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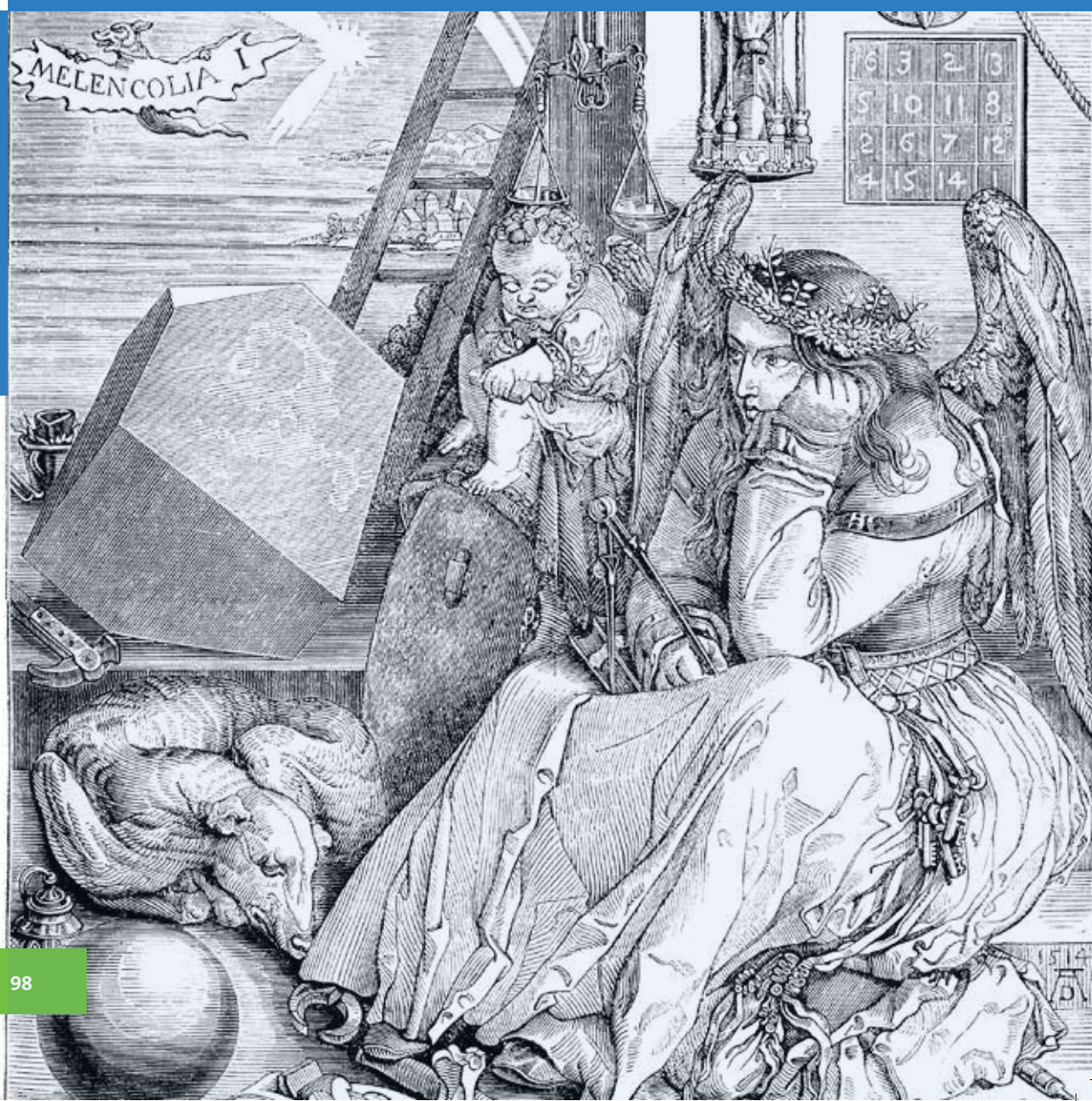
Irina Holma

Long-Term Follow-Up Study Focusing on MDD Patients' Maintenance Treatment, Adherence, Disability and Smoking



RESEARCH

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ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Medicine,
Institute of Clinical Medicine, Department of Psychiatry, University of Helsinki,
for public examination at the Christian Sibelius Auditorium
located at Välskärinkatu 12, Helsinki on March 22th 2013, at 12 noon.

