-attempters despite comparable rates of objective severity for depression or psychosis. One stressor is normally the onset or acute worsening of a psychiatric disorder, but other types of stressors, such as a psychosocial crisis, can also contribute. The diathesis for suicidal behaviour includes a combination of factors such as sex, religion, familial and genetic components, childhood experiences, psychological support system, availability of highly lethal suicide methods, substance abuse, head injury and various other factors (Mann, 2002; Mann et al., 2008). However, although the stress-diathesis model is a valid conceptual framework, it has one significant limitation – it does not account for the role of time. However, we know that major depression is a time-varying illness with besides depressive episodes, also periods of partial and full remission, which are likely to be associated with different amounts of risk for suicide behavior.

4.7.4.3 Epidemiology and risk factors of suicidal ideation

Suicidal thoughts are common; approximately 11-18% in population samples across Western countries report having suicidal ideation at some point during their lives (Weissman et al., 1999). However, huge differences exist worldwide in reported prevalence rates across countries: from 3% to 25% of population have experienced suicidal ideation and from 1% to 16% made suicide plans (Weissman et al., 1999; Bertolote et al., 2005; Bernal et al., 2007). Some of the differences across the sites are most probably affected, besides the various ways of asking about suicidal ideation, by the differences in the readiness of respondents from different cultures to report suicidal thoughts (Bertolote et al., 2005). In the U.S., large population surveys (NCS, NCS-R) reported 12-month prevalence of suicidal ideation at around 3% and of suicide plans around 1% (Kessler et al., 2005a). In a Finnish study the 12-month prevalence was much higher, 15%, and contrary to most other countries, the prevalence was higher in men than in women (Hintikka et al., 2001).

Suicidal thoughts in clinical patient samples are more frequent than in the general population. While depression is a major risk factor for suicidal ideation, it is not unexpected that among patients with MDD, more than a half in psychiatric settings (Sokero et al., 2003) and a third in primary care have reported suicidal ideation (Ahrens et al.,

2000). However, about half of individuals with suicidal thoughts do not perceive the need for care, and many of those who do experience difficulties in receiving it (Brook et al., 2006).

The most consistently identified risk factors of suicidal ideation have been depression and hopelessness (Hintikka et al., 2001; Casey et al., 2006). In addition, suicidal ideation has been associated with younger age, female gender and a low level of education (Kessler et al., 2005a; Bernal et al., 2007). Getting older and having meaningful social relations have acted as protective features (Casey et al., 2006). Other reported risk factors consist of severe depression, and co-morbid dysthymia, anxiety and personality disorders (Van Gastel et al., 1997; Hintikka et al., 1998; Alexopoulos et al., 1999; Schaffer et al., 2000), as well as female gender, younger age and severe adverse life events (Schaffer et al., 2000; Monroe et al., 2001; Casey et al., 2006). Previous suicide attempts have also predicted suicidal ideation (Alexopoulos et al., 1999). In VDS, independent risk factors for suicide ideation have been hopelessness, alcohol problems, low level of social and occupational functioning and poorly received social support among psychiatric in- and outpatients with MDD (Sokero et al., 2003).

4.7.4.4 Epidemiology of suicide attempts

A suicide attempt, especially if it is followed by death, is the worst complication of depression. Most countries do not have official suicide attempt rates available. The WHO/EURO Multicentre Project on Parasuicide gathered comparable information in 13 European countries in 1989-1992, and found the highest rate of suicide attempts to be in Finland among males and the lowest in Spain representing a 7-fold difference (Schmidtke et al., 1996). Around the world even higher variations across nations has been reported (from 0.4% to 4.2%) (Bertolote et al., 2005). Part of this variation may be explained by different cultural attitudes towards suicidal behaviour and by the willingness to report suicide attempts (Schmidtke et al., 1996). Depending on the site, the ratios between attempts, plans and thoughts of suicide seem to differ substantially and the burden of undetected attempted suicide is high in many cultures (Bertolote et al., 2005). In the WHO/EURO Multicentre Project on Parasuicide more than half of the suicide attempters made more than one attempt, and nearly a fifth of the second attempts were within 12 months of the first attempt (Schmidtke et al., 1996). Nearly all suicide attempters have suffered from one or more psychiatric disorder (Suominen et al., 1996; Kessler et al., 2005a). In the WHO/EURO Multicentre Project on Parasuicide, with only one exception (Helsinki), suicide attempt rates were higher among women than men. In the majority of centres, the highest rates were found in the younger age groups. Risk for suicide attempts has also been related to being divorced or widowed, and to low educational levels (Kessler et al., 1999a).

4.7.4.5 Suicide attempts in patients with MDD

The lifetime risk of a non-fatal suicide attempt in MDD is estimated at 16-40% (Malone et al., 1995a; Oquendo et al., 2006). Of individuals with a lifetime diagnosis of MDD, 16% acknowledged having attempted suicide at some point in their lifetime in the ECA survey (Chen and Dilsaver, 1996); the first suicide attempt seems to occur within 5 years from the onset of MDD in 40% of patients with depression (Malone et al., 1995a). One-fourth may repeat the attempt within a year (Bradvik, 2003).

According to studies investigating suicide attempts, the risk factors have included a history of suicide attempt or suicide in the family (Duggan et al., 1991; Malone et al., 1995a; Mann et al., 1999; Maser et al., 2002; Oquendo et al., 2002; Oquendo et al., 2004; Sokero et al., 2005), female gender (Mann et al., 1999; Oquendo et al., 2007), younger age (Sokero et al., 2003; Oquendo et al., 2004), presence of MDE (Oquendo et al., 2002), early age at onset (Malone et al., 1995a), severe or recurrent depression, or failure to achieve remission (Oquendo et al., 2002; Sokero et al., 2005), hopelessness (Mann et al., 1999; Maser et al., 2002; Oquendo et al., 2004), suicidal ideation (Mann et al., 1999; Oquendo et al., 2004; Mann et al., 2008), melancholic (Oquendo et al., 2006), or psychotic subtype of depression (Warman et al., 2004; Oquendo et al., 2006), comorbid personality disorder (especially borderline) (Mann et al., 1999; Hawton et al., 2003a), alcohol dependence or misuse (Duggan et al., 1991; Malone et al., 1995a; Mann et al., 1999; Maser et al., 2002; Sokero et al., 2003; Oquendo et al., 2004), chronic physical illness (Duggan et al., 1991), aggressive or impulsive traits (Malone et al., 1995a; Mann et al., 1999; Maser et al., 2002; Oquendo et al., 2004; Mann et al., 2008), cigarette smoking (Mann et al., 1999; Oquendo et al., 2004), and social factors (Malone et al., 1995a; Mann et al., 1999; Malone et al., 2000; Sokero et al., 2003; Sokero et al., 2005). Sokero et al. investigated medium term longitudinal variations in the risk for suicide attempts among psychiatric patients with major depressive disorders (Sokero et al., 2005). The risk of attempts was almost 8-fold during major depressive episodes compared with a period of full remission, and they were effectively predicted by time spent depressed, history of previous suicide attempts, and the lack of a partner.

Despite its clinical importance, not all depressed patients at the time of the suicide attempt are receiving treatment or adequate pharmacotherapy (Oquendo et al., 2002). Haw et al. (2002) found that one-third of attempters were receiving treatment for depression in psychiatric services and another in primary care (Haw et al., 2002). In a Finnish study the majority of elderly suicide attempters had had recent contact with primary care, but their mood disorders had often remained undiagnosed before the attempt (Suominen et al., 2004a). Even in psychiatric hospitals a fourth of clinicians may fail to document the history of suicidal behaviour in patients with MDD and past suicidal attempts (Malone et al., 1995b).

4.7.4.6 Epidemiology and risk factors of suicide

Suicide is among the leading causes of death, and suicide accounts for more deaths than the number due to HIV and AIDS combined, or due to homicide and war combined. Every year, almost one million people die 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 among the three leading causes of death among those aged 15-44 years in some countries, and the second leading cause of death in the 10-24 years age group; these figures do not include suicide attempts which are up to 20 times more frequent than completed suicides (WHO, 2010a). In Finland the suicide rate is among the highest in Europe (19.7/100 000 in 2004, 1033 suicides in 2008), although there has been a 30% decline during the past 15 years. In the U.S., for example, the suicide rate is 13.9/100 000 (2002) and in Sweden 13.4 /100 000 (2001). The highest annual suicide rates exist in Eastern Europe, especially in the Baltic countries and former Soviet republics (>27/100 000) and the lowest in Latin American and Islamic countries (<6.5/100 000). Men have a higher rate of completed suicide than women, the male to female ratio being approximately 3-4:1 (WHO, 2010b). Almost everywhere in the world, suicide rates among males are much higher than in female for all age groups (Schmidtke et al., 1996). As an exception, the suicide rates in China are higher among female compared to males (Weiyuan, 2009). As suicide acts are affected by culture, ethnicity and religion, the rates of suicide vary significantly among the various age groups, gender and different countries (De Leo, 2002; Oquendo et al., 2004b). In addition, the official rates depend on suicide legislation, the death certification procedures (Schmidtke et al., 1996) and the prevalence of undetermined deaths (Marusic et al., 2003).

The major obstacle to an understanding of suicide is that the victim cannot be interviewed and the reason directly ascertained. Psychological autopsy is probably the most direct technique for determining the relationship between particular risk factors and suicide (Isometsä, 2001; Cavanagh et al., 2003). *Psychiatric disorders*, present in nine out of ten suicide victims (Arsenault-Lapierre et al., 2004), are the most significant predictors of suicide risk (Cavanagh et al., 2003) especially when necessitating hospital admission (Bostwick and Pankratz, 2000; Mortensen et al., 2000; Pirkola et al., 2005b). Particularly vulnerable periods seem to occur during admission and soon after discharge (Mortensen et al., 2000). In the majority of suicides more than one psychiatric illness has been present, most frequently affective disorders especially among women and substance use disorders in men (Henriksson et al., 1993; Cheng et al., 2000; Cavanagh et al., 2003; Arsenault-Lapierre et al., 2004; Mann et al., 2006). *Medical illnesses* increase the risk for suicide (Koponen et al., 2007) especially in the elderly and in patients suffering from disorders of the central nervous system (Breslau et al., 1991). In other potentially fatal illnesses, such as cancer, the increase in risk is only modest unless a combined psychiatric disorder is present (Henriksson et al., 1995).

Hopelessness, defined as a state of negative expectations, is an important psychological variable of suicidal behaviour which is believed to mediate the association between depression and suicidal behaviour (Beck et al., 1993). Whether it leads to suicidal behaviour depends upon the presence or absence of risk and protective factors (Beck et al., 1993). *Psychosocial and other environmental factors* influencing the risk of suicidal death are male gender, advancing age (Hawton et al., 2003b), lack of a social network, recent adverse life events and socioeconomic difficulties (Cheng et al., 2000; Suokas et al., 2001). Other risk factors of suicide are *availability of lethal methods* such as domestic coal gas, barbiturates and firearms (Oliver, 1972; Kreitman, 1976; Wintemute, 1988), and *suicide stories of high publicity* (Hassan, 1995). *A family history of suicide* has been shown to increase the the risk for suicide in other family members (Brent et al., 1996; Cheng et al., 2000). *Past suicidal behaviour*, both ideation and attempts, are strong risk indicators for future suicide (Brown et al., 2000). Within the year following a suicide attempt, the risk of eventual death by suicide is about 100 times greater than that of the general population (Hawton, 1987). Suicides seem to accumulate even years after an attempt (Suominen et al., 2004b). It has been postulated that a lifetime history of suicide attempts can lower the threshold of new attempts and thus suicide related structures may become more easily triggered (Joiner and Rudd, 2000). It has to be remembered, however, that over half of suicide victims die at their first suicide attempt and thus, even if a suicide attempt is a powerful single predictor of completed suicide, its sensitivity as a risk factor is limited (Isometsä and Lönnqvist, 1998).

4.7.4.7 Suicide in patients with MDD

A highly quoted meta-analysis of Guze & Robins (1970) suggested that 15% of psychiatric patients with severe affective disorders will die due to suicide (Guze and Robins, 1970). Thereafter this high figure has been uncritically generalized to concern all depressive disorders and not until lately been debated and reassessed. Bostwick & Pankratz (2000) have demonstrated a hierarchy of risk based on the intensity of the treatment setting; they found a lifetime risk of 4.0% for suicide in their meta-analysis for affective disorder patients hospitalized without specification of suicidality (Bostwick and Pankratz, 2000). Furthermore, suicide mortality among depressed patients in primary care has been shown to be much lower than in psychiatric settings (Simon and VonKorff, 1998).

In patients with depression the risk factors for completed suicide tend to overlap the general risk factors for suicide attempt. Risk factors for completed suicide (Fawcett et al., 1990; Angst et al., 2002; Hansen et al., 2003; Hoyer et al., 2004; Coryell and Young, 2005; Dumais et al., 2005; Mann et al., 2005; Oquendo et al., 2006; Gonda et al., 2007; Oquendo et al., 2007) have been male gender, prior suicide behaviour, family history of

suicide, hopelessness, suicidal ideation, psychotic symptoms, comorbid personality disorders, alcohol dependence or misuse, and anxiety disorders, adverse events and previous psychiatric hospitalizations. Especially in depressive men, impulsive-aggressive personality and alcohol disorders may be independent risk factors (Dumais et al., 2005).

4.7.4.8 Prevention of suicidal behaviour

Though nearly 2% of those who harm themselves may die within the following year by committing suicide (Owens et al., 2002), the aftercare in medical emergency units appear varying and insufficient (Kapur et al., 1999): only about half of suicide attempters have received psychosocial assessment and in most studies only a few get admission to psychiatric services (Kapur et al., 1999; Suominen et al., 2004a). In a Finnish study, half of young suicide attempters were not given any health care contact in the month following their visit to the emergency unit (Suominen et al., 2004b), while most elderly suicide attempters were referred for aftercare mainly to psychiatric services (Suominen et al., 2004a). In addition, it has been reported that a minority of those offered medical care stayed in contact (Haw et al., 2002), and that most suicide attempters have not communicated their suicidal thoughts, even though the majority have had recent contact with the medical services (Houston et al., 2003). A recent Finnish study, investigated the associations between suicide risk, and different ways of organisizing mental-health services, and concluded that the prominence of outpatient services was associated with the lowest suicide rate compared to inpatient and emergency services (Pirkola et al., 2009).

To address the multiple causes of suicidal behaviour, prevention strategies usually involve a multifaceted approach with particular attention to mental health. Primary prevention of suicide requires focusing on preventive measures or protective factors such as restricting access to lethal methods (firearms, pesticides, toxic gas, barbiturates etc.), which is a major component of current international suicide prevention strategies (WHO, 2010a), the toning down of reporting of suicides in the media and public education campaigns to increase knowledge on mental illness and suicide (Mann et al., 2005). Secondary prevention options include early detection of suicidal individuals as well as accurate diagnosis and effective treatment of psychiatric disorders – another major component of international prevention strategies (WHO, 2010a). While more than half of those who die by committing suicide had recently contacted a primary care doctor (Luoma et al., 2002) detection of their suicidal intent might have been possible in some cases. However, in non-psychiatric patients with depression the suicidal intent has usually not been communicated to health care professionals and the depression has remained untreated (Isometsä et al., 1995).

Despite their importance for planning, the relative impact of various strategies on national suicide rates has been difficult to estimate. In a systematic review (Mann et al., 2005) physician education, means restriction and gatekeeper education have been the most promising interventions. Public education campaigns have increased knowledge and improved attitudes toward mental illness and suicide, but measures for suicide prevention have been insufficient (Mann et al., 2005). Studies examining suicidal behaviour in response to primary care physician education programmes, mostly targeting depression recognition and treatment in limited regions in Sweden, Hungary, and Japan (Rihmer et al., 1995; Oyama et al., 2006; Szanto et al., 2007), have all reported an increased prescription rate of antidepressants and often a decline in suicide rates.

Despite the huge burden caused by suicide mortality, the number of national policies for preventing suicides is low; Finland was the first country worldwide to publish a national strategy of suicide prevention and an action plan for implementation in 1991. It was a part of the National Suicide Prevention Project, which was carried out from 1986 to 1996. The aim was to stop the increasing trend and decrease suicide mortality by 20% by the year 1995. During the first years the number of suicides increased, followed by a reduction of 20% between 1991 and 1996, since then the suicide rate has decreased steadily and the annual number of suicides has declined to below 1000 (Lönnqvist, 2007). However, Finland still has a relatively high suicide rate compared with other Western EU countries (Schmidtke, 1997), suicide being the leading cause of death in Finland among those under the age of 35 years (Tilastokeskus, 2009).

4.7.5 Switch to bipolar disorder

A number of patients who initially suffer from major depressive episode (MDE) will over time develop bipolar disorder, which has clinical consequences for both treatment and prognosis. Bipolar disorder begins in approximately half of cases (51-60%) with depression and in the other half with mania (34-79%); bipolar disorder type II begins more often with a depressive episode, while bipolar type I begins more often with a manic episode (Akiskal et al., 1985; Roy-Byrne et al., 1985; Tondo et al., 1998; Perugi et al., 2000; Mantere et al., 2004; Goodwin and Jamison, 2007).The first hypomanic or manic episode emerges after approximately 5 - 8 years from the onset of first MDE (Akiskal et al., 1983; Mantere et al., 2004) In two foremost studies, the Zürich follow-up study and the NIMH Collaborative Depression Study, 15.5% and 10.7% of subjects with unipolar MDD switched to bipolar disorder, and of these 7.2% and 3.9% to type I, and 8.25% and 8.6% to type II, respectively (Akiskal et al., 1995; Angst et al., 2005). The switch rates to types I or II have ranged from similar to 2.3-fold to type II, and the switch to type I has occurred twice faster compared to type II (Akiskal et al., 1995; Coryell et al., 1995; Goldberg et al., 2001; Angst et al., 2005). The annual rate of subsequent diagnostic switch from type

II to type I has been estimated to be about 2% (Angst et al., 2005) with a largest risk during the first 5 years from age at onset, or in childhood and early adulthood (approximately 3-5% per year), and thereafter being constant across the lifetime (approximately 1% per year).

4.7.5.1 Predictors of switch to bipolar disorder

The switch from MDD to bipolar disorder has been predicted by bipolar family history (Strober and Carlson, 1982b; Akiskal et al., 1983; Winokur et al., 1993; Angst and Preisig, 1995; Goldberg et al., 2001; Othmer et al., 2007), younger age (Akiskal et al., 1983; Winokur and Wesner, 1987), earlier age at onset (Akiskal et al., 1983; Winokur et al., 1993; Angst and Preisig, 1995; Othmer et al., 2007), higher severity of depression (Akiskal et al., 1995; Angst et al., 2005), psychotic depression (Strober and Carlson, 1982b; Akiskal et al., 1983; Weissman et al., 1984; Strober et al., 1993; Goldberg et al., 2001; Othmer et al., 2007), higher number of depressive episodes (Angst, 1985; Winokur and Wesner, 1987; Winokur et al., 1993; Angst and Preisig, 1995), atypical features of depression (Akiskal et al., 1983), pharmacological hypomania (Strober and Carlson, 1982a; Akiskal et al., 1983), postpartum episodes (Akiskal et al., 1983), and psychiatric hospitalizations (Winokur and Wesner, 1987). The predictors of diagnostic switch to bipolar disorder type I compared to type II haven been partly different, e.g. the switch to type I has been predicted by male gender (Angst et al., 2005), positive family history (Coryell et al., 1995), psychotic symptoms (Akiskal et al., 1995; Coryell et al., 1995; Angst et al., 2005), and severity and acuteness of symptoms (Akiskal et al., 1995; Angst et al., 2005); while the switch to type II has been predicted by female gender (Baldassano et al., 2005), younger age (Coryell et al., 1995), early (Akiskal et al., 1995; Coryell et al., 1995; Benazzi, 2007) or later (Angst et al., 2005) age at onset, atypical or mixed depressive symptoms (Benazzi, 2007), chronicity of index episode (Coryell et al., 1995), shorter well intervals (Akiskal et al., 1995), and mood lability (Akiskal et al., 1995; Benazzi and Akiskal, 2005).