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Cover photo: iStockphoto
Cover illustration Melencolia by Albrecht Durer.
Melencolia was a melancholic character who was the ruler of Saturn. In Greco-Roman mythology, he was defeated by Jupiter. The image also shows Jupiter's table (tabula iovis). The table shown has a protective role. Time attributed objects may also refer to the fact that a melancholic person experiences time differently, or is simply beyond it.

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"For all sorrow or pain is either for something that is truly evil, or for something that is apparently evil, but good in reality. Now pain or sorrow for that which is truly evil cannot be the greatest evil: for there is something worse, namely, either not to reckon as evil that which is really evil, or not to reject it."

Summa Theologiae, IaIIae, q.39, a.4.

"To my husband and my sons,
And to my parents and my brother"

Abstract

Irina Holma. Long-Term Follow-Up Study Focusing on MDD Patients' Maintenance Treatment, Adherence, Disability and Smoking. Tutkimus 98. 139 pages. Helsinki, Finland 2013. ISBN 978-952-245-836-0 (printed); ISBN 978-952-245-837-7 (online publication)

This study is a part of a collaborative depression research project between the Department of Mental Health and Substance Abuse Services of the National Institute for Health and Welfare, Helsinki (the former Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki), and the Department of Psychiatry of Helsinki University Central Hospital (HUCH), and Peijas Hospital in 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).

Overall, the VDS involved screening of 806 adult patients (aged 20-59 years) in Peijas Hospital for depressive symptoms beginning February 1, 1997, for a possible new episode of DSM-IV MDD, and interviewing the 542 consenting patients with a semi-structured interview (SCAN, version 2.0 at baseline, at six and 18 months after baseline and SCID-I at 5 years). Thereby, 269 patients were diagnosed with DSM-IV MDD and included in the study, and further interviewed with semi-structured interviews 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 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.

One aim of this 5-year prospective study was to investigate the prevalence, duration and predictors of maintenance pharmacological treatment. A graphic life chart was used for the exact duration of the maintenance treatment. To do this, an indication for maintenance treatment was defined to exist after a major depressive episode among patients having already had more than three lifetime episodes and then achieving full remission for more than 2 months. Treatment was to commence 4 months after achievement of full remission. Only 57% of patients received maintenance treatment and only for a small proportion (16%) of the time indicated. Good adherence to pharmacotherapy in the acute phase independently predicted maintenance treatment.

Next, our aim was to investigate temporal patterns of attitudes and adherence towards pharmacotherapy and psychotherapeutic treatments, and factors influencing these patterns among psychiatric MDD patients. During follow-up, treatment attitudes and adherence to both forms of treatment were and remained mostly positive. While attitudes became more critical over time, adherence to psychosocial treatment improved, but remained unchanged for pharmacotherapy. It

was found that employment predicted a positive attitude, and a larger social network good adherence to pharmacotherapy at the last follow-up. Attitudes and adherence to psychosocial treatments were associated with types of personality disorders; cluster B personality disorder symptoms predicted a negative attitude and poor adherence, while cluster C symptoms predicted a positive attitude and living alone good adherence to psychosocial treatment.

In addition, prospective factors predicting the granting of a long-term disability pension for psychiatric patients with MDD were investigated. During the follow-up of 5 years, one-fifth of the cohort of psychiatric patients with MDD belonging to the labour force at baseline was eventually granted a disability pension. Higher age, introversion, the perception held at baseline of being unable to work at baseline, lack of vocational education and a higher number of comorbid somatic disorders all independently predicted the granting of a disability pension. Of those receiving such a pension 95.7% had been granted one with major depression as the primary diagnosis.