A number of methodological limitations exist in studies on diagnostic switch making the diagnostics of especially hypomanic episodes more uncertain. Only a few studies have investigated bipolar switch among outpatients (Akiskal et al., 1983; Othmer et al., 2007). Studies showing the highest estimates of manic onset have used first hospitalization as the onset criterion, which may lead to underestimation of bipolar disorder type II as hypomanic and depressive states have required less frequently hospitalization (Goodwin and Jamison, 2007). The majority have also been from tertiary-care studies from major universities, which makes the epidemiological generalizability of these findings more uncertain, especially regarding bipolar type II (Strober and Carlson, 1982a; Winokur and Wesner, 1987; Coryell et al., 1995; Goldberg et al., 2001; Angst et al., 2005; Othmer et al., 2007). In addition, only a few studies have used life-chart methods (Akiskal et al.,

1995; Coryell et al., 1995), possibly leading to onsets of bipolar II being missed due to lack of information on hypomanic episodes. Furthermore, few prospective studies have investigated the role of psychiatric comorbidity in predicting diagnostic switch, and an overall view of axis I and II disorders in predicting switch is missing. The diagnostic criteria have changed over time especially regarding DSM-IV criteria of bipolar disorder type II; thus, some type II disorders might have been earlier diagnosed as MDD. Since switching is relatively uncommon, the follow-up periods should be long in order to achieve adequate statistical power to detect significant differences.

4.8 Treatment of MDD

In order to improve the detection and treatment of MDD, several sets of evidence-based treatment guidelines have been published during the last decade. These guidelines cover the basics and objectives for the management of depression with various regimes, including pharmacotherapy, psychotherapy, combination of pharmaco- and psychotherapy, electroconvulsive therapy (ECT) and bright light therapy (Cohen and Guthrie, 1997; Schulberg et al., 1998; Crismon et al., 1999; APA, 2000b; Bauer et al., 2002a; Bauer et al., 2002b; NICE, 2004; Fochtmann and Gelenberg, 2005; Anderson et al., 2008; Suehs et al., 2008; NICE, 2009; Patten et al., 2009; Suomen Psykiatriyhdistys, 2009). Other treatments that have been used for MDD are among others exercise (Ernst et al., 2006) and sleep deprivation (Wirz-Justice, 2006). There exists some variation in the recommendations; the main treatment modalities in all of them, however, consist of pharmacotherapy, psychotherapy and electroconvulsive therapy. The most used treatments for MDD in Finland are antidepressant treatment with or without augmenting and adjunctive medications; psychotherapy and ECT.

4.8.1 Antidepressant treatment

Adequate antidepressant treatment of MDD consists of an acute phase, during which remission is induced, a continuation phase, during which remission is preserved, and a maintenance phase, during which the vulnerable patient is protected against recurrence of subsequent episodes (APA, 2000b; Suomen Psykiatriyhdistys, 2009). The more severe the depression is, the more important the antidepressants are for the treatment of MDD. In severe or psychotic depression antidepressant treatment is always indicated, whereas in mild or moderate cases of depression, effective psychotherapy can be used alone or combined with pharmacotherapy. In psychotic depression, the combination of antidepressants and antipsychotics is recommended (Suomen Psykiatriyhdistys, 2009). The NICE guideline from UK does not recommend antidepressants for mild depression, unless other treatments have failed (NICE, 2009). The response to treatment and adverse events vary individually, and there are some differences in the efficacy and tolerability between different

antidepressants. A multiple treatments meta-analysis investigated 12 new-generation drugs, and reported mirtazapine, escitalopram, venlafaxine, and sertraline to be significantly more efficacious compared to others, and escitalopram and sertraline showing the best profile of acceptability (Cipriani et al., 2009). The choice of medication depends on the history of responses to medication, medication tolerability, adverse effects and likelihood of adherence, concurrent with other medical conditions and drug therapies and also the cost of medication (Suomen Psykiatriyhdistys, 2009). If full remission is not achieved or the response is only partial, the dosage should normally be increased until full remission is achieved or maximum dosage reached. If however, the patient is experiencing significant adverse effects or the response is still inadequate, a switch to another antidepressant should be performed (Suomen Psykiatriyhdistys, 2009).

In the STAR-D study (National Institute of Mental Health) of 2876 out-patients, 37% remitted after the first antidepressant, 50% after two treatment steps and the theoretical cumulative remission rate after four active treatment steps during 8 months was 67% (Rush et al., 2006). An association between treatment response and marker alleles of e.g. the GRIK4 (Paddock et al., 2007) and 5-HTR2A (McMahon et al., 2006) has been detected, indicating that the individual variation in antidepressant treatment outcome seems to have at least a partial genetic basis. Approximately 2/3 of MDD patients respond to antidepressant medication and about half will be nearly symptom free after 6 to 8 weeks treatment (Suomen Psykiatriyhdistys, 2009). The continuation phase should generally last 3 to 9 months after the induction of remission in order to prevent relapses, and after that, maintenance phase treatment should be considered after 3 or more lifetime episodes to prevent recurrences, or sooner if the depressive episodes have been particularly severe (APA, 2000b; Suomen Psykiatriyhdistys, 2009). The factors that influence the decision whether to use maintenance phase treatment include severity of the episodes (presence of suicidality, severe functional impairments and psychotic features), the risk of recurrence (residual symptoms between episodes, the presence of comorbid conditions and the number of prior episodes), possible side effects and patient preference (APA, 2000b).

4.8.2 Psychosocial treatment

Psychosocial treatment consists of specific psychotherapy and social support. This treatment should be considered regularly when substantial psychosocial stressors, interpersonal difficulties, or coexisting developmental or personality disorders are present (APA, 2000b). Specific psychotherapies that are used in the treatment of MDD include cognitive and cognitive-behavioural therapy, interpersonal psychotherapy, brief psychodynamic psychotherapy and certain problem-solving therapies (Roth and Fonagy, 2005). In the acute phase treatment of mild or moderate depression, psychotherapy can be used alone or in combination with antidepressants. In the continuation and maintenance phase treatment, psychotherapy alone or in combination with antidepressants may reduce the risk of a relapse or recurrence (APA, 2000b; Nierenberg et al., 2003; Suomen Psykiatriyhdistys,

2009). The frequency of visits usually decreases in the maintenance phase (APA, 2000b; Suomen Psykiatriyhdistys, 2009). The Canadian CANMAT guideline states that cognitive therapy, cognitive behavioural therapy (CBT), and interpersonal therapy (IPT) have efficacies equivalent to that of antidepressants for first-line treatment of mild or moderate depression (Patten et al., 2009).

The combination of psychotherapy and medication is recommended for those with psychosocial/interpersonal problems, or comorbid axis II disorder together with moderate to severe MDD. The APA guidelines advise psychotherapy or antidepressant monotherapy, depending on patient preference, but combination treatment if the patient has a history of partial response to a single mode of treatment (APA, 2000b). A systematic review concluded that combined antidepressant therapy and psychosocial treatment is associated with a higher improvement rate than pharmacotherapy alone (Pampallona et al., 2004).

4.8.3 Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) was developed 70 years ago and since then it has been used as a treatment for mental disorders. It has been found to be effective treatment for severe and psychotic depression and should be considered for MDD patients who have medication resistance or when rapid relief of depressive symptoms is needed e.g. severe suicidality (Suomen Psykiatriyhdistys, 2009). Response rates of 80% or higher have been reported with ECT although there are few comparisons between ECT and first-line antidepressants (Kennedy et al., 2009). Evidence exists that ECT is effective for all subtypes of MDD, but may be especially effective for psychotic depression (Petrides et al., 2001) and depression with prominent suicidal ideation (Kellner et al., 2005). A report from the Consortium for Research of ECT (CORE) concluded that antidepressant medication treatment failure does not predict a lower response to ECT (Rasmussen et al., 2007). In a review and meta-analysis on the efficacy of ECT, it was concluded that ECT is an effective short-term treatment for depression, and is probably more effective than drug therapy; bilateral ECT being moderately more effective than unilateral, and high dose ECT more effective than low dose therapy (The UK ECT review group, 2006).

4.8.4 Other treatment methods

New treatments for MDD being evaluated include other neurostimulation therapies, repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS) and vagal nerve stimulation (VNS) (Eitan and Lerer, 2006; Ressler and Mayberg, 2007; Kennedy et al., 2009). Of these, rTMS is a safe treatment method with minimal adverse effects with an efficacy resembling that of antidepressant medication (Gross et al., 2007). Evidence to support VNS is less robust, and deep brain stimulation DBS is still an investigational

treatment (Kennedy et al., 2009). Other targets for future agents include N-methyl-D-aspartate (NMDA) antagonist ketamine (Machado-Vieira et al., 2009), neuropeptide Y, vasopressin V1b, nicotinic cholinergic, delta-opiate, dopamine D1, cytokine, and corticotrophin-releasing factor 1 receptors, as well as, GABA, intracellular messenger systems, and transcription, neuroprotective and neurogenic factors (Manji et al., 2003; Mann, 2005).

4.8.5 The realization of treatment

Despite of the high prevalence of MDD, a large proportion of depressed patients are still out of treatment. In Finland, the Mini Finland Health Survey reported that only one-third of those diagnosed with depression were actually receiving treatment, although they were assessed to be in need of it (Lehtinen et al., 1990; Lehtinen and Joukamaa, 1994). The Finnish Health Care Survey also found that a considerable proportion (41%) of patients with even the most severe depression were not receiving any treatment (Hämäläinen et al., 2004). More recently, the Health 2000 project reported that of subjects with MDD, only 34% used health services (Hämäläinen et al., 2008). However, a Finnish study reported also improved detection and pharmacotherapy of major depression from 1989 to 2001 in psychiatric outpatient care, and concluded problems in care to be more related to suboptimal intensity and monitoring of treatment than to mere lack of treatment. Among US adults in the NCS-R, health care treatment for depression was found to be adequate in only a fifth of the cases with 12-month MDD (Kessler et al., 2003). In the World Mental Health Survey, although disorder severity was correlated with probability of treatment in almost all countries, 35.5% to 50.3% of serious cases in developed countries and 76.3% to 85.4% in less-developed countries received no treatment in the 12 months before the interview (Demyttenaere et al., 2004).

In reports of treatments provided or used, the Health 2000 project reported that of subjects with MDD, only 24% used antidepressants, and 17% received psychosocial treatment (Hämäläinen et al., 2009). In the VDS, among patients in psychiatric care, most patients (88%) received antidepressants in the early acute phase, but about half (49%) terminated treatment prematurely. Moreover, the realization of maintenance treatment recommendations among psychiatric patients was found to be poor, only 57% received treatment and only for 16% of the time indicated (Holma et al., 2008).

5 Aims of the study

This study investigated the prospective 5-year outcome of a sample of 269 patients with DSM-IV MDD in secondary level psychiatric care.

The specific aims of the study were:

I. To investigate the long-term outcome of MDD among psychiatric patients, and the influence of various sociodemographic factors, clinical variables, temperamental, and psychosocial factors.

II. To investigate long-term variations in incidence of attempted suicide between psychiatric patients in states of MDEs, partial remission, and full remission, and whether other risk and protective factors modify this risk.

III. To investigate the long-term rate, time course, and risk factors for a diagnostic change from unipolar MDD to bipolar disorder among psychiatric patients.

IV. To investigate how family histories of mood disorders, alcohol use disorders, or psychotic disorders correlate with psychosocial and clinical features, comorbidity, and the prospective long-term outcome of MDD.

6 Materials and methods

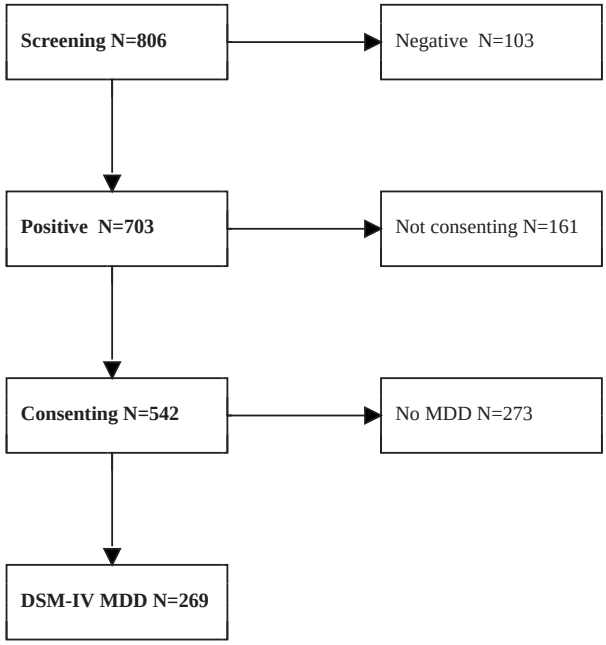
6.1 General study design

The Vantaa Depression Study (VDS) is a naturalistic and prospective cohort study concerning major depressive disorder (MDD) in psychiatric care. It forms a collaborative depression research project between the Mood, Depression, and Suicidal Behaviour Unit of the National Institute for Health and Welfare, Helsinki (former Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki), and the Department of Psychiatry of Helsinki University Central Hospital (HUCH), Peijas Hospital, Vantaa, Finland. The Department of Psychiatry at Peijas Hospital (PMCD) provided secondary care psychiatric services to all residents of Vantaa (179 856 inhabitants in 2002); these included a psychiatric inpatient unit, a general hospital outpatient clinic, six community mental health care centres – each covering a specified catchment area – and two day hospitals. The Ethics Committee of Peijas Hospital approved the study on 2nd December 1996, and the 5-year follow-up study on 23rd January 2002.

6.2 Screening

All patients in the department of psychiatry in PMCD were screened with depressive symptoms for a possible new episode of DSM-IV MDD between 1st February 1997 and 31st May 1998 in the first phase of the study (Figure 1). These were patients (N=806) aged 20-59 years 1) seeking treatment at, 2) being referred to, or 3) already receiving care and now showing signs of deteriorating clinical state. Patients with clinical diagnosis of ICD-10 schizophrenia or bipolar I disorder, were excluded at this stage. The screening instrument included the five screening questions for depression from the WHO Schedule for Clinical Assessment in Neuropsychiatry (SCAN), Version 2.0 (Wing et al., 1990). In addition, the Scale for Suicidal Ideation (SSI) (Beck et al., 1979) was also completed to recognize patients with moderate to severe suicidal ideation or plans. After receiving either 1) a positive response to any of the SCAN screening questions, or 2) a score of six or more in the SSI, irrespective of the presence of depressive symptoms, the patient was fully informed about the study project, and written informed consent requested. Of the 703 eligible patients, 161 (22.9%) refused to participate in the study, but 542 (77.1%) agreed and gave their written informed consent. The patients who refused did not differ significantly (P>.05) by age or gender from those who consented.

Figure 1. Flow-chart of the screening process in the Vantaa Depression Study.



6.3 Baseline evaluation

6.3.1 Diagnostic measures

The 542 consenting patients were interviewed in the second phase of sampling face-to-face using the WHO SCAN 2.0 by interviewers who had all received relevant training by a WHO certified training centre. They investigated whether or not the current mood episode fulfilled the criteria for (unipolar) DSM-IV MDD. All psychiatric and medical records in the PMCD, including a standardized set of laboratory tests, were also available at the interview. Patients currently abusing alcohol or other substances were interviewed after two to three weeks of abstinence, in order to exclude substance-induced mood disorders. On the basis of interviews, 269 patients were diagnosed with DSM-IV MDD and included in the study (Figure 1). Diagnostic reliability was investigated using 20 videotaped diagnostic interviews; the kappa coefficient for MDD was 0.86 [0.58-1.0] with 95% observed agreement rate.

The decision to include a patient in the study cohort was made by the researcher during the interview, after which the entire SCAN interview was conducted to achieve a full picture of axis I comorbid disorders. In addition, the Structured Clinical Interview for DSM-III-R personality disorders (SCID-II) (Spitzer et al., 1987) was used to assess diagnoses on axis II. Current axis III diseases were assessed via a self-report checklist with 44 items (corresponding to ICD-10 diagnoses). Only axis III diseases diagnosed by a physician and currently being treated were included.

6.3.2 Exclusion criteria

Patients with a diagnosis of DSM-IV bipolar I or II disorder, schizoaffective disorder, schizophrenia or another psychotic disorder, organic or substance-induced mood disorder were excluded from the study, although they fulfilled the symptom criteria of current MDE. In addition, patients with a history of MDD, not fulfilling the criteria of the disorder in the current episode were excluded.

6.3.3 Observer and self-report scales

The 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) and the 21-item Beck Depression Inventory (BDI) (Beck et al., 1961) were used to assess severity of depression, the Scale for Suicidal Ideation (SSI) for suicidal behaviour (Beck et al., 1979); the Social and Occupational Functioning Assessment Scale for DSM-IV (SOFAS) (Goldman et al., 1992) for functional level; the Interview for Recent Life Events (IRLE) (Paykel, 1983), and the Interview Measure of Social Relationships (IMSR) (Brugha et al., 1987) and the Perceived Social Support Scale Revised (PSSS-R) (Blumenthal et al., 1987) for social support. Self-report scales, in addition to the BDI, included the Beck Anxiety Inventory (BAI) (Beck et al., 1988), the Beck Hopelessness Scale (HS) (Beck et al., 1974), the Social Adjustment Scale-Self Report (SAS-SR) (Weissman and Bothwell, 1976), and the Eysenck Personality Inventory (EPI) (Eysenck and Eysenck, 1964). The distinction between melancholic and non-melancholic depression was based on the SCAN and DSM-IV criteria.

6.3.4 Sosiodemographic and clinical features at baseline

At baseline, the majority of the patients in the cohort were females (73%) and outpatients (83%), half (50%) were married or cohabited, and 60% were employed. Over a third (35%) suffered from their first MDD. Their mean HAM-D value was 19.5 (SD=5.9), and mean BDI 27.7 (SD=8.6). Most (79%) of the patients (79%) suffered from at least 1 comorbid disorder, and over half (54%) had 2 or more. Over half (57%) suffered from an anxiety disorder, a fourth (25%) from alcohol abuse or dependence, and nearly half (44%) from at least 1 personality disorder. At baseline, most patients (88%) received antidepressants, and, for the majority (78%), the dosage was adequate for the acute phase. More than half (57%) received

selective serotonin reuptake inhibitors (SSRIs) alone at baseline, about one-fifth (18%) received newer antidepressants (tetracyclics, serotonin-norepinephrine reuptake inhibitors SNRI, RIMA reversible inhibitors of monoamine oxidase), only 8% received tricyclic antidepressants (TCAs), and 6% received combination treatment, usually an SSRI and a TCA. Nearly all the patients (98%) received psychotherapeutic support in the early acute phase, but only a few had weekly psychotherapy (16%) (Melartin et al., 2002; Melartin et al., 2005).