Lastly, long-term associations between smoking behaviour and depression among psychiatric MDD patients and the co-variation of tobacco smoking and MDD with comorbid alcohol use disorder as a potential confounding factor were investigated. Smoking in our cohort of MDD patients was very prevalent, only one-fourth of subjects had never smoked. Smoking patients differed from non-smoking patients with regard to age, alcohol use disorders, personality disorders, lifetime suicide attempts, personality factors, and social support. The level of depression and smoking did not go hand in hand during the follow-up; they both had an independent course.

Keywords: major depressive disorder, maintenance treatment, treatment attitudes, adherence, disability pension, tobacco smoking, personality disorders, alcoholism

Tiivistelmä

Irina Holma. Long-Term Follow-Up Study Focusing on MDD Patients' Maintenance Treatment, Adherence, Disability and Smoking. [Pitkäaikaistutkimus liittyen masennuspotilaiden ylläpitohoitoon, hoitomyöntyvyyteen, työkykyyn ja tupakointiin] Tutkimus 98. 139 sivua. Helsinki, Suomi 2013. ISBN 978-952-245-836-0 (painettu); ISBN 978-952-245-837-7 (verkkojulkaisu)

Tämä tutkimus on osa Terveyden ja Hyvinvoinnin Laitoksen Mielenterveys- ja päihdepalvelut – osaston ja Uudenmaan sairaanhoitopiirin Peijaksen sairaalan psykiatrian tulosyksikön vakavan masennustilan prospektiivista, naturalistista seurantatutkimusta, Vantaan Depressioprojektia (VDS), jossa on tutkittu 269 DSM-IV luokituksen mukaista vakavaa masennustilaa sairastavaa psykiatrista avohoito- ja sairaalapotilasta.

Tutkimuksen alussa seulottiin 1.2.1997 lähtien 806 aikuista potilasta (ikä 20–59 vuotta) masennusoireiden suhteen; alun perin tutkimukseen suostuivat 542 potilasta. Tutkimukseen valikoitui seulontavaiheen jälkeen 269 potilasta, jotka täyttivät ajankohtaisen vakavan masennustilan oirekriteerit; heitä tutkittiin puolistrukturoiduin haastattelumenetelmin sisäänottovaiheessa ja 6- ja 18-kk seurannoissa SCAN-haastattelulla sekä viiden vuoden seurannassa SCID-I- haastattelulla. Poissulkutekijöitä olivat DSM-IV kaksisuuntainen mielialahäiriö tyyppi I ja II, skitsoaffektiivinen häiriö, skitsofrenia tai muu psykoosi, sekä orgaaninen tai kemiallisen aineen aiheuttama mielialahäiriö. Viisivuotisseurantahaastattelut suoritettiin 12.4.2002–27.4.2004 Vantaan psykiatrisilla poliklinikoilla ja HYKS psykiatrian poliklinikalla; 182 potilasta osallistui haastatteluihin.

Tämän tutkimuksen yhtenä tavoitteena oli tutkia masennuslääkityksen ylläpitohoidon toteutumista, kestoa ja ennustetekijöitä. Tutkimuksessa käytettiin. mm graafista elämänjana-menetelmää, jonka avulla ylläpitohoidon toteutumista pystyttiin tutkimaan ajan suhteen. Indikaationa ylläpitohoidolle pidettiin hoitosuositusten mukaisesti kolmea elinaikaista vakavan masennustilan jaksoa ja uutta masennusjaksoa vähintään kaksi kuukautta kestäneen oireettoman vaiheen jälkeen. Täydellä remissiolla tarkoitettiin masennuksen suhteen täysin oireetonta tilaa. Osittaisessa remissiossa sai olla 1-4 yhdeksästä oireesta. Masennustilassa oli viidestä yhdeksään oiretta. Ylläpitohoito laskettiin alkaneeksi jatkohoitovaiheen jälkeen, kun toipuminen oli jatkunut vähintään neljä kuukautta. Totesimme, että seurannan aikana vain 57 % potilaista, joille ylläpitohoito olisi ollut indisoitu, saivat sitä ja vain hyvin lyhyen (16 %) ajan indisoidusta ajasta. Hyvä lääkehoitomyöntyvyys hoidon akuutissa vaiheessa ennusti toteutunutta ylläpitohoitoa.