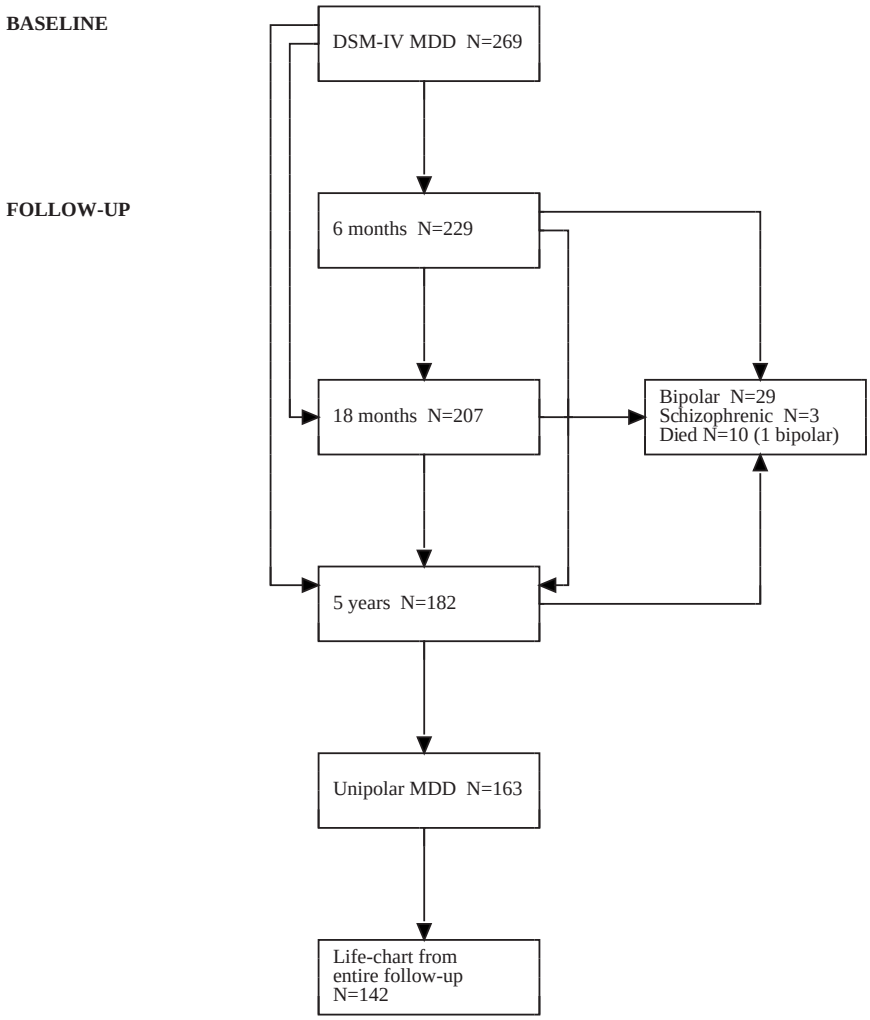
6.4 Follow-up procedure

6.4.1 Study participants

After the baseline, patients were investigated at 6 and 18 months, and 5 years with a life-chart methodology and the same observer and self-report scales used at baseline. Of the total of 269 patients initially included in the study, 229 patients participated in the 6-month follow-up, 207 in the 18-month follow-up, and 182 in the 5-year follow-up (Figure 2). The median times of follow-up interviews were 6.5 and 18.8 months, and 65.2 months from baseline, respectively.

The 5-year follow-up interviews were performed individually by 2 interviewers (K.M.H. or I.A.K.H.); all available medical and psychiatric records were used to complement the information. The average duration of an interview was 2-3 hours and took place in psychiatric outpatient units of Vantaa and HUCH, between April 12, 2002 and April 30, 2004. By 18 months, 13 patients' diagnoses had switched to bipolar disorder; at the 5-year follow-up, 16 patients were diagnosed as having bipolar disorder, 1 was diagnosed with schizophrenia, and 2 were diagnosed with schizoaffective disorders. Ten patients had died, one of whom had switched to bipolar disorder. Thus, after 5 years, 163 unipolar patients (71.5% of those eligible [N=228]) remained for the analyses, and 65 patients dropped out. Life-chart information on 142 of the 163 patients was available from the entire follow-up period.

Figure 2. Flow-chart of the follow-up process in the Vantaa Depression Study.



6.4.2 Study drop-outs

The causes for dropping out (N=65) from the 5-year follow-up were as follows: withdrawal of consent (63.1%, N=41) patients unreachable despite several efforts (33.8%, N=22), and patients living too far away (3.1%, N=2). The dropouts were younger (median age=35.3 vs. 42.3 years, Z=-2.20, p=.028), were more likely to be male (36.9% vs. 22.1%, χ^2=5.28, df=1, p=.022), were more likely to have been inpatients (24.6% vs. 12.3%, χ^2=5.33, df=1, p=.021), had greater percentages of alcohol dependence (26.2% vs. 6.7%, χ^2=16.2, df=1, p < .001) and psychotic depression (13.8% vs. 4.3%, χ^2=6.50, df=1, p =.011), were more likely to be not married or cohabiting (60.0% vs. 42.9%, χ^2=5.42, df=1, p=.020), and had a slightly lower level of functioning (median SOFAS score=50 vs. 55, Z=χ^2.69, p=.007) than patients included in the 5-year cohort.

In Cox's proportional hazard analyses, all the information available for different lengths of follow-up time was used. In this case, only patients not participating in any of the follow-up interviews were dropped out (N=20). They were compared with participants who remained in the study, at baseline younger (mean age: 33.0 years [SD=9.1] vs. 40.1 years [SD=11.0]; t=2.81, p=.005), had a lower age at onset (mean age: 27.1 years [SD=8.8] vs. 31.8 years [SD=12.7]; t=2.22, p=.035), more often had dysthymia (35.0% vs. 10.0%; χ^2=11.0, df=1, p=.001) and panic disorder with agoraphobia (20.0% vs. 6.4%; χ^2=4.96, df=1, p=.026), had more antisocial personality disorder symptoms (z=-2.73, p=.006), perceived less social support (t=2.01, p.046), were more often unemployed (70.0% versus 37.9%; χ^2=7.93, df=1, p=.005), and were less often married or cohabiting (80.0% vs. 47.4%; χ^2=7.87, df=1, p=.005).

Despite a number of characteristics often associated with a poorer outcome, the dropouts did not differ from those participating, in terms of index episode duration, time to full remission, number of relapses or recurrences during the period they participated in the study; nor were they different in terms of suicidal ideation or attempts at baseline or prior to entry. Thus it appears unlikely they would have significantly biased these findings

6.4.3 Outcome measures

After baseline, the patients were asked to complete the BDI monthly for six months. The outcome of MDD and the comorbid disorders was investigated at six and 18 months by SCAN 2.0 and SCID-II interviews. In the 5-year follow-up, the SCID-I for DSM-IV-TR Axis I Disorders (First et al., 2002) was used instead of SCAN. Besides that, all observer- and self-report scales were included in the follow-up assessments. All available medical and psychiatric records were used to fill in and check the interview information. The diagnoses and timing of depressive episodes were based on the structured interviews as well as patient records.

6.4.3.1 Life-chart methodology

The duration of the index episode and the timing of possible relapses and recurrences during follow-up were examined by gathering all available data, which were then integrated into a graphic life chart after reviewing with the patient all the information from the follow-up period. In order to improve the accuracy of assessment, in addition to symptom ratings and visits to attending personnel, change points in the psychopathologic states using probes related to important life-events were also asked

The life-chart was based on DSM-IV criteria and definitions. The time after the first baseline interview was divided into three periods: (1) state of full remission (none of the 9 MDE criteria symptoms), (2) state of partial remission (1-4 of the 9 symptoms), or (3) state of MDE (5+ of the 9 symptoms). As a categorical variable, remission (further specified as full or partial) was defined according to the DSM-IV, as at least two consecutive months in which criteria for a MDE were not met. Relapse was defined as return of symptoms fulfilling the DSM-IV criteria for MDE after a period of less than two months (but more than 2 weeks) with symptoms below the MDE threshold. Recurrence was defined as in the DSM-IV definition for 296.3x MDD, as a return of symptoms sufficiently severe to satisfy criteria for an MDE after at least two consecutive months of partial or full remission. Two alternative definitions for duration of the index episode after the first baseline interview were used: (1) the uninterrupted duration of the episode in the state of MDE (Time with full MDE criteria), and (2) time to the first onset of state of full remission lasting at least two consecutive months (Time to full remission).

6.5 Statistical methods

The Pearson chi-square statistic with Yates' continuity correction test, and Fisher's exact test were used to evaluate categorical and parametric data, the Mann-Whitney or Kruskal-Wallis test to compare continuous variables non-parametric, and the two-sample t-test for continuous variables normally distributed. The multivariate analyses were based on the hypotheses. After detailed univariate analyses, predictors for final models were chosen by considering their clinical and statistical validity, significance, and relevance. In all of these, multivariate methods were used to control for possible confounding factors. Besides baseline values, also follow-up values of variables were used in some analyses (time spent in MDE, partial or full remission; highest levels of HAM-D, BDI, BAI; number of lifetime MDEs, and suicide attempts; lifetime anxiety, alcohol use, and personality disorders, and psychotic depression; values of hopelessness [HS], perceived social support [PSSS-R], neuroticism and extraversion [EPI] during the lowest level of depression).

Statistically non-significant variables were omitted from the final models, but the analyses were adjusted for age and gender, and; regression analyses were also controlled for the time at risk. In these, censored data included (1) patients who did not participate in any follow-up interview, (2) had not met the criteria for the endpoint event of analysis, either by the end of the follow-up period, or by the time they left the study and (2) patients whose diagnoses changed before the endpoint event from unipolar to bipolar disorder or schizophrenia. A p-value <.05 was considered significant in hypothesis testing, and p-values between .05 and .10 were reported as trends. Odds ratios with 95% confidence interval not including 1 were considered significant. The Statistical Package for Social Sciences software, version 17.0 (SPSS, Inc., Chicago), and an R package (R Development Core Team, Vienna, Va.) were used.

Logistic models were used to adjust for confounding factors in analyses for the propability of an event, and linear regression for number of events. The Kaplan-Meier survival curves were used to estimate the probability of remaining ill, experiencing a recurrence, switching to bipolar disorder, and attempting suicide during the 5-year follow-up. Cox proportional hazards models (Cox, 1972) were used in the analyses for predicting time to symptom state below MDE criteria or to full remission, time to first recurrence, time to switch to bipolar disorder, and suicide attempts. The Poisson regression model was used to investigate the univariate rate ratio for explanatory variables for suicide attempts. The association between the concurrent level of depression (full remission, partial remission, or major depressive episode) and suicide attempts in the life chart was analyzed using the level of depression as a time varying covariate in

the Cox proportional hazard model. For each individual, the follow-up assessment was divided into time periods in which the value of the time varying variable (i.e., level of depression) was constant. The interactions between the time varying phase and other risk factors were tested using the Cox model with the likelihood ratio test. The model describes how the hazard of event (suicide attempt) is predicted by the current values of explanatory variables. For continuous variables, hazard ratios were calculated for 10-unit increments. Simple random effects (frailty) term were included in the Cox model to take into account variations between individuals (Therneau et al., 2003). The population attributable fraction was calculated by comparing the time in major depressive episodes with other phases and using a formula for multicategory exposures (Rockhill et al., 1998).

7 Results

7.1 Long-term outcome of MDD (Study I)

7.1.1 Sosiodemographic and clinical characteristics of the sample

Table 2 summarizes the baseline sosiodemographic and clinical characteristics of the unipolar patients participating to 5-year follow-up (N=163). A majority of the patients were females (78%), outpatients (88%), married or cohabited (57%), employed (64%), had a comorbid axis I disorder (64%), and two-fifths an axis II disorder (41%). At 5 years the mean scores were for the 17-item HAM-D 9.8 (SD=8.3), for the 21-item BDI 10.3 (SD=10.2), for the BAI 12.8 (SD=10.8), and 66.8 (SD=15.0) for the SOFAS, and over one-half (54.6%) suffered from comorbid axis I disorders, and nearly two-fifths (38.7%) from axis II disorders. At 5 years, 49.7% (N=81) of the patients did not receive any treatment. One-fourth (24.5%, N=40) were currently receiving psychosocial treatment, 15.3% (N=25) were receiving psychotherapeutic support, and 9.2% (N=15) weekly psychotherapy. Nearly half (44.8%, N=73) were currently using an antidepressant. One-sixth (14.7%, N=24) had been hospitalized between the 18-month and 5-year follow-ups (median number of psychiatric hospitalizations=1.0, SD=1.2).

Table 2. Baseline sociodemographic and Clinical Characteristics in the Vantaa Depression Study, 5-year follow-up (unipolar, N=163).

Characteristic	N	%	Characteristic	N	%
Sex					
Female	127	(77.9)	**Axis I comorbidity**	104	(63.8)
Outpatient	143	(87.7)	Dysthymia	17	(10.4)
Married or cohabiting	93	(57.1)	Anxiety disorders	89	(54.6)
Professional education	60	(36.8)	Phobic/ Nonphobic	60	(36.8)
Employed	105	(64.4)	Panic disorder	24	(14.7)
Low income	64	(39.3)	with/	9	(5.5)
Recidential area (east Vantaa)	62	(38.0)	without agoraphobia	15	(9.2)
Melancholic	51	(31.3)	Agoraphobia without panic	16	(9.8)
Atypical	18	(11.0)	Specific phobia	43	(26.4)
Psychotic	7	(4.3)	Social phobia	22	(13.5)
			OCD	7	(4.3)
	Mean	**SD**	GAD	26	(16.0)
			Alcohol use disorders	29	(17.8)
Age (years)	40.7	(11.3)	Dependence	11	(6.7)
Age at onset of MDE	33.0	(12.7)	Abuse	18	(11.0)
HAM-D	18.6	(5.8)	**Axis II comorbidity**		
BDI	27.0	(8.6)	Personality disorders	66	(40.5)
BAI	21.3	(10.6)	Cluster A	26	(16.0)
SOFAS	53.5	(9.4)	Cluster B	21	(12.9)
Hopelessness (HS)	10.2	(4.7)	Cluster C	46	(28.2)
Neuroticism [a]	17.2	(3.7)			
Extroversion [a]	9.8	(4.5)			
Size of social network	7.8	(3.6)		**Mean**	**(SD)**
PSSS-R	39.1	(12.7)			
Negative life events [b]	4.0	(11.0)	No. of psychiatric disorders	2.8	(1.6)
			Axis III comorbidity		
	Quar-tiles		No. of current somatic diseases	0.7	(1.2)
			No. of all axis I-III disorders	3.5	(2.1)
Suicidal ideation (SSI)	25th	0.0			
	50th	0.0			
	75th	12.0			
Number of previous MDEs	25th	0.0			
	50th	1.0			
	75th	2.0			
MDE length prior to entry	25th	2.0			
(months)	50th	3.4			
	75th	6.0			

a Eysenck Personality Inventory: for dimensions of neuroticism and extroversion.
b Interview for Recent Life Events: objective measure of negative impact of adverse life events.

Abbreviations:
HAM-D = Hamilton Rating Scale for Depression
BDI = Beck Depression Inventory
BAI = Beck Anxiety Inventory
HS = Beck Hopelessness Scale
SSI = Scale for Suicidal Ideation
SOFAS = Social and Occupational Functioning Assessment Scale
OCD = Obsessive-Compulsive Disorder
GAD = Generalized Anxiety Disorder
PSSS-R = Perceived Social Support Scale-Revised

7.1.2 Overall outcome

At 5 years, nearly one-half were currently in full remission (49.7%), nearly one-fourth in MDE (23.9%), and the rest (26.4%) in partial remission. During 5 years the patients on average spent over half of the follow-up period in full remission (median 37.4 months, SD=21.6), one-fifth of the time in MDE, (median 7.5 months, SD=14.6), and one-third of the time in partial remission (median 17.2 months, SD=16.8) (Figure 3). The proportion of time spent in major depressive episodes per follow-up year was highest during the first year of observation (mean: 3.9 months [SD=3.6]), declining thereafter during the second to sixth year (mean: 2.5, 2.1, 2.1, 1.3, 1.5 months, respectively [SD=4.1, 3.5, 3.6, 2.2, 3.6]). For descriptive purposes, the cohort was divided into 3 groups on the basis of time spent in various symptom states, i.e. most of the time spent in full remission, partial remission, or MDE. On the basis of this division, half (54.9%) of the patients had a quite good outcome, one-tenth (10.6%) a poor outcome, and one-third (34.5%) an intermediate outcome (Figure 4).

Figure 3. Time spent in a major depressive episode (MDE), in partial remission, and in full remission in the Vantaa depression study over a 5-year follow-up (N=142).

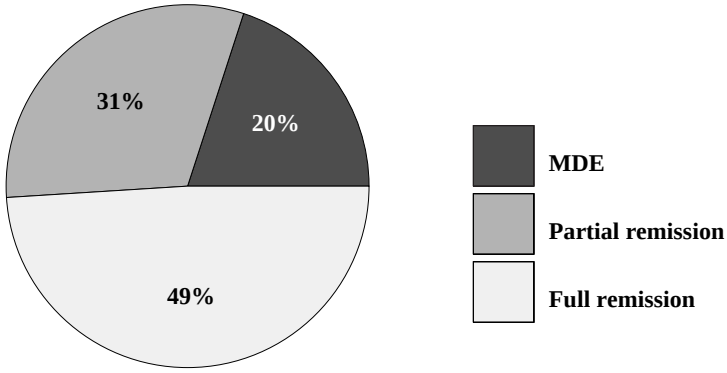
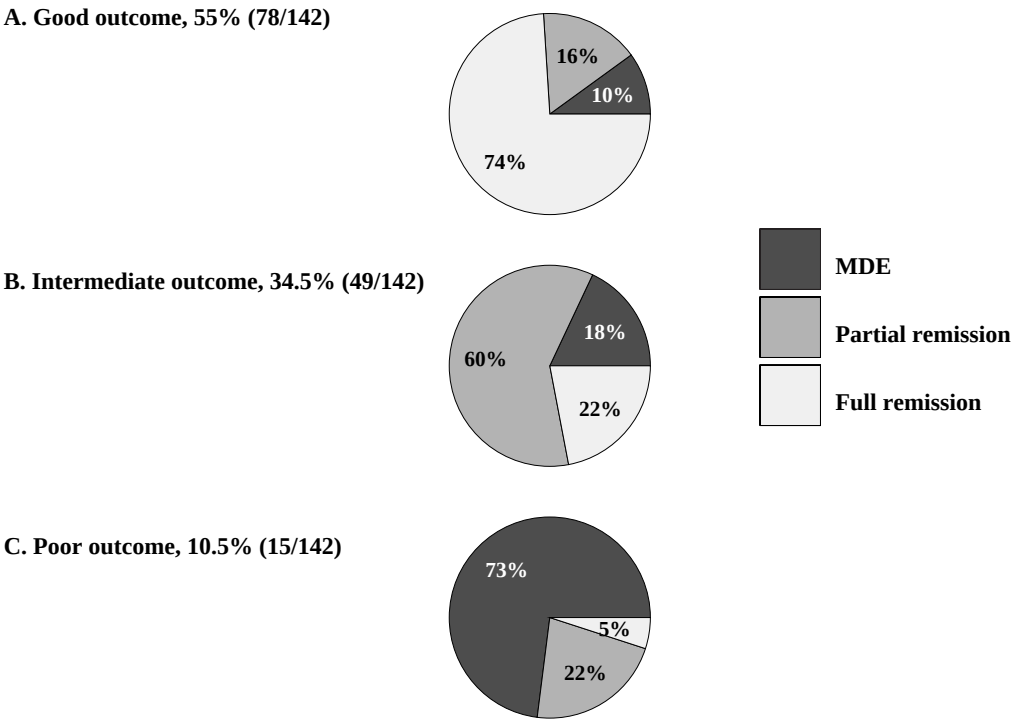


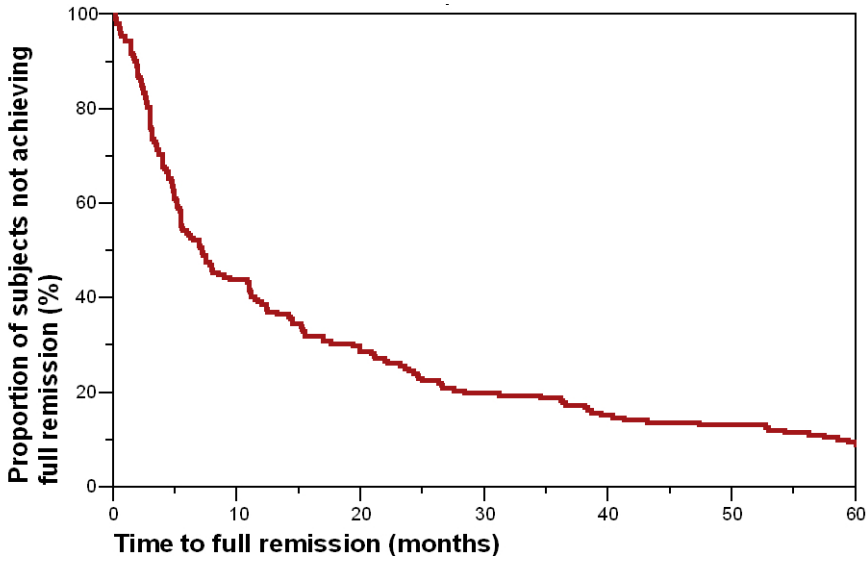
Figure 4. Type of outcome and time spent in a major depressive episode (MDE), in partial remission, and in full remission in the Vantaa depression study over a 5-year follow-up (N=142).