Seurannan aikana tutkittiin myös hoitoasenteita ja -myöntyvyyttä. Suurimmalla osalla potilaista oli positiivinen asenne sekä lääkehoitoa, että psykoterapeuttista hoitoa kohtaan, mutta asenteet tulivat ajan kuluessa jonkun verran kriittisemmiksi. Hoitomyöntyvyys psykososiaaliseen hoitoon tuli paremmaksi, kun taas lääkehoitomyöntyvyys pysyi samanlaisena. Työssäolo ennusti positiivista asennetta

ja laaja sosiaalinen verkosto hyvää lääkehoitomyöntyvyyttä. Asenne ja myöntyvyys psykososiaalisen hoidon suhteen liittyivät persoonallisuudenhäiriöihin: ryhmä B persoonallisuushäiriö ennusti negatiivista asennetta ja huonoa hoitomyöntyvyyttä, kun taas ryhmän C ennusti positiivista asennetta. Yksin asuminen taas ennusti hyvää hoitomyöntyvyyttä psykososiaalisen hoidon suhteen.

Seurannan aikana tutkittiin myös masennuspotilaiden riskitekijöitä työkyvyttömyyseläkkeelle jäämisen suhteen. Viiden vuoden seurannassa viidesosa potilaista, jotka kuuluivat työvoimaan ennen tutkimuksen alkua, jäi työkyvyttömyyseläkkeelle. Korkeampi ikä, introversio, oma käsitys työkyvyttömyydestä, ammattikoulutuksen puute ja somaattinen oheissairaus ennustivat eläkkeelle jäämistä. Lähes kaikilla (95,7 %) oli vakava masennustila ensisijaisena syynä työkyvyttömyyseläkkeeseen.

Lisäksi tutkittiin vakavan masennustilan ja tupakoinnin pitkäaikaisyhteyksiä, alkoholihäiriötä mahdollisena sekoittavana tekijänä ja niiden keskinäisiä suhteita ajan kuluessa. Tupakointi oli tutkimuskohortissamme hyvin yleistä: vain neljäsosa potilaista ei ollut koskaan polttanut. Tupakoivat potilaat erottuivat tupakoimattomista merkitsevästi iän, alkoholihäiriön, persoonallisuudenhäiriön, itsemurhayritysten, temperamentin ja koetun sosiaalisen tuen osalta. Masennustilalla ja tupakoinnilla oli kummallakin itsenäinen kulku, jonka vaikutukset toisiinsa välittyivät alkoholinkulutuksen kautta.

Avainsanat: vakava masennustila, ylläpitohoito, hoitoasenteet, hoitomyönteisyys, työkyvyttömyys, tupakointi, persoonallisuushäiriöt, alkoholihäiriö.

Contents

List of original publications

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

I Holma IAK, Holma KM, Melartin TK, Isometsä ET. Maintenance pharmacotherapy for recurrent major depressive disorder: 5-year follow-up study. Br J Psychiatry. 2008 Aug;193(2):163–4.

II Holma IAK, Holma KM, Melartin TK, Isometsä ET. Treatment attitudes and adherence of psychiatric patients with major depressive disorder: A five-year prospective study. J Affect Disord 2010 Dec;127(1-3):102–12.

III Holma IAK, Holma KM, Melartin TK, Rytsälä HJ, Isometsä ET. A five-year prospective study of predictors for disability pension among patients with major depressive disorder. Acta Psychiatr Scand 2012 Apr; 125(4): 325–34.

IV Holma IAK, Holma KM, Melartin TK, Mikko Ketokivi, Isometsä ET: Depression and smoking: a five-year prospective study of patients with major depressive disorder (Submitted to Depression and Anxiety)

Abbreviations

ADM	Antidepressant Treatment
ALCO	Alcohol use disorders
APA	American Psychiatric Association
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BDNF	Brain-derived Neurotrophic Factor
CT	Cognitive 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
DLPFC	Dorsolateral prefrontal cortex
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
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
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-amonobutyric Acid
GAD	Generalized Anxiety Disorder
Ham-D	Hamilton Rating Scale for Depression
HPA	Hypothalamic-Pituitary-Adrenal
HR	Hazard Ratio
HS	Beck Hopelessness Scale
5-HT	5-Hydroxytryptamine (Serotonin)
5-HTR2A	5-Hydroxytryptamine Receptor 2A
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
IMSR	Interview Measure of Social Relationships
IPT	Interpersonal Therapy
IRLE	Interview for Recent Life Events
LIFE	Longitudinal Interval Follow-up Evaluation
LLD	Late-life depression
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
SMOKE	Smoking
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
TCA	Tricyclic Antidepressant
TERVA	Finnish Health Care Survey
THL	Terveyden ja Hyvinvoinnin Laitos
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 Introduction

There are seven basic emotions: anger, disgust, fear, joy, surprise, contempt and sadness (Ekman, 1972; Tomkins, 1984). Normally, a lowered mood usually does not markedly affect one´s functional, social, or occupational ability or social adjustment. More severe depressive symptoms and disorders can be seen as a continuum of those normal negative feelings.

Major depressive disorder (MDD) is considered as a severe highly prevalent, aetiologically multifactorial, clinically heterogeneous illness whose picture is 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 a commonly occurring and burdensome disorder and 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 (Lopez et al., 2006; Rytsälä et al., 2006) and adversely affects interpersonal relationships (Wade and Cairney, 2000). The Global Burden of Disease Study estimated in 1990`s that MDD is worldwide the fourth leading cause of functional impairment, and days lost from work (Murray and Lopez, 1997). In 2004 MDD was considered to be the third leading illness in terms of global disease burden, and by the year 2030 it is predicted to be the leading cause of functional disability and the major disease or injury burden followed by ischaemic heart disease and road traffic accidents (WHO, 2004).

Effective MDD treatments have been available for decades. During the last 50 years, effective medicines, different types of psychotherapy and electroconvulsive therapy have been found and developed to treat depression. But only a realized treatment is useful for patients. Poor adherence to treatment for depression is common, and an important limiting factor to what can be achieved by treatment. Understanding factors influencing attitudes and adherence is important to better engage patients in treatment and improve their prognosis.

MDD is usually recurrent. National practice guidelines recommend maintenance pharmacotherapy for most patients with a history of three or more major depressive episodes or who are vulnerable to future recurrences (Depression Guideline Panel, 1993; Geddes et al., 2003; Isometsä et al., 2003; APA, 2010). Maintenance therapy is an effective tertiary preventive intervention. Occasionally there is debate on whether antidepressant medications are needed. However, the majority of studies on pharmacotherapy are from acute stage studies (Geddes et al., 2003), and there is a lack of long-term maintenance treatment studies with contemporary madications (Viguera et al., 1998). This fact is likely to cause confusion.

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. One comorbid illness is nicotine dependence. The relationship between smoking and depression is complex, smoking appears to increase the risk of depression approximately twofold (Lindeman et al., 2000; Breslau et al., 2004). However, long-term successful cessation of smoking might provide protection from depression (Rose, 2009; Berlin et al., 2011; Korhonen et al., 2011; cMDermott et al., 2013).

2 Review of the literature

2.1 Definition of depression

2.1.1 Depression as an affect or symptom

Sadness is one of the seven basic emotions (Ekman, 1972; Tomkins, 1984) of human being that can affect a person's thoughts, behavior, feelings and physical well-being. A person with depression displays a cognitive bias towards negative information and away from positive information, thus contributing to the maintenance of a depressed mood state (Disner et al., 2011). A depressed person may lose interest in activities that once were pleasurable, experience loss of appetite or overeating, or problems concentrating, remembering details or making decisions; and may contemplate or attempt suicide, have insomnia, excessive sleeping, fatigue, loss of energy, or aches, pains or digestive problems that are resistant to treatment (National Institute of Mental Health, 2009). In addition, three main points of view from evolutionary psychiatry exist: 1) a depressive reaction develops as a part of infectious defence (advantage: a protection against infections harms social and psychological functions) (Anders et al., 2012; Raison and Miller, 2013) 2) depression is a mechanism that helps to separate from impossible objectives (Nesse, 2000), and 3) depression protects a membership in a social group (Allen and Badcock, 2006).