7.1.3 Time to full remission

By 5 years, nearly all followed-up patients (98.8%) recovered to a symptom state below MDE criteria. The median index episode duration (time with full criteria) was 1.6 months from baseline and 5.5 months when taken into account MDE beginning prior to baseline. Within 5 years, 88.4% of the patients (130/147) reached full remission lasting at least 2 months. The median time to first full remission was 11.0 months (95% CI 7.4-14.6) (Figure 5). Seven percent of patients (10/142) suffered from MDE continuously for 2 years or more, and 2 patients (1.2%) during the entire period.

Figure 5. Survival curve to full remission of a major depressive episode (MDE) or to 60 months.



7.1.3.1 Predictors of time to full remission

In univariate analyses, several individual factors predicted the time to full remission (Table 3). Predictors for the final models were chosen on the basis of the primary hypothesis, but their clinical and statistical validity and relevance (e.g. state vs. trait) were considered before inclusion. In the final Cox proportional hazards model, the predetermined independent variables comprised age, gender, duration of MDE before entry, mean BDI (severity of depression), BAI (severity of anxiety), HS (hopelessness), SSI (suicidal ideation), melancholic or psychotic subtype of depression, comorbid dysthymia, anxiety disorders, personality and alcohol use disorders, mean PSSS-R (perceived social support), mean extraversion, and professional education. After removing all non-significant findings, in multivariate Cox proportional hazards analyses, preceding dysthymia (HR=1.96, 95% CI 1.07-3.58, p=.028), cluster C personality disorder (HR=1.43, 95% CI 1.02-2.01, p=.041), and longer MDE preceding entry (HR=1.28, 95% CI 1.06-1.54, p=.011) prolonged the time to full remission significantly. Median time to full remission increased over twice for patients with preceding dysthymia (14.2 vs. 6.5 months), nearly twice with cluster C personality disorder (11.5 vs. 6.1 months), and three times with longer MDE prior to entry (15.2 vs. 5.5 months). Among cluster C personality disorders, avoidant personality was the strongest predictor for prolonged recovery (HR=1.49, 95% CI 1.02-2.17, p=.040). Severity of MDD predicted a longer time to full remission only as a trend (HR=1.02, 95% CI 1.00-1.05, p=.096).

Table 3. Univariate predictors of time to full remission in the Vantaa depression study, 5-year follow-up.

Predictor at entry	HR	95% CI	P
Age (yrs)	1.02	[1.00 - 1.03]	.011
Gender (male)	0.94	[0.66 - 1.32]	n.s.
Outpatient status	1.09	[0.70 - 1.70]	n.s.
Clinical features of MDD			
Age of onset (yrs)	1.00	[0.99 - 1.02]	n.s.
Longer MDE prior entry	1.30	[1.08 - 1.57]	.006
No. of previous episodes	1.00	[0.93 - 1.08]	n.s.
Symptoms and functional ability			
17-item HAM-D	1.02	[1.00 - 1.05]	.094
21-item BDI	1.02	[1.00 - 1.04]	.057
BAI	1.02	[1.00 - 1.03]	.052
HS	1.03	[1.00 - 1.07]	.039
SSI	1.18	[0.99 - 1.40]	.061
SOFAS	0.99	[0.97 - 1.01]	n.s.
Axis I comorbidity			
Dysthymia	1.96	[1.07 - 3.57]	.029
Anxiety disorders	0.97	[0.72 - 1.31]	n.s.
Phobic/ Nonphobic	0.99	[0.73 - 1.34]	.037
Panic disorder with/	0.79	[0.38 - 1.62]	n.s.
without agoraphobia	0.95	[0.56 - 1.58]	n.s.
Agoraphobia without panic	0.97	[0.59 - 1.57]	n.s.
Specific phobia	1.12	[0.79 - 1.59]	n.s.
Social phobia	0.76	[0.51 - 1.14]	n.s.
OCD	0.80	[0.39 - 1.65]	n.s.
GAD	1.08	[0.68 - 1.71]	n.s.
Alcohol use disorders	0.71	[0.48 - 1.05]	.085
Dependence	0.69	[0.41 - 1.18]	n.s.
Abuse	0.77	[0.47 - 1.28]	n.s.
Axis II comorbidity			
Personality disorders	1.21	[0.89 - 1.64]	n.s.
Cluster A	0.82	[0.54 - 1.24]	n.s.
Cluster B	1.00	[0.65 - 1.55]	n.s.
Cluster C	1.42	[1.01 - 2.00]	.041
No. of psychiatric disorders	1.03	[0.94 - 1.13]	n.s.
Axis III comorbidity			
Number of current somatic			
diseases	1.06	[0.93 - 1.20]	n.s.
No. of all axis I-III disorders	1.04	[0.97 - 1.11]	n.s.
MDD subtype features			
Melancholic	0.72	[0.53 - 0.98]	.039
Atypical	0.76	[0.46 - 1.25]	n.s.
Psychotic	1.71	[0.95 - 3.08]	n.s.
Psychosocial and personality factors			
Size of social network	0.97	[0.93 - 1.01]	n.s.
PSSS-R	0.99	[0.97 - 1.00]	.015
Negative life events [a]	0.97	[0.94 - 1.01]	n.s.
Neuroticism [b]	1.03	[0.99 - 1.07]	n.s.
Extroversion [b]	0.97	[0.93 - 1.00]	.044
Married or cohabiting	1.13	[0.84 - 1.53]	.412
Income	0.94	[0.67 - 1.30]	.701
Employed	0.86	[0.62 - 1.18]	.351
Professional education	1.35	[0.98 - 1.84]	.063
Residential area (east)	1.62	[1.19 - 2.21]	.002

Cox proportional hazards models; all analyses controlled for age and gender; risk reported for increasing time.

a Interview for Recent Life Events: objective measure of negative impact of adverse life events.
b Eysenck Personality Inventory: for dimensions of neuroticism and extroversion.

Abbreviations:
HAM-D= Hamilton Rating Scale for Depression
BDI = Beck Depression Inventory
BAI = Beck Anxiety Inventory
HS = Beck Hopelessness Scale
SSI = Scale for Suicidal Ideation
SOFAS = Social and Occupational Functioning Assessment Scale
OCD = Obsessive-Compulsive Disorder
GAD = Generalized Anxiety Disorder
PSSS-R= Perceived Social Support Scale-Revised

7.1.4 Recurrence

Within 5 years, over two-thirds (70.7%, 99/140) of followed-up patients had a recurrence (return of symptoms sufficiently severe to satisfy criteria for an MDE after at least two consecutive months of partial or full remission). The median duration of recurrent episodes was 2.9 months (SD=1.4), i.e., shorter than the index episodes (median 5.5 months).

7.1.4.1 Predictors of recurrence

Recurrence was predicted by several baseline factors (Table 4). In the final logistic regression model, the predetermined inependent variables comprised age, gender, inpatient status, age at onset, number of previous MDEs, mean HAM-D (severity of depression), BAI (severity of anxiety), HS (hopelessness), SSI (suicidal ideation), SOFAS (social and occupational functioning), anxiety disorders, and neuroticism. However, after removing non-significant variables, younger age (baseline age under 30) (OR=0.96, 95% CI 0.92-0.99, p=.018), higher severity of depression (HAM-D) (OR=1.11, 95% CI 1.04-1.20, p=.003), and social phobia (OR=8.26, 95% CI 1.04-66.7, p=.045), remained significant in multivariate logistic regression analyses. There was also a non-significant trend for number of previous episodes to predict recurrence (OR=1.31, 95% CI 0.99-1.74, p=.062). Recurrence was experienced by 88% (59/67) of patients with severe or psychotic depression, 66% (55/84) of patients with moderate, and 56% (5/9) of patients with mild depression (χ^2=11.75, df=2, p=.003). A majority of patients with social phobia, 94% (16/17), had a recurrence compared to those without social phobia [68% (83/123) (χ^2=6.55, df=1, p=.017)].

Table 4. Univariate predictors of recurrence in the Vantaa depression study, 5-year follow-up.

Predictor at entry	HR	95% CI	P
Age (yrs)	0.97	[0.94 - 1.00]	.070
Gender (male)	0.91	[0.40 - 2.08]	n.s.
Outpatient status	0.27	[0.06 - 1.25]	.094
Clinical features of MDD			
Age of onset (yrs)	0.96	[0.92 - 1.00]	.069
Longer MDE prior entry	0.96	[0.91 - 1.02]	n.s.
No. of previous episodes	1.34	[1.01 - 1.77]	.038
Symptoms and functional ability			
17-item HAM-D	1.12	[1.04 - 1.20]	.002
21-item BDI	1.07	[1.02 - 1.13]	.008
BAI	1.03	[1.00 - 1.07]	.084
HS	1.07	[0.99 - 1.16]	.098
SSI	1.07	[1.01 - 1.13]	.018
SOFAS	0.96	[0.92 - 1.00]	.073
Axis I comorbidity			
Dysthymia	0.72	[0.24 - 2.20]	n.s.
Anxiety disorders	1.06	[0.51 - 2.21]	n.s.
Phobic/ Nonphobic	1.54	[0.70 - 3.38]	n.s.
Panic disorder with/	1.25	[0.13 - 12.1]	n.s.
without agoraphobia	0.53	[0.17 - 1.67]	n.s.
Agoraphobia without panic	1.04	[0.31 - 3.51]	n.s.
Specific phobia	1.04	[0.45 - 2.44]	n.s.
Social phobia	8.93	[1.14 - 71.4]	.037
OCD	1.39	[0.27 - 7.24]	n.s.
GAD	1.00	[0.35 - 2.84]	n.s.
Alcohol use disorders	1.31	[0.47 - 3.66]	n.s.
Dependence	1.50	[0.29 - 7.63]	n.s.
Abuse	1.15	[0.34 - 3.92]	n.s.
Axis II comorbidity			
Personality disorders	1.21	[0.56 - 2.58]	n.s.
Cluster A	2.14	[0.67 - 6.76]	n.s.
Cluster B	1.38	[0.41 - 4.59]	n.s.
Cluster C	2.00	[0.82 - 4.83]	n.s.
No. of psychiatric disorders	1.22	[0.95 - 1.55]	n.s.
Axis III comorbidity			
Number of current somatic			
diseases	1.05	[0.41 - 2.13]	n.s.
No. of all axis I-III disorders	1.10	[0.92 - 1.31]	n.s.
MDD subtype features			
Melancholic	1.68	[0.75 - 3.76]	n.s.
Atypical	0.79	[0.22 - 2.76]	n.s.
Psychotic	0.61	[0.13 - 2.79]	n.s.
Psychosocial and personality factors			
Size of social network	0.95	[0.86 - 1.04]	n.s.
PSSS-R	0.99	[0.96 - 1.02]	n.s.
Negative life events [a]	0.98	[0.90 - 1.07]	n.s.
Neuroticism [b]	1.09	[0.99 - 1.20]	.071
Extroversion [b]	0.96	[0.89 - 1.04]	n.s.
Married or cohabiting	1.24	[0.59 - 2.58]	n.s.
Income	0.85	[0.39 - 1.86]	n.s.
Employed	1.56	[0.72 - 3.37]	n.s.
Professional education	1.38	[0.63 - 3.01]	n.s.
Residential area (east)	1.33	[0.63 - 2.81]	n.s.

Logistic regression models; all analyses controlled for age and gender, and time at risk.

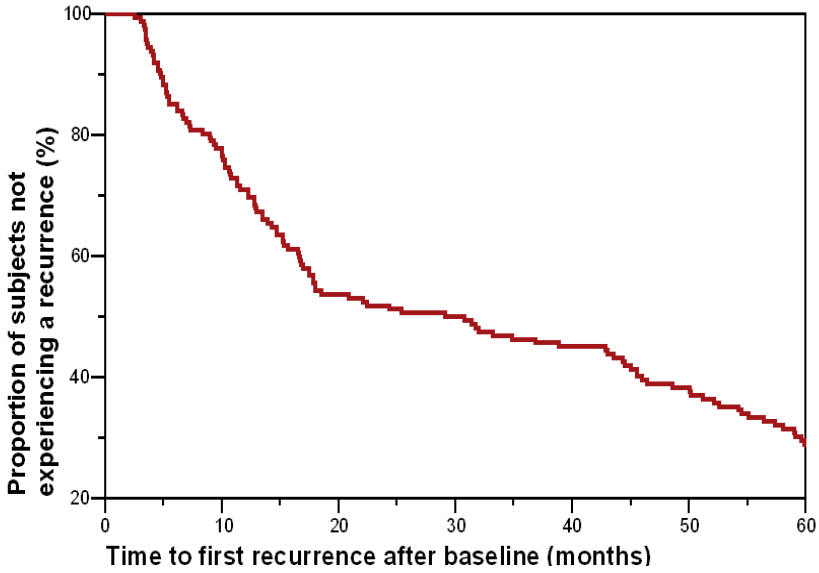
a Interview for Recent Life Events: objective measure of negative impact of adverse life events.
b Eysenck Personality Inventory: for dimensions of neuroticism and extroversion.

Abbreviations:
HAM-D= Hamilton Rating Scale for Depression
BDI = Beck Depression Inventory
BAI = Beck Anxiety Inventory
HS = Beck Hopelessness Scale
SSI = Scale for Suicidal Ideation
SOFAS = Social and Occupational Functioning Assessment Scale
OCD = Obsessive-Compulsive Disorder
GAD = Generalized Anxiety Disorder
PSSS-R= Perceived Social Support Scale-Revised

7.1.5 Time to first recurrence

During the follow-up, the median time to first recurrence was 25.4 months (95% CI 11.4-39.4) from baseline and 21.2 months (95% CI 9.5-32.9) from the end of the index episode excluding time with full MDE criteria (Figure 6).

Figure 6. Survival curve to first recurrence of a major depressive episode (MDE) or to 60 months.



7.1.5.1 Predictors of time to first recurrence

Time to first recurrence after the baseline was predicted in univariate analyses by many baseline factors (Table 5). In the final Cox proportional hazards model, the predetermined inependent variables comprised age, gender, inpatient status, age at onset, number of previous MDEs, mean HAM-D (severity of depression), BAI (severity of anxiety), HS (hopelessness), SSI (suicidal ideation), SOFAS (social and occupational functioning), comorbid anxiety and personality disorders, alcohol dependence, and neuroticism. However, after removing non-significant variables, higher severity of MDD (HR=0.94, 95% CI 0.92-0.98, p=.001) and social phobia (HR=0.41, 95% CI 0.25-0.66, p<0.001) remained

significant in the Cox model. The mean time to first recurrence was 26.8 months (95% CI=20.2 to 33.3) for patients with severe or psychotic depression, 42.9 months (95% CI=36.6 to 49.2) for patients with moderate, and 50.9 months (95% CI=35.4 to 66.4) for patients with mild depression (log-rank χ^2=14.6, df=2, p= .001). Patients with social phobia experienced a recurrence over twice as fast compared to those without social phobia, i.e., after a mean time of 17.9 months vs. 40.1 months (95% CI 9.4-26.3 vs. 35.1-45.2) (log-rank χ^2=12.0, df=1, p=.001).

7.1.6 Number of recurrences

Within 5 years, the patients experienced a median of one recurrence (SD=1.7). Nearly one-third (29.3%, 41/140) of patients had no recurrences, and over one-fourth (27.9%, 39/140) experienced 3 or more recurrences (Figure 7 a).

7.1.6.1 Predictors of number of recurrences

The number of recurrences during the 5-year follow-up was predicted in univariate linear regression analyses significantly by baseline higher severity of depression (HAM-D and BDI), anxiety (BAI), suicidal ideation (SSI), social phobia, and alcohol dependence, and as a trend by inpatient status, higher number of previous MDEs, hopelessness, neuroticism, and number of comorbid psychiatric disorders. After multivariate linear regression analyses, severity of depression (HAM-D), social phobia, and younger age at onset as a trend remained significant (β=.04, 95% CI=0.02 to 0.06, p=.001; β=.60, 95% CI= 0.21 to 0.99, p=.003; and β=-.01, 95% CI=-0.02 to 0.002, p=.084, respectively). Figure 7 b shows the difference in number of recurrences between mild or moderate, and severe or psychotic depression (z=-3.40, p=.001).

Table 5. Univariate analyses of predictors of time to first recurrence of major depressive disorder (MDD) in the Vantaa depression study during a 5-year follow-up.

Predictor at entry	HR	95% CI	P
Age (yrs)	1.00	[0.98 - 1.01]	n.s.
Gender (male)	1.06	[0.70 - 1.58]	n.s.
Outpatient status	1.68	[1.04 - 2.71]	.034
Clinical features of MDD			
Age of onset (yrs)	1.02	[1.00 - 1.04]	.031
Longer MDE prior entry	0.98	[0.95 - 1.02]	n.s.
No. of previous episodes	0.91	[0.86 - 0.96]	.001
Symptoms and functional ability			
17-item HAM-D	0.95	[0.92 - 0.98]	.001
21-item BDI	0.97	[0.95 - 0.99]	.002
BAI	0.98	[0.96 - 1.00]	.019
HS	0.96	[0.92 - 1.00]	.039
SSI	0.97	[0.95 - 0.99]	.005
SOFAS	1.02	[1.00 - 1.04]	.036
Axis I comorbidity			
Dysthymia	0.99	[0.52 - 1.89]	n.s.
Anxiety disorders	0.84	[0.58 - 1.21]	n.s.
Phobic/ Nonphobic	0.70	[0.49 - 1.01]	.056
Panic disorder with/ without agoraphobia	0.83	[0.30 - 2.30]	n.s.
	0.84	[0.42 - 1.65]	n.s.
Agoraphobia without panic	1.03	[0.59 - 1.81]	n.s.
Specific phobia	0.86	[0.57 - 1.28]	n.s.
Social phobia	0.42	[0.26 - 0.68]	<.001
OCD	0.80	[0.37 - 1.72]	n.s.
GAD	0.97	[0.56 - 1.68]	n.s.
Alcohol use disorders	0.72	[0.46 - 1.14]	n.s.
Dependence	0.55	[0.31 - 0.98]	.041
Abuse	1.00	[0.54 - 1.83]	n.s.
Axis II comorbidity			
Personality disorders	0.81	[0.56 - 1.17]	n.s.
Cluster A	0.67	[0.43 - 1.04]	.073
Cluster B	0.75	[0.45 - 1.26]	n.s.
Cluster C	0.74	[0.50 - 1.10]	n.s.
No. of psychiatric disorders	0.86	[0.77 - 0.96]	.005
Axis III comorbidity			
Number of current somatic diseases	1.01	[0.86 - 1.18]	n.s.
No. of all axis I-III disorders	0.92	[0.85 - 1.00]	.040
MDD subtype features			
Melancholic	0.86	[0.59 - 1.25]	n.s.
Atypical	0.83	[0.46 - 1.52]	n.s.
Psychotic	1.23	[0.54 - 2.82]	n.s.
Psychosocial and personality factors			
Size of social network	0.99	[0.94 - 1.04]	n.s.
PSSS-R	1.01	[0.99 - 1.02]	n.s.
Negative life events [a]	1.00	[0.96 - 1.04]	n.s.
Neuroticism [b]	0.95	[0.90 - 1.00]	.044
Extroversion [b]	1.02	[0.97 - 1.06]	n.s.
Married or cohabiting	0.85	[0.59 - 1.22]	n.s.
Income	0.95	[0.64 - 1.39]	n.s.
Employed	0.82	[0.55 - 1.21]	n.s.
Professional education	0.89	[0.62 - 1.29]	n.s.
Residential area (east)	0.97	[0.66 - 1.42]	n.s.

Cox proportional hazards models; all analyses controlled for age and gender; risk reported for increasing time.

a Interview for Recent Life Events: objective measure of negative impact of adverse life events.
b Eysenck Personality Inventory: for dimensions of neuroticism and extroversion.

Abbreviations:
HAM-D= Hamilton Rating Scale for Depression
BDI = Beck Depression Inventory
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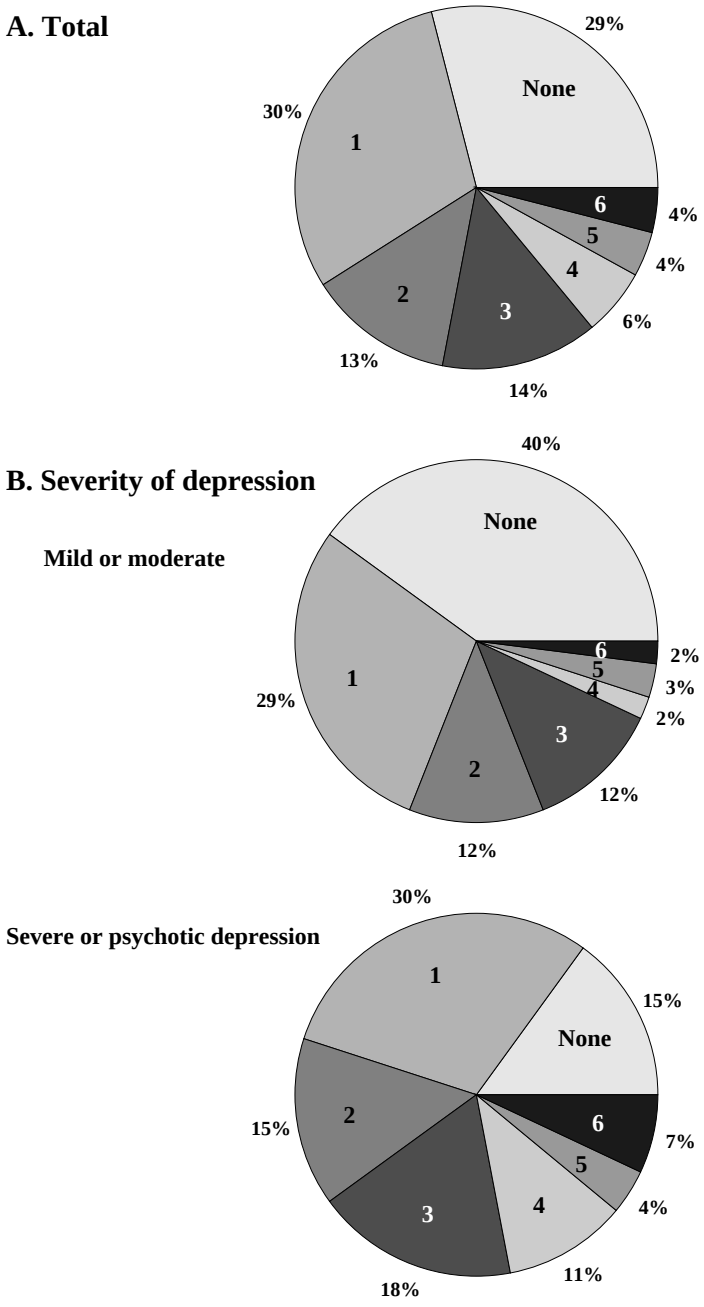
SSI = Scale for Suicidal Ideation
SOFAS = Social and Occupational Functioning Assessment Scale
OCD = Obsessive-Compulsive Disorder
GAD = Generalized Anxiety Disorder
PSSS-R = Perceived Social Support Scale-Revised

Figure 7. Number of recurrences in the Vantaa depression study over a 5-year follow-up, (N=140).

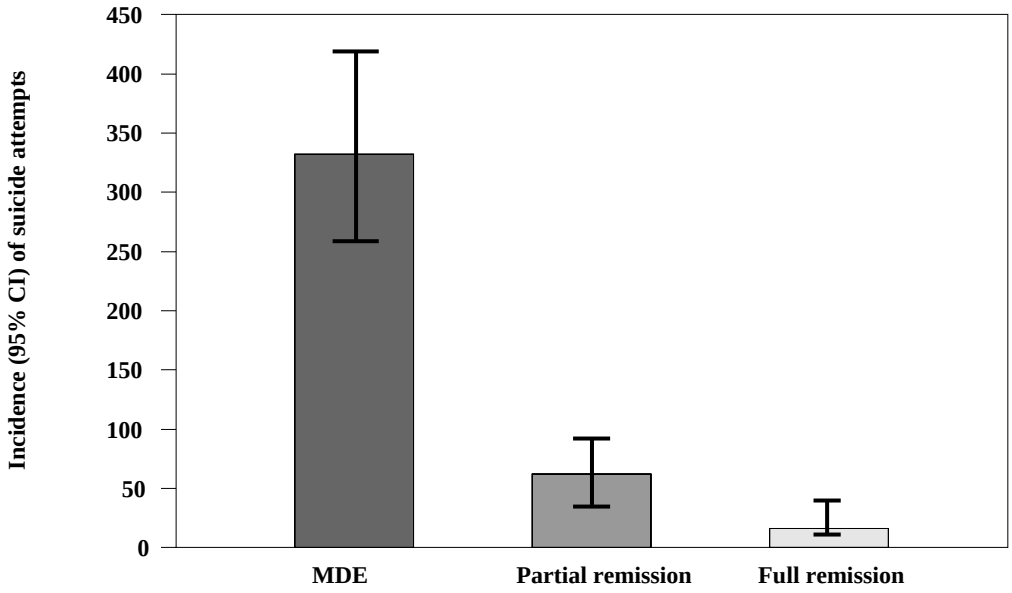


7.2. Risk factors of suicide attempts during the prospective follow-up (Study II)

7.2.1 Incidence of suicide attempts

During the 5-year follow-up, one-seventh of the patients (14.5%, N=36/249) attempted suicide at least once. More than half of the patients (N=19/249) attempted suicide at least twice, one eight times, and one attempted suicide even 13 times. In all, there were 106 suicide attempts (SAs) per 1,017.9 patient-years (incidence: N=104.1 per 1,000 patient-years [95% CI=86.0-127.1]). The incidence rate corresponded for women and men (N=111 [92.2-134.8] vs. N=83 [65.9-102.7]; z=-0.55, p=0.58). The majority, 73% (N=73/100) of the SAs took place during MDE, 19% (N=19/100) in the state of partial remission, and 8% (N=8/100) of full remission. The timing of six attempts was uncertain, i.e., one patient attempted several times. One SA took place during antidepressant-induced hypomania. During the follow-up, 219.6 patient-years were spent in MDE, 308.4 patient-years in partial remission, 489.6 patient-years in full remission. Therefore, the incidence rate of SAs during MDEs was 332 per 1,000 patient-years (95% CI=258.6-419.2), during partial remission 62 per 1,000 patient-years (95% CI=34.6-92.4), and full remission 16 per 1,000 patient-years (95% CI=11.2-40.2) (Figure 8). The risk of SA was highest within the first year of observation 219.4 per 1,000 patient-years [95% CI=191.3-250.5] declining after that during the second to fifth year (45.0-114.2 [95% CI 32.8-137.2] per 1,000 patient-years respectively). The risk ratio of SAs during MDE (linear effect per year) was 0.88 (95% CI=0.76-1.02), and during periods not in MDE (combined full and partial remission) 0.55 (95% CI=0.40-0.75) according to the Poisson analyses. Therefore, the risk of SAs in depressive episodes relative to time remained unchanged, but during the other periods it declined over the 5 years.

Figure 8. Incidence per 1000 patient years of suicide attempts during a major depressive episode (MDE), partial remission, and full remission over a 5-year follow-up (N=249). (Based on Poisson distribution.)



7.2.2 Differences between suicide attempters and non-attempters

Patients who attempted suicide during the follow-up period differed significantly from those who did not in terms of age, inpatient status, severity of depression (HAM-D), anxiety (BAI), levels of suicidal ideation (SSI), hopelessness (HS), functional ability (SOFAS), comorbidities, size of social network, perceived social support (PSSS-R), and income level (Table 6).

Table 6. Differences in characteristics between those who did and those who did not attempt suicide during a 5-year prospective follow-up (baseline values if not otherwise specified).

	No suicide attempt		Suicide attempt		Total		
Characteristics	**N**	**%**	**N**	**%**	**N**	**%**	**P**
Total	213	85.5	36	14.5	249	100	
Sociodemographic features							
Gender							n.s.
Male	56	26.3	8	22.2	64	25.7	
Female	157	73.7	28	77.8	185	74.3	
Married or cohabiting	117	54.9	14	38.9	131	52.6	
Income lower	84	43.3	20	64.5	104	46.2	
Employed	130	62.5	21	60.0	151	62.1	
Professional education	85	39.9	12	33.3	97	39.0	
Outpatient status	185	86.9	23	63.9	208	83.5	.001
Psychiatric comorbidity							
Axis I comorbidity	138	64.8	24	66.7	162	65.1	n.s.
Dysthymia	23	10.8	2	5.6	25	10.0	n.s.
Anxiety disorders	120	56.3	22	61.1	142	57.0	n.s.
Alcohol use disorders during follow-up	71	33.3	24	66.7	95	38.2	<.001
Axis II comorbidity							
Personality disorder during follow-up	114	53.5	26	72.2	140	56.2	.036
Depression-related characteristics							
Psychotic features during follow-up	25	11.7	11	30.6	6	14.5	.003
Melancholic features	78	36.6	14	38.9	92	36.9	n.s.
Atypical features	21	9.9	1	2.8	22	8.8	n.s.
History of suicidal behavior							
Suicide ideation prior to entry	131	61.5	28	80.0	159	64.1	.034
Suicide attempt prior to entry	63	29.6	22	61.1	85	34.1	<.001
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P**
Sociodemographic features							
Age years	40.8	11.1	36.2	10.0	39.6	11.1	.020
Clinical features of MDD							
Age of onset years	32.2	12.9	29.6	11.3	31.5	12.5	n.s.
No. of previous episodes	1.7	2.6	1.9	3.7	1.7	2.7	n.s.
Symptoms and functional ability							
HAM-D max [a]	19.3	16.2	23.4	7.6	19.7	6.5	<.001
BDI max [b]	27.2	8.2	31.7	8.8	27.9	8.4	.003
BAI max [c]	24.2	10.9	29.2	11.5	24.7	10.9	.011
SSI	5.1	7.1	12.5	9.9	6.4	8.1	<.001
HS (HAM-D min) [d]	6.1	4.7	8.7	6.0	6.9	5.1	.020
SOFAS	52.7	10.5	48.2	12.5	51.8	10.9	.021
Comorbidity							
No. of cluster A symptoms	2.3	2.5	3.4	2.6	2.5	2.6	.012
No. of cluster B symptoms	3.8	4.3	5.1	6.0	4.1	4.8	n.s.
No. of cluster C symptoms	5.9	4.5	6.5	4.0	6.0	4.5	n.s.
No. of comorbid psychiatric disorders	2.9	1.7	3.6	2.1	3.1	1.8	.027
No. of current somatic diseases	0.6	1.1	0.4	0.8	0.6	1.1	n.s.
No. of suicide attempts prior to entry	0.6	1.7	1.7	3.6	0.7	2.0	<.001
Psychosocial and personality factors							
Perceived social support (HAM-D min) [e]	43.3	2.9	39.3	13.9	41.9	13.3	n.s.
Size of social network (HAM-D min) [f]	7.9	3.9	5.9	2.9	7.5	3.8	.002
Negative life events [g]	8.3	4.5	9.3	4.6	8.5	4.5	n.s.
Neuroticism [h]	17.2	4.0	18.1	2.9	17.4	3.9	n.s.
Extroversion [h]	10.1	4.6	9.4	4.4	10.0	4.6	n.s.

Statistical methods:
Categorical variables: Chi-square test with Yates' continuity correction, or Fisher's exact test when the expected cell count less than 5 in the 2x2 table.
Continuous variables: two-sample t-test for normal distribution; Mann-Whitney and Kruskal-Wallis tests for non-normal distribution.

a Maximum score of HAM-D during follow-up
b Maximum score of BDI during follow-up
c Maximum score of BAI during follow-up
d HS when minimum score of HAM-D during follow-up (trait)
e Perceived social support when minimum score of HAM-D during follow-up (trait)
f Size of social network when minimum score of HAM-D during follow-up
g Interview for Recent Life Events: objective measure of negative impact of adverse life events
h Eysenck Personality Inventory: for dimensions of neuroticism and extroversion

Abbreviations:
MDD = Major Depressive Disorder
MDE = Major Depressive Episode
HAM-D = Hamilton Rating Scale for Depression
BDI = Beck Depression Inventory
BAI = Beck Anxiety Inventory
HS = Beck Hopelessness Scale
SSI = Scale for Suicidal Ideation
SOFAS = Social and Occupational Functioning Assessment Scale
OCD = Obsessive-Compulsive Disorder
GAD = Generalized Anxiety Disorder

7.2.3 Predictors of suicide attempt during the follow-up

After removing non-significant variables, SAs were predicted by 1) time spent in MDEs, 2) time spent in partial remission, 3) previous suicide attempt, 4) lower age, and 5) lower perceived social support in the the Cox proportional hazards model. Time spent in MDE was the strongest predictor, increasing the risk of SA nearly eightfold (Table 2). Incorporating individual frailty in the model, the variance of random effect was 3.77, with a p value <.001 (e.g., relatively high compared with fixed effects), indicating a significant individual variance. No significant interaction was detected between high-risk time periods (MDE) and other risk factors. The adjusted population attributable fraction (PAF) of time spent in MDEs for suicide attempts was 78% (95% CI=59-86).

7.3. Switch to bipolar disorder during the prospective follow-up (Study III)

Within 5 years 29 patients (11.7%) who previously suffering from unipolar MDD switched to bipolar disorder (BD) type I or II. A diagnostic change to BD type II was 3 times more common: e.g., 22 (8.9%) to type II vs. 7 (2.8%) patients to type I. Therefore, the annual incidence of switch was 2.8% (95% CI 1.86-4.04): 0.68% for type I (95% CI 0.27-1.40) and 2.14% for type II (95% CI 1.34-3.23). Four (57.1%) BD type I patients had experienced mixed episodes. Three of the followed-up patients experienced substance-induced hypomanic or manic episodes. The median (SD) time to the first hypomanic or manic episode was 22.0 (SD=13.0) months from baseline: to manic episode, 4.2 (SD=0.5) months and to hypomanic 25.0 (SD=4.7) months (χ^2=10.7, df=1, p=.001). The median (SD) time from age at onset to diagnostic switch was 7.7 (SD=1.9) years: to BD type I, 2.8 (SD=0.6) years and to type II, 7.7 (SD=2.7) years (Figure 9).

7.3.1 Differences between patients switching and not switching to bipolar disorder

The sociodemographic characteristics of unipolar MDD patients and bipolar patients were not significantly different. All BD type I patients were female, but this was statistically insignificant because of the small number of patients in this subgroup. The clinical characteristics differed in some respects, bipolar patients having younger age at onset, more severe, and psychotic MDD at baseline, more comorbid psychiatric disorders, especially Axis I comorbid disorders, more social phobia, OCD, and alcohol dependence than unipolar patients (Table 7). BD type I patients suffered at baseline more from psychotic symptoms compared with BD type II and unipolar patients (42.9% vs. 9.1% and 6.8%, χ^2=11.9, df=2, p=.003), while BD type II patients had significantly more MDEs prior to the switch than type I patients, i.e., mean number of 4.7 (SD=2.7) vs. 2.1 (SD=0.7) episodes,

(t=-3.77, df=24.0, p=.001). There were also differences in comorbidity: BD type I patients compared with type II and unipolar MDD patients had more alcohol dependence (57.1% vs. 13.6% and 11.9%, χ^2=12.0, df=2, p=.002), phobic anxiety disorders (85.7% vs. 45.5% and 37.4%, χ^2=6.97, df=2, p=.031), panic disorder with agoraphobia (28.6% vs. 9.1% and 5.5%, χ^2=6.27, df=2, p=.043), and OCD (28.6% vs. 22.7% and 4.6%, χ^2=15.6, df=2, p<.001); BD type II patients had significantly more social phobia than the other 2 groups (36.4% vs. 28.6% and 16.0%, χ^2=6.12, df=2, p=.047). Patients who switched to BD received antidepressant treatment for a significantly longer time than patients who remained unipolar (t=-2.21, df=246, p=.028). However, the difference was insignificant after adjusting for the number of MDE recurrences, suggesting that these patients were proportionally more ill during their follow-up.

Figure 9. Survival curve to switch to bipolar disorder I and II of unipolar MDD.

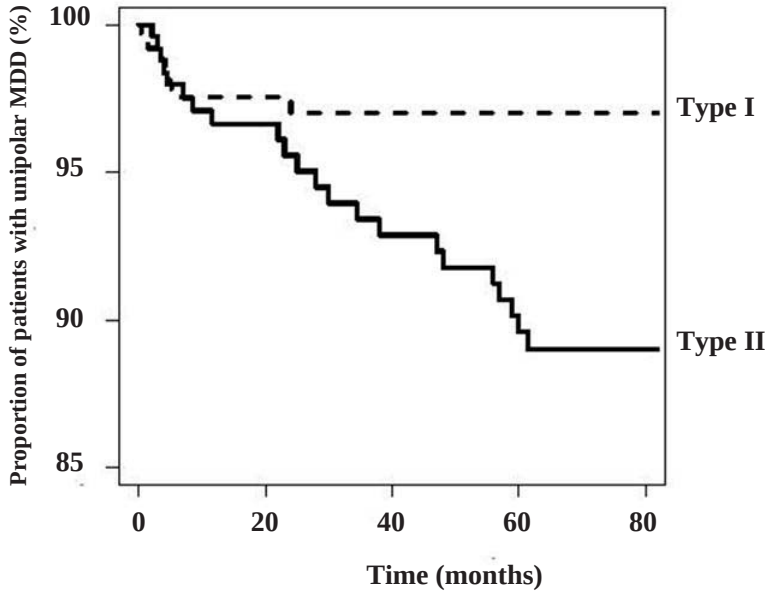


Table 7. Sociodemographic and clinical characteristics of subjects who switched from unipolar depression to bipolar disorder (N=29) vs. unipolar subjects (N=219) in the Vantaa Depression Study, 5-year follow-up.

Predictor at entry	OR	95% CI	P
Age	0.98	[0.94 - 1.01]	0.175
Gender (female)	1.40	[0.54 - 3.64]	0.487
Employed	0.61	[0.27 - 1.37]	0.233
Professional education	1.14	[0.51 - 2.52]	0.748
Residential area (east)	1.20	[0.54 - 2-67]	0.646
Income	0.59	[0.25 - 1.39]	0.226
Married or cohabiting	0.73	[0.33 - 1.59]	0.423
Professional education	1.14	[0.51 - 2.52]	0.748
Outpatient status	0.73	[0.33 - 1-59]	0.423
Age at onset	0.81	[0.66 - 0.99]	0.041
Number of previous MDEs	1.06	[0.88 - 1.29]	0.519
MDE duration prior entry	0.88	[0.76 - 1.01]	0.060
Melancholic	1.47	[0.67 - 3.25]	0.338
Psychotic	2.90	[0.96 - 8.85]	0.060
HAM-D	1.10	[1.02 - 1.17]	0.008
BDI	1.04	[0.99 - 1.08]	0.144
BAI	1.03	[1.00 - 1.07]	0.087
SOFAS	0.99	[0.96 - 1.03]	0.752
HS	0.99	[0.91 - 1.07]	0.759
SSI	0.98	[0.93 - 1.03]	0.440
Size of social network	0.97	[0.86 - 1.09]	0.612
PSSS-R	1.00	[0.97 - 1.04]	0.883
Negative life events [a]	1.10	[0.99 - 1.21]	0.067
Neuroticism [b]	1.08	[0.96 - 1.21]	0.192
Extroversion [b]	0.98	[0.90 - 1.07]	0.599
Axis I comorbidity	2.43	[0.89 - 6.67]	0.084
Dysthymia	1.20	[0.33 - 4.39]	0.781
Anxiety disorders	1.76	[0.77 - 4.08]	0.182
Alcohol use disorders	1.61	[0.67 - 3.91]	0.290
Dependence	2.52	[0.94 - 6.71]	0.066
Abuse	0.62	[0.14 - 2.79]	0.529
Axis II comorbidity			
Personality disorders	1.23	[0.56 - 2.71]	0.609
Cluster A	1.57	[0.62 - 4.00]	0.344
Cluster B	1.21	[0.42 - 3.48]	0.725
Cluster C	1.60	[0.72 - 3.56]	0.253
No. of psychiatric disorders	1.32	[1.08 - 1.62]	0.007
Axis III comorbidity			
No. of current somatic diseases	0.58	[0.30 - 1.14]	0.112
No. of all axis I-III disorders	1.16	[0.97 - 1.38]	0.116

Logistic regression models; all analyses controlled for age and gender, and time at risk.

a Interview for Recent Life Events: objective measure of negative impact of adverse life events.
b Eysenck Personality Inventory: for dimensions of neuroticism and extroversion.