A depressed mood state does not necessarily implicate a psychiatric disorder. It is a normal reaction to disappointment, loss or other painful life events. It may be a symptom of some medical conditions, for example, pancreatic carcinoma and a side-effect of some medical treatments, for example interferon treatment for C-Hepatitis. A depressed mood is also a main or common feature of certain psychiatric syndromes such as major depressive disorder. There has been debate on whether depression and grief are the same thing. Grief is considered as a transient experience, which however can be prolonged and be pathological especially among those with a history of psychological symptoms, even before the grief-provoking event has occurred (Bonanno et al., 2002; Bonanno and Mancini, 2008).

2.1.2 Diagnosis of major depressive disorder (MDD)

There are currently two diagnostic classification systems in use, the DSM-IV (American Psychiatric Association 2010), which has been used in this thesis and ICD-10 (World Health Organization 2007; Tautiluokitus 2010). DSM-IV MDD is characterized by having one or more major depressive episodes lasting at least two weeks. In order to warrant a diagnosis of MDD, persistent depressive mood or 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. significant weight or appetite change, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or extreme or inappropriate guilt, a diminished ability to think or to concentrate or indecisiveness, and recurrent thoughts of death or suicidal ideation, or a suicide attempt or a specific plan for committing suicide (APA, 2003). Moreover, the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and should not be due to the direct physiological effects of a substance or a general medical condition. In addition, mood-incongruent delusions or hallucinations, bipolar mixed episode, or bereavement must be ruled out. The diagnosis of MDD in both DSM-IV and ICD-10 (WHO, 2007) are almost compatible. 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. In this thesis, unless otherwise specified, depression refers to unipolar DSM-IV MDD.

2.1.3 Subgroups of MDD and diagnosis of other depressive disorders

There are three levels of severity of MDD in DSM-IV: mild, moderate or severe (with or without psychotic features) based on the number and severity of the diagnostic criteria, and gradation of functional disability and distress. Psychotic MDE includes delusions or hallucinations, where the psychotic features are mood congruent or mood incongruent (APA, 2000). The melancholic features specifier includes loss of pleasure in all, or almost all, activities, lack of reactivity to usually pleasurable stimuli, a distinct quality of the depressive mood, depression regularly worse in the morning, early morning awakening, marked psychomotor change, either retardation or agitation, significant loss of appetite or weight loss, and excessive or inappropriate guilt (APA, 2000). Melancholic features and psychotic features may represent a distinctive form of severe depression arising from a different pathophysiology than other forms of depression (Parker et al., 2000; Parker and Manicavasagar, 2005). The validity criteria of the atypical features include mood reactivity plus at least two of the following four symptoms: significant weight gain or increased appetite, hypersomnia, severe lethargy, and a pathological rejection sensitivity (APA, 2000). Seasonal pattern depression has 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 disorder). Postpartum depression may develop into an MDE if the onset is within 4 weeks after delivery (APA, 2000). Dysthymic disorder in DSM-IV consists of chronic but milder symptoms than in MDE. Dysthymia features criteria include a depressed mood for most of the day or for more days than not for

at least two years; the presence, while depressed, of at least two of the following: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty in making decisions, or feelings of hopelessness (APA, 2000). When an intense episode of depression occurs on top of dysthymia the state is called "double depression" (Klein et al., 2006). A number of subjects with disabling depressive symptoms fail to meet the diagnostic criteria for MDE or dysthymia, some of these subsyndromal conditions are included in the category depression not otherwise specified (NOS), which includes several forms of briefer or milder periods of depression (APA, 2000). Appendix B in DSM-IV (APA, 2000) 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. Depression can also include a few depressive symptoms diagnosed as minor depressive disorder (MinD), although not considered an official clinical diagnosis, the American Psychiatric Association defined research diagnostic criteria in Appendix B of DSM-IV (APA, 2000). Those patients have never met the criteria of MDE or manic episode.