Abbreviations:
HAM-D = Hamilton Rating Scale for Depression
BDI = Beck Depression Inventory
BAI = Beck Anxiety Inventory
HS = Beck Hopelessness Scale
SSI = Scale for Suicidal Ideation
SOFAS = Social and Occupational Functioning Assessment Scale
OCD = Obsessive-Compulsive Disorder
GAD = Generalized Anxiety Disorder
PSSS-R = Perceived Social Support Scale-Revised

7.3.2 Predictors of a switch to bipolar disorder during the follow-up

The probability and time to a diagnostic switch from unipolar MDD to BD were predicted by many univariate variables (Table 8). However, after removing all non-significant factors, in multivariate Cox proportional hazards analyses, severity of MDD (HAM-D; HR=1.08, 95% CI 1.00-1.15, P=.036), OCD (HR=5.00, 95% CI 2.04-12.5, P<.001), social phobia (HR=2.33, 95% CI 1.00-5.26, P=.050), and a large number of cluster B personality disorder symptoms (HR=1.10, 95% CI 1.02-1.20, P=.022) predicted the switch to BD type I or II most significantly. Within cluster B personality disorders, the numbers of narcissistic (HR=0.72, 95% CI 0.57-0.90, p=.003) and antisocial (HR=0.47, 95% CI 0.30-0.74, p=.001) personality disorder symptoms were the strongest predictors. After multivariate analyses of different cluster B items, only attention seeking predicted a switch to BD as a trend (OR=2.57, 95% CI0.93-7.14, p=.069).

Table 8. Significant baseline univariate predictors for switch from unipolar depression to bipolar disorder in the Vantaa Depression Study, 5-year follow-up.

Predictor at entry	HR	95% CI	P
17-item HAM-D	1.10	[1.03 - 1.16]	0.003
No. of anxiety disorder symptoms	1.09	[1.04 - 1.15]	<0.001
No. of phobic disorder symptoms	1.10	[1.03 - 1.19]	0.007
Social phobia	2.78	[1.27 - 5.88]	0.010
OCD	5.88	[2.50 - 14.3]	<0.001
Alcohol dependence	2.94	[1.23 - 7.14]	0.014
Psychotic MDD	3.33	[1.25 - 9.09]	0.016
No. of psychiatric disorders	1.30	[1.08 - 1.56]	0.004
No. of cluster A personality disorder symptoms	1.16	[1.03 - 1.32]	0.015
No. of cluster B personality disorder symptoms	1.19	[1.10 - 1.28]	<0.001
No. of cluster C personality disorder symptoms	1.09	[1.01 - 1.16]	0.025
Negative life events [a]	1.10	[1.00 - 1.19]	0.048

Cox proportional hazards models; all analyses controlled for age and gender

a Interview for Recent Life Events: objective measure of negative impact of adverse life events

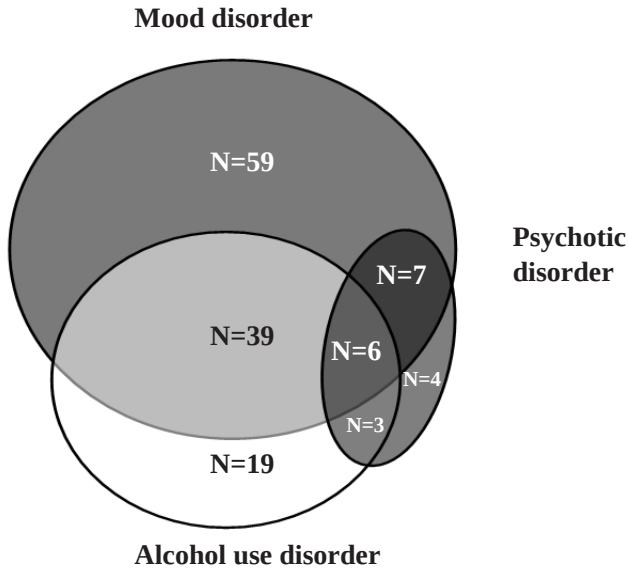
Abbreviations:
HAM-D = Hamilton Rating Scale for Depression
OCD = Obsessive-Compulsive Disorder
MDD = Major Depressive Disorder

7.4. Family history and outcome of MDD (Study IV)

7.4.1 Prevalence of family history

Three-fourths of the followed up patients (74.9%, N=137/183) had a FH of mood disorders, alcoholism, or psychotic disorders; more specifically, three-fifths had (60.7%, N=111) a family history of mood disorders, over one-third (36.6%, N=67) of alcoholism, and a tenth (10.9%, N=20) of psychotic disorders. Only two patients reported FH of bipolar disorder. An overlap of FH was common (Figure 10), one-fourth (24.6%, N=45) having histories of both mood disorders and alcoholism. Eight patients (4.4%) had a first-degree relative, who had died by committing suicide, all also having suffered from mental disorders (seven of mood disorder, six of alcoholism). Women and men reported nearly equally positive FHs of any of the mental disorders (75.7% vs. 71.8%, NS).

Figure 10. Overlap of family history of mood disorder (N=111), alcohol use disorder (N=67), and psychotic disorder (N=20) in the Vantaa Depression Study.



7.4.2 Family history of any of the mental disorders

Patients with and without a FH of any of the mental disorders (mood disorder, alcohol use disorder, and psychotic disorders) had differences in sociodemographic and clinical features in many aspects: those with FH were older, had significantly more previous and lifetime MDEs, suffered from a higher severity of depression and anxiety, more neuroticism (during mildest depression), had attempted suicide during their lifetime more often, had a larger number of lifetime suicide attempts, and spent more time in MDE during the follow-up (Table 9). They also had significantly more comorbid psychiatric disorders, and specifically cluster C personality disorders (Table 10). In the final multivariate logistic regression model, the predetermined independent variables comprised gender, age, duration of follow-up, age at onset, lifetime number of MDEs, highest level of depression (Ham-D), and anxiety (BAI) during follow-up, lifetime suicide attempt, perceived social support, hopelessness, neuroticism (during lowest depression), time spent in MDE, comorbid anxiety and personality disorders. However, after removing non-significant variables, lifetime suicide attempt (OR=3.75, 95% CI 1.57-8.93, P=.003), and cluster C personality disorder (OR=2.92, 95% CI 1.18-7.19, P=.021) persisted in the logistic regression model. The number of suicide attempts prior to or during follow-up was nearly four-fold among patients with a FH of mental disorders (mean number 1.31 [SD=3.34] vs. 0.30 [SD=0.81]) compared to those without this FH. Of different cluster C personality disorders, avoidant personality disorder associated the strongest with FH. The associations remained unchanged in sensitivity analyses, after omitting from analyses, or adjusting for, patients switching to bipolar disorder during follow-up.

Table 9. Sociodemographic and clinical features of patients with or without a family history of mental disorders, mood disorders, or alcohol use disorders during a 5-year follow-up of the Vantaa Depression Study (baseline values if not otherwise specified).

	Mental disorder [a]					Mood disorder					Alcoholism				
	Yes		No			Yes		No			Yes		No		
Characteristics	**N / mean**	**% / SD**	**N / mean**	**% / SD**	**P**	**N / mean**	**% / SD**	**N / mean**	**% / SD**	**P**	**N / mean**	**% / SD**	**N / mean**	**% / SD**	**P**
Total	137	(74.9)	46	(25.1)		111	(60.7)	72	(39.3)		67	(36.6)	116	(63.4)	
Sociodemographic features															
Gender	28	(20.4)	11	(23.9)	n.s.	21	(18.9)	18	(25.0)	n.s.	16	(23.9)	23	(19.8)	n.s.
Male	109	(79.6)	35	(76.1)	n.s.	90	(81.1)	54	(75.0)	n.s.	51	(76.1)	93	(80.2)	n.s.
Female	41.4	(11.2)	36.4	(10.6)	.008	41.6	(10.8)	38.1	(11.5)	.037	41.5	(11.5)	39.4	(11.0)	n.s.
Age (years)	116	(84.7)	42	(91.3)	n.s.	96	(86.5)	62	(86.1)	n.s.	58	(86.6)	100	(86.2)	n.s.
Outpatient status	75	(54.7)	27	(58.7)	n.s.	62	(55.9)	40	(55.6)	n.s.	38	(56.7)	64	(55.2)	n.s.
Married or cohabiting	1.7	(0.8)	2.1	(0.8)	n.s.	1.7	(0.7)	2.1	(0.9)	n.s.	1.7	(0.7)	1.9	(0.8)	n.s.
Number of minor children	7.8	(3.6)	7.8	(3.4)	n.s.	7.9	(3.5)	7.7	(3.7)	n.s.	7.4	(3.8)	8.0	(3.4)	n.s.
Size of social network	38.5	(12.7)	42.7	(11.2)	n.s.	38.7	(12.8)	40.8	(11.9)	n.s.	36.5	(12.4)	41.3	(12.2)	.011
PSSS-R score	8.3	(4.5)	8.2	(4.6)	n.s.	8.7	(4.7)	7.7	(4.3)	n.s.	8.3	(4.8)	7.9	(4.5)	n.s.
Negative life events [b]	54	(43.9)	18	(43.9)	n.s.	46	(44.7)	26	(42.6)	n.s.	22	(38.6)	50	(46.7)	n.s.
Income (lower)	91	(67.4)	26	(59.1)	n.s.	70	(64.2)	47	(67.1)	n.s.	46	(69.7)	71	(62.8)	n.s.
Employed	52	(38.0)	17	(37.0)	n.s.	43	(38.7)	26	(36.1)	n.s.	22	(32.8)	47	(40.5)	n.s.
Professional education	49	(36.0)	20	(43.5)	n.s.	39	(35.5)	30	(41.7)	n.s.	25	(37.3)	44	(38.3)	n.s.
Residential area (socioeconomically poorer)	8	(6.9)	0	(0.0)	n.s.	7	(7.3)	1	(1.7)	n.s.	6	(10.5)	2	(2.1)	(.056)
Family history of suicide	33.0	(12.6)	31.3	(12.4)	n.s.	32.9	(12.1)	32.2	(13.3)	n.s.	32.3	(12.9)	32.8	(12.3)	n.s.
Clinical features															
No. of previous episodes	1.8	(2.8)	0.9	(1.3)	.006	1.7	(2.5)	1.3	(2.6)	(.074)	1.9	(3.5)	1.3	(1.7)	n.s.
Highest HAM-D during follow-up	21.1	(5.9)	18.2	(5.8)	.005	21.1	(5.6)	19.2	(6.4)	.035	21.4	(5.9)	19.7	(5.9)	(.060)
Highest BDI during follow-up	29.0	(8.5)	26.3	(9.4)	(.070)	28.6	(8.2)	28.0	(9.6)	n.s.	30.4	(8.3)	27.2	(8.8)	.018
Highest BAI during follow-up	25.5	(10.5)	20.8	(11.0)	.010	25.2	(10.4)	23.0	(11.3)	n.s.	27.3	(10.1)	22.7	(10.9)	.005
SSI	6.1	(7.9)	5.1	(7.5)	n.s.	6.3	(7.7)	5.2	(7.9)	n.s.	5.7	(7.3)	6.0	(8.1)	n.s.
HS during lowest depression	6.6	(4.7)	5.2	(4.7)	(.080)	6.6	(4.6)	5.7	(4.9)	n.s.	6.4	(4.5)	6.1	(4.8)	n.s.
SOFAS	52.7	(10.4)	54.8	(7.3)	n.s.	53.5	(10.5)	52.9	(8.5)	n.s.	51.0	(10.7)	54.5	(8.9)	.025
Melancholic features	48	(35.0)	14	(30.4)	n.s.	40	(36.0)	22	(30.6)	n.s.	21	(31.3)	41	(35.3)	n.s.
Atypical features	14	(10.2)	4	(8.7)	n.s.	12	(10.8)	6	(8.3)	n.s.	9	(13.4)	9	(7.8)	n.s.
Psychotic features	10	(7.3)	2	(4.3)	n.s.	9	(8.1)	3	(4.2)	n.s.	5	(7.5)	7	(6.0)	n.s.
Neuroticism (during mildest depression) [c]	14.2	(5.3)	11.5	(5.3)	.007	14.4	(4.7)	12.1	(6.1)	.015	14.3	(6.0)	12.9	(5.1)	n.s.
Extroversion (during mildest depression) [c]	11.0	(4.3)	12.1	(4.4)	n.s.	10.7	(4.3)	12.1	(6.1)	(.056)	11.1	(3.9)	11.5	(4.6)	n.s.
Lifetime suicide attempt	59	(43.1)	8	(17.4)	.003	46	(41.4)	21	(29.2)	(.092)	22	(38.6)	29	(29.9)	n.s.
Number of lifetime suicide attempts	1.3	(3.4)	0.3	(0.8)	.002	1.1	(2.7)	1.1	(3.4)	n.s.	1.4	(3.5)	0.9	(2.6)	(.100)
Lifetime number of MDEs	3.5	(3.2)	2.3	(1.9)	.006	3.3	(2.9)	2.9	(3.0)	n.s.	3.7	(3.7)	2.8	(2.3)	(.062)
Time spent in MDE (months)	12.5	(14.0)	8.5	(11.7)	.017	12.8	(14.1)	9.6	(12.5)	n.s.	14.2	(15.7)	10.0	(12.0)	.042

Statistical methods:
Categorical variables: Chi-square test with Yates' continuity correction, or Fisher's exact test when the expected cell count was less than 5 in the 2x2 table.
Continuous variables: two-sample t-test for normal distribution; Mann-Whitney and Kruskal-Wallis tests for nonnormal distribution.

a Mental disorder= Psychotic disorder, mood disorder, or alcoholism.
b Interview for Recent Life Events: objective measure of negative impact of adverse life events.
c Eysenck Personality Inventory: for dimensions of neuroticism and extroversion.

Abbreviations:
PSSS-R = Perceived Social Support Scale-Revised
MDE = Major Depressive Episode
HAM-D = Hamilton Rating Scale for Depression
BDI = Beck Depression Inventory
BAI = Beck Anxiety Inventory
HS = Beck Hopelessness Scale
SSI = Scale for Suicidal Ideation
SOFAS = Social and Occupational Functioning Assessment Scale

Table 10. Comorbid disorders of patients with or without a family history of mental disorders, mood disorders, and alcohol use disorders in the Vantaa Depression Study (VDS) (baseline values if not otherwise specified).

	Mental disorder [a]					Mood disorder					Alcoholism				
	Yes		No			Yes		No			Yes		No		
Characteristics	**N / mean**	**% / SD**	**N / mean**	**% / SD**	**P**	**N / mean**	**% / SD**	**N / mean**	**% / SD**	**P**	**N / mean**	**% / SD**	**N / mean**	**% / SD**	**P**
Axis I comorbidity	94	(68.6)	28	(60.9)	n.s.	73	(65.8)	49	(68.1)	n.s.	50	(74.6)	72	(62.1)	(0.083)
Dysthymia	17	(12.4)	2	(4.3)	n.s.	14	(12.6)	5	(6.9)	n.s.	13	(19.4)	6	(5.2)	0.005
Anxiety disorders during follow-up	94	(68.6)	24	(52.2)	(0.066)	74	(66.7)	44	(61.1)	n.s.	47	(70.1)	71	(61.2)	n.s.
Phobic	57	(41.6)	15	(32.6)	n.s.	43	(38.7)	29	(40.3)	n.s.	29	(43.3)	43	(37.1)	n.s.
Panic disorder	45	(32.8)	10	(21.7)	n.s.	37	(33.3)	18	(25.0)	n.s.	25	(37.3)	30	(25.9)	n.s.
with/	23	(16.8)	2	(4.3)	(0.060)	18	(16.2)	7	(9.7)	n.s.	12	(17.9)	13	(11.2)	n.s.
without agoraphobia	24	(17.5)	5	(10.9)	n.s.	19	(17.1)	10	(13.9)	n.s.	16	(23.9)	13	(11.2)	0.040
Agoraphobia without panic	20	(14.6)	4	(8.7)	n.s.	13	(11.7)	11	(15.3)	n.s.	11	(16.4)	13	(11.2)	n.s.
Specific phobia	48	(35.0)	15	(32.6)	n.s.	38	(34.2)	25	(34.7)	n.s.	27	(40.3)	36	(31.0)	n.s.
Social phobia	30	(21.9)	7	(15.2)	n.s.	23	(20.7)	14	(19.4)	n.s.	14	(20.9)	23	(19.8)	n.s.
OCD	22	(16.1)	8	(17.4)	n.s.	19	(17.1)	11	(15.3)	n.s.	11	(16.4)	19	(16.4)	n.s.
GAD	27	(19.7)	4	(8.7)	n.s.	23	(20.7)	8	(11.1)	n.s.	10	(14.9)	21	(18.1)	n.s.
Alcohol use disorders during follow-up	52	(38.0)	14	(30.4)	n.s.	42	(37.8)	24	(33.3)	n.s.	29	(43.3)	37	(31.9)	n.s.
Dependence	35	(25.5)	10	(21.7)	n.s.	27	(24.3)	18	(25.0)	n.s.	23	(34.3)	22	(19.0)	0.032
Abuse	17	(12.4)	4	(8.7)	n.s.	15	(13.5)	6	(8.3)	n.s.	6	(9.0)	15	(12.9)	n.s.
Axis II comorbidity (Personality disorders)	59	(43.1)	17	(37.0)	n.s.	46	(41.4)	30	(41.7)	n.s.	33	(49.3)	43	(37.1)	n.s.
Cluster A	23	(16.8)	5	(10.9)	n.s.	20	(18.0)	8	(11.1)	n.s.	13	(19.4)	15	(12.9)	n.s.
Number of cluster A symptoms	2.5	(2.7)	1.7	(2.2)	(0.073)	2.5	(2.7)	2.0	(2.5)	n.s.	2.9	(2.9)	1.9	(2.4)	0.028
Cluster B	20	(14.6)	7	(15.2)	n.s.	13	(11.7)	14	(19.4)	n.s.	12	(17.9)	15	(12.9)	n.s.
Number of cluster B symptoms	3.5	(3.8)	3.4	(3.5)	n.s.	3.0	(3.2)	4.3	(4.3)	0.075	4.2	(4.3)	3.1	(3.3)	(0.082)
Cluster C	48	(35.0)	8	(17.4)	0.039	36	(32.4)	20	(27.8)	n.s.	26	(38.8)	30	(25.9)	(0.096)
Number of cluster C symptoms	6.1	(4.8)	5.5	(3.9)	n.s.	6.0	(4.8)	5.9	(4.3)	n.s.	6.9	(5.0)	5.4	(4.3)	(0.051)
Number of psychiatric disorders	3.2	(1.9)	2.5	(1.5)	0.033	3.1	(1.8)	2.9	(1.9)	n.s.	3.4	(2.0)	2.8	(1.7)	0.037
Axis III comorbidity	68	(52.7)	25	(56.8)	n.s.	56	(53.3)	37	(54.4)	n.s.	32	(50.8)	61	(55.5)	n.s.
Number of current somatic diseases	0.7	(1.2)	0.4	(1.0)	n.s.	0.7	(1.1)	0.5	(1.2)	n.s.	0.7	(1.2)	0.6	(1.1)	n.s.
Number of all Axis I-III disorders	3.8	(2.2)	3.0	(1.8)	0.011	3.7	(2.1)	3.4	(2.2)	n.s.	4.1	(2.2)	3.3	(2.1)	0.019

Statistical methods:
Categorical variables: Chi-square test with Yates' continuity correction, or Fish er's exact test when the expected c ell count less than 5 in the 2x2 t able.
Continuous variables: two-sample t-test for normal distribution; Mann-Whitney and Kruskal-Wallis tests for nonnormal distribution.

a Mental disorder = Psychotic disorder, mood disorder, or alcoholism.

Abbreviations:
OCD = Obsessive compulsive disorder
GAD = Generalized anxiety disorder

7.4.3 Family history of mood disorders

Patients who had a positive FH of mood disorders were significantly older, had more severe depression, higher neuroticism (during their mildest depression), and also tended to have lower extroversion and have attempted suicide during their lifetimes more often, than those without FH. Among women the association with lower extroversion and FH was significant (t=2.11, p=0.037), but among men it was not. Patients with FH were not significantly different in terms of age at onset, time spent in MDE, or time to their first recurrence (Table 9). In addition, the prevalence of comorbid psychiatric disorders was not significantly different (Table 10). In the *multivariate logistic regression model*, the predetermined independent variables comprised gender, age, duration of follow-up, age at onset, highest severity of depression during follow-up (Ham-D), lifetime suicide attempt, neuroticism (during lowest depression), comorbid anxiety, and personality disorders. After removing non-significant variables, only higher neuroticism (OR=1.08, 95% CI 1.02-1.15, P=.014) persisted in the logistic regression model. There was a gender difference, as the association with neuroticism existed only in women (OR=1.12, p=0.005 vs. in men OR=1.01, p=0.798). Patients with higher neuroticism had significantly more comorbid personality disorders, especially cluster C disorders. When adjusting in the model for FH of alcoholism, the findings persisted. However, the association became weaker in sensitivity analyses, after omitting from analyses patients switching to bipolar disorder during follow-up omitting patients switching to bipolar disorder during follow-up: neuroticism remained associated with FH, but only as a non-significant trend (OR=1.06, p=0.078).

7.4.4 Family history of alcoholism

Patients who reported FH of alcoholism perceived significantly less social support, had more severe depression, anxiety, lower social and occupational functioning, and spent more time in MDE during the follow-up, compared to those without (Table 9). In addition, they had more comorbid somatic and psychiatric disorders, more often alcohol dependence, dysthymia, panic disorder, and comorbid cluster A personality disorder symptoms, and cluster B and C symptoms as a trend (Table 10). In the *multivariate logistic regression model*, the predetermined independent variables comprised gender, age, duration of follow-up, highest severity of depression during the follow-up (BDI), of anxiety (BAI), social and occupational functioning (SOFAS), lifetime number of depressive episodes, neuroticism (during their lowest depression), perceived social support, time spent in MDE, comorbid dysthymia, anxiety, alcohol use disorders, and personality disorders. After removing the non-significant variables, alcohol dependence during follow-up (OR=2.27, 95% CI 1.01-5.08, P=.047), larger number of comorbid cluster B personality disorder symptoms (OR=1.11, 95% CI 1.01-1.23, P=.030), and comorbid dysthymia (OR=4.35, 95% CI 1.51-12.5, P=.007) persisted in the logistic regression model. There were gender differences: in men,

alcohol dependence (OR=4.13, p=0.063) and cluster B personality features (OR=1.34, p=0.064), in women dysthymia (OR=6.67, p=0.001) were significantly associated with familial alcoholism. When FH for mood disorder was adjusted in the model in order to eliminate the possible role of confounding, alcohol dependence during the follow-up remained associated with familial alcoholism, but only as a non-significant trend (OR=2.04, p=0.059). However, the association with number of cluster B personality disorder symptoms lost significance in sensitivity analyses, after omitting from the analyses the patients switching to bipolar disorder during follow-up.

7.4.5 Family history of psychotic disorders

Patients who reported FH of mood disorders spent significantly more time in MDE, less time in full remission, and had more depressive episodes prior to the baseline. They were not significantly different in terms of psychotic symptoms, or cluster A personality disorders. In the *multivariate logistic regression model*, the predetermined independent variables comprised gender, age, duration of follow-up, time spent in full remission, number of previous depressive episodes, psychotic symptoms, and comorbid cluster A personality disorder. After removing non-significant variables, shorter time spent in full remission persisted in the logistic regression model (OR=0.97, 95% CI 0.96-1.04, P=.039). The associations remained unchanged in sensitivity analyses, after omitting from analyses, or adjusting for, patients switching to bipolar disorder during the follow-up.

8 Discussion

8.1 Main findings

The long-term outcome of major depressive disorder (MDD) in psychiatric (community-care) patients seems to be more variable than in earlier, mostly inpatient studies. Only one-tenth of these secondary-care MDD patients had a poor outcome, while half had a favourable outcome. Almost all patients recovered over time from their index episode, with 88% reaching full remission at some point. Nevertheless, nearly three-fourths experienced at least 1 recurrence within 5 years, but most of these recurrences were briefer than the index episode.

During the 5-year follow-up, one-seventh of patients attempted suicide at least once, and three-fourths of suicide attempts (SAs) took place during major depressive episodes (MDEs). The incidence rate of SAs was 21-fold during time depressed and fourfold during time in partial remission compared with time in full remission. Besides longer time spent in depressive states, previous suicide attempt, younger age, and lower perceived social support also independently increased the risk of SA.

Within 5 years, over a tenth of patients previously suffering from unipolar MDD switched to bipolar disorder (BD), and of these the majority (three-fourths) switched to type II. The switch to BD type I usually occurred much faster than to type II, when estimated both from both age at onset and baseline. In multivariate Cox proportional hazards analyses, higher severity of MDD, OCD, social phobia, and higher number of cluster B personality disorder symptoms independently predicted a diagnostic switch to BD.

Positive family histories (FHs) of various psychiatric disorders were found to be very common. Three-fourths of patients had a FH of some mental disorder, including in three-fifths of mood disorder, over one-third of alcoholism, and one-tenths of psychotic disorder. Furthermore, a significant overlap in FHs existed; a fourth of the patients had FH of both mood and alcohol use disorders. All types of FHs appear to be associated with a poorer clinical outcome; with an elevated risk for suicide attempt, a more chronic course, and comorbid personality disorders. More specifically, FH of mood disorders appeared independently associated with high neuroticism among female, and that of alcoholism with alcohol dependence among male patients. However, among patients with familial mood and alcohol use disorders the temperamental associations found relied partly, and personality associations significantly, on patients who switched to BD over time.

8.2 Methods

8.2.1 Representativeness of the cohort sample

The present naturalistic study (I-IV) involved a prospective, long-term follow-up assessment of a representative cohort of both outpatients and inpatients with MDD, effectively representing psychiatric patients with a new episode of MDD in the city of Vantaa. The study was initiated during the era of modern antidepressants in 1997-1999 in a community psychiatric setting. On the basis of an epidemiological survey, two-thirds of all depressed patients in the general population of Vantaa seeking treatment from psychiatrists were treated in the PMCD (Rytsälä et al., 2001). Clinical studies conducted on representative unselected samples of commonly met, highly comorbid, depressive patients are very sparse. Although the outcome of MDD has been extensively investigated in short- and medium-tem studies, a limited number of major studies have explored the long-term (five years or more) course of the illness. The different diagnostic criteria, the availability of only tricyclic antidepressants, and the lack of recommendations for widespread continuation and maintenance phase treatments are all major changes that undermine the generalizability of earlier findings to current practice. Only a few studies have studied long-term outcome among outpatients. The majority of the previous studies have been inpatient or tertiary-care studies from major universities, which compromises the epidemiological generalizability of their findings.

The familiar tendency for patients to have undergone many prior treatments in studies conducted in tertiary-level treatment centres may produce bias towards more chronic, severe and recurrent illnesses compared with more unselected cohorts of MDD patients (Furukawa et al., 2000; Roy-Byrne et al., 2000; Spijker et al., 2002). In addition, some studies have not used life-chart methods or structured or semistructured interviews. Furthermore, despite comorbid MDD being common, the effect of comorbidity on long-term outcome of MDD has been surprisingly the subject of few studies. In many studies, the reported prevalences of comorbid disorders appear too low to be plausible from the current perspective. There is also a lack of studies investigating the impact of both axis I and II comorbidity on the long-term outcome of depression.

This study (I-IV) is from the modern era in terms of the use of DSM-IV diagnoses and definitions, modern antidepressants, and maintenance treatment recommendations. It seems that no previous study has investigated the impact of both axis I and II comorbidity on the long-term outcome of depression. We used structured and semistructured measures, both objective and subjective, investigating a broad range of factors from several other domains; sociodemographic factors, clinical variables, temperamental, and psychosocial factors. We used a life-chart methodology, which enabled us to investigate the impact of variations in clinical state and longitudinal outcome.

8.2.2 Diagnostic measures

At intake, the patients were diagnosed using semi-structured interviews with excellent reliability (kappa=0.86) for the diagnosis of MDD with SCAN, Version 2.0 (Wing et al., 1990). However, the reliability of comorbid disorders is unknown. In addition, diagnoses of axis III disorders were based on self-report, although only those diagnosed by a physician were included. Axis II diagnoses were assessed using the semi-structured SCID-II interview for DSM-III-R, as the SCID-II for DSM-IV was not yet available in February 1997. This was also used in the 5-year follow-up interviews. Differences between DSM-III-R and DSM-IV were taken into account by excluding masochistic personality disorder. Passive-aggressive personality disorder was included because it belongs to the personality disorder NOS in DSM-IV. Patients were also interviewed with the SCID-II during their depression, which may (Stuart et al., 1992; Peselow et al., 1994; Ferro et al., 1998), or may not (Loranger et al., 1991) have influenced the prevalence of personality disorders. This, as well as the inclusion of patients with current alcohol use disorders, was done deliberately in order to investigate the persistence and effects of these disorders in the follow-up. In the 5-year follow-up, the SCID-I for DSM-IV-TR Axis I Disorders (First et al., 2002) was used instead of SCAN. Sensitivity analyses to ensure uniformity of ratings were conducted, and inner consistencies (Cronbach alphas) of the rating scales were also checked. No reliability problem that could bias the findings was uncovered.

8.2.3 Life-chart and definitions for outcome

A number of methods for the longitudinal measurement of psychopathology have been developed. Probably one of the most influential measurements is the Longitudinal Interval Follow-up Evaluation (LIFE) methodology, first used to investigate the outcome of depression in the NIMH-CDS (Keller et al., 1987). LIFE is a semi-structured interview and rating system for assessing the longitudinal course of psychiatric disorders in sufficient detail to provide the basis for calculating the length of episodes and time to remission (Keller et al., 1987). In the VDS the outcome of MDD was investigated by using a graphic life chart, which is similar, but not identical to LIFE. Besides symptom ratings and case notes by attending personnel, we also asked the patients about change points in the psychopathological states, using probes related to important life-events in order to improve the accuracy of the assessment. In cases of conflicting information the researchers weighted and integrated all available information, creating a best estimate. Unlike LIFE, patients' follow-up time was classified into periods of DSM-IV MDE, or partial (1-4 criteria symptoms) or full (no symptoms) remission. The major advantage of this classification is that it counts episodes and defines recurrences precisely, as does any clinician when using the DSM-IV. However, comparison of the findings with studies using LIFE can be undertaken only with some caution. For example, it appears that the

criteria for full remission in the VDS were more stringent than those used for recovery in the CDS (Psychiatric Status Ratings, 1-2; no symptoms or 1 to 2 symptoms to a mild degree). Nevertheless, in most longitudinal studies, recurrence/relapse follows a period of remission, which is relatively consistently defined as the presence of only one or two minimal symptoms of major depression to a mild degree, or complete absence of symptoms for at least two months (Keller, 2003). So, having used the same criteria for duration for remission, it is likely that the findings from the VDS are comparable to other studies.

8.2.4 Study limitations

The attrition rate of 5-year follow-up was 28.5% of those living and not having switched to bipolar disorder (BD). The causes for dropping out (N=65) from the study were as follows: withdrawal of consent (63.1%, N=41), patients unreachable despite several efforts (33.8%, N=22), and patients living too far away (3.1%, N=2). However, the drop-out rate from the main follow-ups was quite low, as only 21 patients (7.8%) dropped out from all follow-up interviews. Patients diagnosed during follow-up of BD or non-affective psychotic disorder, remained in the cohort until they were censored at the change of diagnosis. The use of Cox proportional hazards model enabled analyses of information on patients remaining in the study for different lengths of time. In addition, logistic regression analyses were adjusted for the duration of follow-up. Despite having characteristics often associated with poor outcome, it appears unlikely that the dropouts would have significantly biased the findings regarding the likelihood of recurrence, as they did not differ from those included in terms of index episode duration, time to full remission, or number of relapses or recurrences during the period they participated in the study. In addition, the dropouts did not differ in terms of suicide attempts or suicidal ideation at or before the baseline. However, the possibility that the dropouts may have affected the results at least to some extent cannot be excluded.

Despite of access to patient records, a long follow-up period, 3.5 years between the last two interviews, could have affected the accuracy of information regarding longitudinal outcome in the life charts. The recurrence rate during the time most remote from the five-year interview after 18 months was probably slightly underestimated (approximately by 10% overall). When comparisons are made with other studies, it should be also noted that the definition for full remission in this study was strict (Melartin et al., 2004b). Because of the naturalistic nature of our study, the treatment received was not controlled for.

Regarding the study concerning risk factors for suicide attempts (SAs) (study II), similar to any study with retrospective assessment, it is possible that SAs might bias recall of depression. Effort after meaning and circularity as a result of diagnostic criteria could in theory affect the timing of when the SAs and when the MDEs were estimated to have happened. However, although patients or the interviewer might have retrospectively

attributed SAs to MDEs, collateral information on the patients' state at the time of the attempts was also available from psychiatric and medical records. We did not have reliable information on impulsive-aggressive behaviour and traits, which could modify risk during MDEs. However, they often correlate with comorbid cluster B personality disorders and alcohol abuse or dependence. We could only investigate average risk for the time spent in risk states. The risk for SAs likely covaries with variations in levels of hopelessness, depression, and anxiety, none of which could be measured on a daily basis.

Regarding the study concerning the switch to bipolar disorder (BD) (study II), the follow-up period of five years was only moderately long for investigation of a phenomenon that may occur even after decades of a follow-up (Angst, 1985; Angst et al., 2005). In particular, the number of BD type I patients (N=7) was insufficient for differentiation of predictors for both bipolar types. A long follow-up interval between the last two interviews, might also affect the temporal accuracy of information and recall of especially hypomanic episodes. Also due to the four-day limit in DSM-IV criteria on hypomanic episodes, the number of BD type II patients may be an underestimate. As DSM-IV criteria were strictly followed, episodes, such as depressive mixed states (Benazzi, 2007) were not investigated, as they are not included in the DSM-IV classification. In addition, the predictive value of bipolar family history on bipolar switch could not be reliably investigated.

Regarding the study on associations of family history (FH) of mental disorders, and outcome of MDD (study IV), only 68% could be included in the analyses of family history as we inquired about FH only at five-years, not in the previous phases of the follow-up. Unlike most family studies, but similar to most clinical and epidemiological FH studies, FH was ascertained only by an interview of the proband, and the family members themselves were not interviewed which limits the accuracy of the assessment, and may have resulted in underestimates. Because of variations in the patients' age and number of relatives, the analyses did not seperate whether they were pedigrees, siblings, or parents, nor the number of relatives with psychiatric disorders. Only FHs of psychiatric disorders for which the most reliable information could be obtained were investigated, and for this reason did not include information on, for example, familial anxiety disorders (Hardt and Franke, 2007). FH of BD could be detected in only two patients which is very likely an underestimate because of clinically unrecognized familial bipolar type II disorders. The subgroup of patients with a positive FH of a non-affective psychosis was small. Finally, only information on first-degree relatives was reported, which does not exclude the possibility of a positive FH in more distant relatives.

8.3 Long-term outcome of MDD (Study I)

The long-term outcome of this mainly outpatient cohort of clinical secondary care patients was as excepted more variable than in earlier mostly inpatient studies. Studies with mostly inpatients have generally reported larger proportions of incapacitation over time (Lee and Murray, 1988; Thornicroft and Sartorius, 1993; Surtees and Barkley, 1994; Kennedy et al., 2003), and smaller proportions of patients having a good outcome (Lee and Murray, 1988; Andrews et al., 1990; Surtees and Barkley, 1994). Moreover, a number of studies have found chronicity to be a major problem. By contrast, in this study, the proportion of patients never achieving even partial remission was small (1.2%), and the rate for chronic, uninterrupted MDE lasting 2 years or more (7%) was lower than in other studies (Keller et al., 1992; Angst et al., 1996; Kennedy et al., 2003). Also, compared to previous studies, the median *index episode duration* (1.6 months from the baseline, 5.5 months altogether) was much shorter (Surtees and Barkley, 1994; Mueller et al., 1999; Furukawa et al., 2000). However, the median time to *full remission* was longer (11 months vs. 3-7 months) (Keller et al., 1992; Mueller et al., 1999; Furukawa et al., 2000; Kennedy et al., 2003) indicating the problem of incomplete recovery (partial remission), although the proportion of time spent in partial remission during the 5 years was still lower than reported in the CDS and the Cambridge cohorts (Judd et al., 1998; Kennedy et al., 2004). The overall more varying outcome in this study is likely to be due to the less selected nature of this cohort compared with previous predominantly inpatient cohorts from a preceding treatment era. It seems that the prevailing psychiatric view of MDD as a uniformly chronic disorder needs to be revised. Respectively, the estimates of lifetime suicide mortality related to MDD have undergone a similar revision, as the earlier high estimates of 15% of depressed patients dying by suicide were based on biased generalizations from inpatient populations (Bostwick and Pankratz, 2000).

The probability of *recurrence* (71%) in this study was somewhat lower compared to previous studies (Keller et al., 1992; Surtees and Barkley, 1994; Angst et al., 1996) but this figure may an underestimate. However, unlike the situation for inpatient studies, the pattern of recurrence resembled that of community samples, i.e., the recurrent episodes were shorter than the index episode (Spijker et al., 2002). The low rate of hospitalizations (15% after 18 months) also likely reflects milder recurrences during the follow-up. Time to first recurrence and median number of recurrences were similar to the results of previous studies (Solomon et al., 2000). However, the more heterogeneous baseline severity of depression in this cohort allowed us to verify the marked impact of severity on the probability of recurrence.

Previous studies have largely either excluded comorbid patients or ignored the role of psychiatric *comorbidity* in the long-term outcome of MDD. Comorbid cases were deliberately included and account the effect of these disorders were taken into account together with known predictors, and a major role in outcome was observed. Sequenced Treatment Alternatives to Relieve Depression, STAR*D (Rush et al., 2006), a large outpatient clinical trial, has taken into account the role of comorbid Axis I disorders on the outcome of MDD, but has not studied the effect of Axis II disorders at all, and does not include investigation of long-term outcome.

In the present study, cluster C personality disorders, especially avoidant personality and preceding dysthymic disorder, significantly delayed the time to full remission. The time to full remission was twice as long for patients with preceding dysthymic disorder or cluster C personality disorder as for those without these diagnoses. Preceding dysthymic disorders reducing the chances for recovery were similar to the findings in CDS (Keller et al., 1992). In addition, previous short- and medium-term studies, have found comorbid cluster C personality disorders to be associated with slower recovery and a longer time to response or non-response in different stages of MDD treatment (Viinamäki et al., 2002; Morse et al., 2005).