2.2 Epidemiology of MDD

2.2.1 Prevalence of MDD

Major depressive disorder is a common disorder. Numerous epidemiological studies have estimated the prevalence of depressive disorder. Retrospective lifetime prevalence of MDD in any general population studies varies from 12% to 17% (Kessler et al., 1994; Bijl et al., 1998; Kessler et al., 2003; Alonso et al., 2004; Hasin et al., 2005). In prospective epidemiological studies, the lifetime prevalence of MDD has been two-fold compared to retrospective studies (Moffitt et al., 2009) The 12-month prevalence of MDD has been 4 to 9% (Offord et al., 1996; Salokangas et al., 1996; Bijl et al., 1998; Lindeman et al., 2000; Kessler et al., 2003; Alonso et al., 2004; Pirkola et al., 2005). National Comorbidity Survey Replication (NCS-R), performed 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 (FINHCS) (Lindeman et al., 2000). In one domestic study, the Tampere Depression (TADEP) Study the 1-year preva-

lence rate of clinical depression was 20% patients of primary care patients whereas lifetime clinical depression was found in a tenth of primary care patients, and in one-half of patients in community mental health centres (Salokangas et al., 1996). The difference in prevalences may be due to the methodological factors, such as diagnostic criteria, different instruments and sampling methods. The prevalence of MDD 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).

2.2.2 Epidemiology of treatment of MDD

Despite of the high prevalence of MDD, a large proportion of depressed patients are still not receiving treatment. The ESEMed project (Alonso et al., 2004) found that only 36.5% of patients with mood disorders had consulted formal health services. The Mini-Finland 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). Half of the treatment received was assessed as inadequate. Of the depressive subjects, only one-third received some kind of treatment. Two of five suffering even from the most severe MDE did not use formal the health services for depression. More recently, the more severe, long-lasting, and disabilitating the depression, the more probable was the use of health services for major depression, (Hämäläinen et al., 2004) The NESARC research found that approximately 60% of patients with MDD reported treatment specifically for the disorder; women were more likely to be treated than men. The Finnish Health Care Survey, consisting of a random population sample of MDD sufferers reported only 24% use of antidepressants, and 17% received psychosocial treatment. According to the Health 2000 project of subjects with MDD only 34% used health services (Hämälainen et al., 2008; Hämäläinen et al., 2009).In VDS, among patients in psychiatric care, most patients (88%) received antidepressants in the early acute phase, but about half (49%) terminated treatment prematurely.

A recent Finnish study reported 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 (Sorvaniemi et al., 2003). 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 a 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).

2.3 Aetiology and pathogenesis of MDD

2.3.1 Multifactorial model

MDD is considered to be a clinically heterogeneous, multifactorial disorder influenced by risk factors from multiple domains that are interrelated through developmental pathways (Kendler et al., 2002; Kendler et al., 2006; Belmaker and Agam, 2008). In the aetiology of depression life stress seems an important component, but also requires other vulnerability factors to explain the onset (Monroe et al., 2001). The associations among the psychopathological and biological endophenotypes are discussed with respect to specificity, temporal stability, heritability, familiarity, and clinical and biological plausibility. Neurochemical signal transduction mechanisms, neural circuits, psychosocial stressors and their complex interaction pose a major impediment to elucidating the genetic and neurobiological basis of this common, severe, and often life-threatening illness (Hasler et al., 2004).

2.3.2 Heritability and genetic risk factors

A combination of genetic and environmental risk factors probably contributes to MDD. The heritability or the proportion of variation due to genetic factors for MDD has been reported to be in the 20–45% range (Sullivan et al., 2000) or 41–50% (Kendler et al., 2011) and has been on average somewhat higher in women (40–45%) compared to men (25-30%). (Sullivan et al., 2000; Kendler et al., 2006c), but even 70% has been reported in twin studies (McGuffin et al., 2007). The heritability can be even up to 75% in clinical cohorts of subjects with more recurrent, difficult depressive episodes, and early age at onset (Uher, 2008). A proposed model of depression incorporates the interacting genetic and environmental factors over the course of life and provides an explanatory framework for the heterogeneous aetiology of depression. Early environmental influences act on the genome to shape the adaptability to environmental changes in later life (Caspi et al., 2003; Uher and McGuffin, 2008; Caspi et al., 2010). Recent genetic studies have contributed by the discovery of multiple genes that predict increased risk for depression. Special interest has been focused on the candidate genes, transporter gene (5-HTTLPR), which associate with the probability of patients responding to antidepressant treatment (Caspi et al., 2003; Caspi et al., 2010), glucocorticoid receptor gene (Frodl et al., 2012; Massart et al., 2012), brain-derived neurotrophic factor gene (Kaufman et al., 2006; Chen et al., 2012) and their possible interactions (Kim et al., 2007). The potential mechanisms include a heightened reactivity to stress 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).