Social phobia was also found to be associated with overall risk of recurrence, a shorter time to first recurrence, and number of recurrences. Earlier community studies have indicated associations between anxiety disorders or social phobia and the development of first MDE or relapse (Coryell et al., 1992; Kessler et al., 1999b; Bittner et al., 2004). However, it seems that they have not specifically investigated the association of social phobia with MDE recurrences. Temperamental predispositions, a tendency for social isolation due to avoidance, or a more cyclic course might explain why comorbid social phobia appears to increase the vulnerability to recurrence. Overall, the predictors for outcome of MDD may, to some extent, be different among outpatient samples than among the previously mostly investigated severely ill inpatients. Further investigation is required on social phobia as a putative predictor of recurrence.

8.4 Long term risk factors of suicide attempts during the prospective follow-up (Study II)

There is a lack of long-term studies investigating variations in the incidence of suicide attempts (SAs) during different levels of depression among patients with unipolar MDD. In this study, the *incidence* rate was strongly variable with time spent in different states, being nearly 21-fold during MDEs compared with states of full remission. This was consistent with findings of the 18-month follow-up assessment of VDS (Sokero et al.,

2005), and in the Jorvi Bipolar Study (JoBS), a comparable study investigating bipolar disorder (Valtonen et al., 2008). Another medium-term study (Oquendo et al., 2002) reported a sevenfold hazard of SAs during depressive episodes, which was similar to the estimates of the present study (HR=7.7). The incidence rate of SAs during MDEs (0.33 per patient-year) was similar to these earlier estimates (0.30-0.42 per patient-year). In accordance with most prospective studies, the risk of SA was highest during the first year of follow-up evaluation, which likely reflected the decline in the time spent in MDE after the first follow-up year. However, the incidence rate of SAs during MDEs remained constant. Shortcomings in the continuity and provision of acute phase, continuation, and maintenance antidepressant and psychosocial treatments are obvious, both in this cohort (Melartin et al., 2005; Holma et al., 2008) and in other settings (Oquendo et al., 2002), and have concerned patients with MDD overall as well as for those attempting suicide. Given the importance of high-risk states for overall risk, reducing the time at risk by effective treatments could be crucial for reducing SAs in the long-term.

Evidence for other *risk and protective factors* affecting the likelihood of SAs was also found. In the earlier 18-month follow-up assessment of the VDS, the risk of SAs was effectively predicted by besides the time spent in MDEs, also lack of a partner, and previous SAs (Sokero et al., 2005). A history of SA has been consistently associated with elevated risk of a later attempt (Fawcett et al., 1990; Duggan et al., 1991; Malone et al., 1995a; Mann et al., 1999; Angst et al., 2002; Maser et al., 2002; Oquendo et al., 2002; Oquendo et al., 2004a; Sokero et al., 2005; Oquendo et al., 2006). Also in the present long-term study, the risk was more than fourfold in patients with compared to those without previous SAs. Also, lack of a partner increased risk as a trend (HR=2.32), repeating the findings of our 18-month follow-up assessment. Marriage has been associated with a lower risk of SAs (Malone et al., 1995a), which could reflect protectiveness toward the family, and child-related concerns (Malone et al., 2000). A partner is often a major factor increasing objective and perceived social support, which in the VDS protected patients from SAs both at baseline (Sokero et al., 2003) and in long-term. In contrast to hypotheses, comorbid cluster B personality disorders were not significantly related to risk. No significant statistical interactions were detected between high-risk time periods (MDEs) and other risk factors, but this does not exclude the possibility that important risk modifying interactions could exist. The significance of individual frailty in the Cox model suggests that unmeasured trait factors (e.g., impulsivity and aggressivity) may well significantly influence suicide attempts. However, the findings of this study do strongly emphasize the significance of state and time varying factors in the risk of suicidal acts.

8.5 Switch to bipolar disorder during the prospective follow-up (Study III)

During the present 5-year follow-up the risk of a diagnostic switch from unipolar MDD to bipolar disorder (BD) was 2.8% annually, which is slightly higher than in previous studies, where the rate has been 1% to 2% (Akiskal et al., 1995). However, the switch rate to BD type I was somewhat low (0.7% per year), which may be due to this study cohort comprising, in contrast to most previous studies, predominantly of outpatients, and not patients from a tertiary care setting. The majority of diagnostic switches were to BD type II; as the annual rate of switch to bipolar II (2.14%) was higher than in previous studies (0.5%-1.8%) (Akiskal et al., 1995; Coryell et al., 1995; Goldberg et al., 2001; Angst et al., 2005) this study may have been more sensitive in its detection. The median time from baseline to the first manic episode was a sixth from the time to hypomanic episode, and about a third from age at onset. Previous reports have described switch rates to manic episodes about 2 times faster than they were to hypomanic episodes (Coryell et al., 1995; Goldberg et al., 2001; Angst et al., 2005). Type I BD patients have been reported in new episodes to have more manic episodes than type II patients have hypomanic episodes (Akiskal et al., 1995; Coryell et al., 1995; Goldberg et al., 2001; Angst et al., 2005). The long time to diagnostic switch from age at onset of MDD, 7.7 years, was consistent with earlier findings of 5 to 8 years (Goodwin and Jamison, 2007; Mantere et al., 2008b). Overall, the results suggest that among outpatients presenting with MDE, a switch to BD type II disorder is more likely than a switch to BD type I. All of the patients with mania were women, which is in accord with the known gender differences in bipolar disorder; among men, manic episodes tend to emerge at an earlier stage and with clinically more acute symptoms, and are also likely to be diagnosed with BD sooner, and thus individuals with this condition have not entered the study cohort as unipolars (Akiskal et al., 1983; Mantere et al., 2004; Goodwin and Jamison, 2007).

A diagnostic switch from unipolar MDD to BD was associated with many *clinical* features, i.e., higher baseline severity of MDD, higher psychiatric comorbidity, psychotic symptoms, and negative life events. Somewhat surprisingly, the number of previous MDEs was not associated with the switch unlike in many previous studies. However, it is important to determine which of the predictors were confounded by other factors, and which appeared as independent predictors. In the multivariate Cox proportional hazards analyses, higher severity of MDD, comorbid OCD, social phobia, and a higher number of cluster B personality disorder symptoms were the most significant independent predictors. Regarding the severity of MDD, the findings were consistent with the results from the Zürich Follow-up Study and

CDS, in which severity of MDD especially predicted the switch to BD type I (Akiskal et al., 1995; Angst et al., 2005). Severity of MDD correlates with the existence of psychotic symptoms, which has, in several studies, predicted the switch to BD (Strober and Carlson, 1982a; Akiskal et al., 1983; Coryell et al., 1995; Goldberg et al., 2001).

Comorbid psychiatric disorders are very common in both MDD and BD. Despite this, whether different comorbid disorders might differentially predict a switch to BD has been rarely systematically investigated. According to this study, both Axis I and II disorders were of importance. Patients with BD have according to investigations twice likely to have social phobia as unipolar MDD patients (Goodwin and Jamison, 2007; Mantere et al., 2008a). Lifetime social phobia has been associated with an earlier age at onset of bipolar disorder OCD contrary to the results of the present study, to delay the onset of bipolarity (Kessler et al., 1999b). As in Study I of this thesis, social phobia seems to be significantly associated with MDE recurrences, which may be related to the switch to BD being frequently associated with a higher number of previous MDEs (Pini et al., 2006). A previous study on temporal relationship between anxiety disorders and (hypo)mania in bipolar patients, found social phobia and OCD to chronologically precede hypomanic episodes (Angst et al., 1978; Angst, 1985; Winokur and Wesner, 1987; Winokur et al., 1993). Nevertheless, it seems that none of these earlier studies have found social phobia or OCD to also predict the diagnostic switch to BD among patients with MDD.

In the analyses of the present study, personality disorders were treated as dimensional variables based on the number of different cluster or individual personality disorder symptoms, as this is also in agreemenr with the current view on personality disorders. A higher number of cluster B personality disorder symptoms was found to significantly predict the diagnostic switch. Within cluster B, the number of antisocial personality symptoms was the strongest predictor in multivariate analyses, while the number of borderline narcissistic, and histrionic personality disorder symptoms predicted the switch in only univariate analyses. In CDS, Akiskal et al. (Akiskal et al., 1995) investigated predictors for a switch to BD type II and reported temperamental and mood instabilities with minor antisocial acts and social anxiety to be significant. Benazzi (Benazzi, 2006) revealed cyclothymic and borderline personality temperaments to be more common in patients with BD type II than in patients with unipolar MDD, finding especially affect instability to be associated with type II. None of these studies have found an association between these features and BD type I. In the present study, the switch to both types of BD was associated with a higher number of cluster B symptoms, but, taking into account the small number of type I patients, these results must be interpreted with caution.

8.6 Family history and outcome of MDD (Study IV)

Family history (FH) of some psychiatric disorder (mood disorder, alcoholism, or psychotic disorder) was very common, as three-fourths (75%) of patients reported psychiatric disorders in their first-degree relatives. Comparison of prevalence to other studies is difficult because of different methods of assessing information on FH. A positive FH was associated with several, clinically significant features of poor outcome, e.g. more recurrent episodes, higher severity of depression and anxiety, more neuroticism, more suicide attempts, and more comorbid, especially anxiety, and cluster C personality disorders. Patients with these traits compared to those without a positive FH spent on average nearly half (47%) more time in MDEs over five years.

Patients with a FH of *alcoholism* compared to those without had a two-fold prevalence of alcohol dependence during the follow-up. This may reflect a specific familial effect and is similar to the findings in the previous literature (Benazzi, 2006). Moreover, these patients suffered significantly more from dysthymia, and had more cluster B personality disorder symptoms, and of these especially borderline, and antisocial disorder symptoms. The relationship of alcoholism and cluster B personality disorders corresponds also to the factor model of externalizing disorders with possible shared genetic factors (Krueger and Markon, 2006). Nevertheless, the predisposition of depressed patients to comorbid alcohol dependence is likely to be influenced not only by a FH of alcoholism alone, but also by other factors, including a FH of mood disorder. Accordingly, when a FH of mood disorder was adjusted in the model for FH of mood disorder, alcohol dependence during follow-up remained associated with familial alcoholism, but only as a non-significant trend.

Patients with a FH of (non-affective) *psychotic* disorders spent a significantly shorter time in full remission during follow-up, and conversely they spent significantly more time in symptomatic states of MDD and partial remission. Contrary to what has beeb hypothesized, psychotic symptoms, or Cluster A disorders or symptoms were not more prevalent among these patients. Therefore, no evidence for a specific predictive value with regard to psychotic features was found; however, the number of MDD patients with positive FH of non-affective psychosis was small.

Three-fifths of the patients (60.7%) had a FH of *mood disorders*. Previous studies investigating first-degree relatives, have reported prevalences of 37.2-55.6% (Prescott et al., 2000; Klein et al., 2001; Kendler et al., 2003b), of which STAR*D reported a prevalence closest to the present study (55.6%), possibly due to a similar method of investigating FH and a similar study cohort comprising clinical outpatients with high comorbidity. One of the central findings was the significant association of FH of mood disorder with higher neuroticism. This is compatible with the findings from a major

population based twin study, which reported neuroticism to reflect a liability to depressive illness, and this relationship being due to common genetic factors (Klein et al., 2001; Verhagen et al., 2008; Husain et al., 2009). There is a lack of clinical studies which have previously investigated this association. In the present study, there were gender differences as neuroticism and FH were significantly associated mainly with women, while the study of Kendler et al. detected no significant interactions with gender (Kendler et al., 2006b). Analogously, lower extroversion was associated with a FH of mood disorders significantly only among female patients. Higher neuroticism was associated with a larger number of cluster C personality disorders, which Study I predicted to result in a poor outcome with more recurrences and a longer time spent in MDE.

Patients with a FH of mood disorders were also older, suffered from more severe depression, and had attempted suicide during their lifetimes more often as a trend compared to those without such a FH. A potential explanation for the association with older age may be a larger number of first degree relatives and a larger interest and knowledge of the matter. Severity of depression has also in previous reports been associated with FH (Kendler et al., 2006b). In the present study, age at onset was not significantly associated with FH, although, earlier age at onset has been one index of familial liability to MDD. However, it has also been questioned as many previous studies have not been controlled for age, the association has been nonlinear, and age at onset has often been reported only with moderate reliability (Lieb et al., 2002; Janzing et al., 2009).

In addition, the definition of age at onset has varied, and been often reported in studies with adolescents. Nevertheless, it is possible that the somewhat earlier age at onset among drop-outs may have slightly affected these findings. An overlap between mood disorder and alcoholism FHs was common as two-thirds of patients with familial mood disorder had also alcoholism among their first-degree relatives. However, when a FH of alcoholism was adjusted in the model, the results remained the same indicating the specificity of the findings. Overall, a FH of mood disorder was associated with clinically higher severity of depression, which likely also increases the risk of a worse outcome. Neuroticism may mediate the familial predisposition, at least among females.

Over a tenth (12.0%) of the patients followed-up and with information on FH, switched to *bipolar disorder (BD)*. Over four fifths (81.8%) of these patients had a FH of mental disorder, while the prevalence of familial mood, alcohol use, and psychotic disorders was largely similar to patients remaining unipolar. The heritability, clinical picture and patterns of comorbidity have been reported to differ between unipolar and bipolar patients (Kendler et al., 2005). It is probable that especially unrecognized or latent bipolar disorder type II patients are included in clinical MDD cohorts, and may potentially bias the findings of family studies. In this study, these patients somewhat affected the findings concerning FH of mood disorders, while the association with neuroticism became

only a trend when patients with BD were omitted from the analyses. However, this likely results from a diminished statistical power due to smaller number of patients, rather than higher neuroticism among bipolar patients. A recent report did not find significant differences in neurotic features among patients with MDD, and BD type I and II (Sullivan et al., 2000; Kieseppä et al., 2004; Sokero et al., 2005; Mantere et al., 2006; Valtonen et al., 2008). The association with familial alcoholism and number of cluster B disorders among probands also lost its significance after omitting patients with BD from the analyses. This fact is likely to be associated with the findings in Study II, where a significant relationship between diagnostic switch and cluster B personality disorders was found.

Overall, positive FHs of the types of mental disorders investigated seem to be associated with significantly more negative outcome of depression, and increased risk of suicidal behaviour. However, despite the clinical significance of these findings, the specificity of effects of different FHs appears limited, with an exception being alcoholism among male patients.

9 Conclusions and future implications

9.1 Conclusions

In conclusion, the long-term outcome of major depressive disorder (MDD) appears to be more variable when its outcome is investigated among modern, community-treated, secondary-care outpatients than among inpatients. MDD is also highly recurrent in these settings, but the recurrent episodes seem shorter, and the outcome is unlikely to be uniformly chronic. Higher severity of MDD predicted significantly the number of recurrences and time spent ill. Besides known predictors, such as episode duration and preceding dysthymic disorder, comorbid cluster C personality disorders and social phobia predicted a worse outcome.

The incidence rate of suicide attempts varied robustly depending on the level of depression, being highest during MDEs. Although a history of previous attempts and poor social support also indicated risk, time spent depressed was the central factor determining overall long-term risk.

The overall switch rate from unipolar MDD to bipolar disorder (BD) (mostly to type II) was to some extent higher than in previous studies. The switch to BD type I usually occurred early, whereas the switch to type II took place more gradually over time. Besides previously known predictors, a higher severity of MDD, comorbid social phobia, OCD, and cluster B features predicted the diagnostic switch.

The followed-up patients typically suffered from comorbid disorders known to be heritable. The majority of them were also likely to have positive family histories (FHs) not exclusively of mood, but also of other mental disorders. Having a positive FH of severe mental disorders was likely to be clinically associated with a significantly more adverse outcome. More specifically, a FH of mood disorder correlated with probands level of neuroticism among females, and that of alcoholism with male alcoholism.

9.2 Clinical implications

The findings that baseline severity of MDD predicts probability of recurrence, shorter time to first recurrence, and number of recurrences not only confirm the results of our 18-month follow-up (Melartin et al., 2004b) over the long term, but also have implications for generalizations about risk of recurrence and potentially also for indications for

maintenance treatment. The severity of depression should influence clinical decision-making regarding the need for maintenance therapy, particularly among patients who are having their first or second MDE, when maintenance therapy is not usually recommended. The use of observer and self-report scales measuring the severity of depression should be used in routine clinical practice. Besides recurrences, an incomplete recovery of MDD (partial remission) is a substantial problem; achieving full remission should be the goal of treatment. Evaluation of recovery should concern several levels; syndromatic, symptomatic, and functional recovery.

It is likely that greater diagnostic precision, and better recognition of comorbid disorders would improve depression outcome. More complete and accurate diagnostic practice could serve as a better predictor of course and outcome, and impact on patients' satisfaction with treatment, their alliance with treating professionals, selection of medication, and recommendation for psychotherapy. In the present studies, comorbid anxiety disorders (especially social phobia) predicted a higher risk of recurrence, shorter time to recurrence, higher number of recurrences, and the risk of diagnostic switch to bipolar disorder. Moreover, comorbid personality disorders were of importance, cluster C personality disorders prolonging the time to recovery from MDD. Thus, comorbid disorders should be taken into account in planning the treatment of individual patients.

Suicide attempts among patients with MDD are strongly associated with the presence and severity of depressive symptoms. The finding that the incidence rate of suicide attempts is considerably elevated during high risk episodes of MDE is of fundamental importance regarding the prevention of suicidal acts. Reducing the time at risk by effective treatments is likely crucial for reducing future suicide attempts in the long-term. Besides this, special attention should be targeted to younger patients with a history of suicidal behaviour, living alone, and lacking social support.

Recognition of bipolar disorder is a major challenge even for psychiatrists and should be improved. Especially diagnosing bipolar disorder type II is problematic and should be improved. The evaluation of diagnosis and treatment of bipolar disorder should be done in psychiatric care. Greater diagnostic precision concerning the type of mood disorder (MDD, BD I, or BD II) is essential for improving the quality of treatment, and thus, the outcome and quality of life of the patients. In addition to observing cross-sectional presentation of illness, clinicians should consider a longitudinal course when making a diagnosis and planning treatment. Besides previously known predictors (family history of mood disorders, early age at onset, high number of MDEs), a clinician should take into account a higher risk of diagnostic switch among patients with severe depressive episodes and comorbid anxiety and cluster B personality features as the change in diagnosis has practical clinical consequences for treatment and prognosis.

A clinician often routinely inquires after the family history of mental disorders, but the practical consequences of this information are not always clear. According to the present findings, a family history of a mental disorder is likely to be clinically associated with significantly more adverse outcome; with an elevated risk of attempted suicide, a more chronic course, and comorbid personality disorders. Especially male patients with a family history of alcoholism are at higher risk of developing alcohol dependence themselves.

9.3 Implications for future research

Future research should take into account MDD as a heterogeneous, and comorbid disorder. Because of the varying course of MDD, follow-up studies should use life-chart methodology in order to improve the longitudinal assessment and to investigate the effects of variations in risk and time at risk. There also is future need for prospective studies to investigate the wide range of risk factors of outcome and use of multivariate statistics, which are needed to differentiate independent risk factors from confounding associations. Further clinical studies with especially psychiatric outpatients should be carried out as the predictors for outcome may be different among outpatient samples than among the severely ill inpatients previously investigated. Studies on comorbid MDD using both the dimensional and categorical models, and investigating factors from several potentially relevant domains should be carried out. Such studies would help us to better understand the nature of the mechanisms underlying comorbidity, and to discover the potential neurobiological and structural variations in MDD in relation to patterns of comorbidity. Further prospective longitudinal studies are needed to search for any logical pattern in the symptom progression, and its relation to the comorbidity of MDD. Future studies based on daily prospective mood ratings could investigate if the predictors for outcome are identical during the whole phase of illness. Future studies on family history of MDD patients should take into account both their variable phenotypes as well as variable family histories. In addition, the possibility of latent or future bipolar disorder should be acknowledged when investigating the family history of MDD patients.

Randomised controlled trials on both drug and psychosocial treatments should be carried out among ordinary, highly comorbid depressive patients, especially beyond the acute phase in order to reduce the risk of recurrences, and time they are ill. Structured treatment stategies which take into account the heterogeneous clinical picture of MDD should be further developed. Information is needed to help to develop better and more effective treatments and treatment facilities, as well as to improve co-operation between various treatment settings. More research is also needed to investigate specific psychotherapies.

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