According to one hypothesis, the polymorphism of the promoter region of the 5-HTR2A gene is associated with MDD patients (Choi et al., 2004). Gene-environment interactions have been reported, e.g. the 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). Functional polymorphism in the brain derived neurotrophic factor gene (BDNF Val66Met) modulates the influence of stressful life events on adolescent depressive symptoms (Elovainio et al., 2007; Chen et al., 2012). In the last decade the serotonin transporter gene promoter polymorphism (5-HTTLPR) was likely the most studied genetic variant most studied as a predictor of antidepressant response. Drug response may depend of genetic differences (Porcelli et al., 2011).

2.3.3 Early and recent psychosocial risk factors

Psychosocial risk factors for MDD can be divided into early and recent risk factors. The risk for adults may be increased by a wide range of negative life events in childhood ranging from physical or sexual abuse and other adult psychopathology, parental death and any history of having experienced poor parenting, parental loss or separation, and depression of parents (Lieb et al., 2002; Gladstone et al., 2004; Veijola et al., 2004; Kendler and Prescott, 2006).

The impact of adverse environmental factors during childhood seems to be composed of a wide range of factors from direct causal associations to complex interacting environmental effects (Pirkola et al., 2005). Childhood adversities might be worse if combined with adult adverse life-events (Korkeila et al., 2005). Poor parenting may increase the risk of MDD through individual specific environment, i.e. individuals respond to parenting in different ways directed in part by genetically predisposed characteristics e.g. temperament (Kendler and Prescott, 2006). Most MDD risk factors had a greater impact on women than on men on the risk of MDD and were not restricted to a specific class of risk factors (Stegenga et al., 2012).

Childhood adversities 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 as burdensome (Korkeila et al., 2010). Interaction between life-events and neuroticism has been found, and that neuroticism strongly reflects a patint's susceptibility to MDD (Kendler et al., 2006). The childhood adversity-depressiveness associations are partly mediated by adult risk factors supporting a pathway from childhood adversities to depressiveness through adult risk factors (Korkeila et al., 2005). Of four psychological dimensions of life-events (entrapment, danger, loss and humiliation), high ratings of loss and humiliation have been related with increased risk for depression among individuals with high-threat events and the combination of high ratings of events and loss creates the highest risk for depression (Farmer and McGuffin, 2003; Kendler and Prescott, 2006). Current stress to-

gether with genetic vulnerability and temperamental factors may be one of the key reasons for propensity for MDD (Kendler et al., 2002; Kendler et al., 2006a). Men have been more affected by divorce and work difficulties, and women more sensitive to events in their proximal social network events (Kendler and Prescott, 2006). Different types of difficulties may lead to different profiles of depressive symptoms (Keller et al., 2007). Low social support has also been found to increase risk for developing future episodes of MDD (Kendler et al., 2006a). Depression may in turn have significant negative consequences on the social support available (Coryell et al., 1993; Leskelä et al., 2008). According to recent findings, the ability to receive and respond to support may be influenced by early negative experiences and relationships with significant others. In the VDS, 91% of the patient's connected the onset of MDE with some adverse event, although no clustering of live events appeared to associate with the time of onset (Leskelä et al., 2004).

2.3.4 Personality and temperamental factors

Temperament is the combination of the mental, physical, and emotional traits of a person; it has been seen as a core that develops early and that forms the foundation for an individual's later personality. There are several personality trait theories, each with a different emphasis and number of temperament dimensions. In the Big Five- theory personality is conceived as (a) an individual's unique variation in the general evolutionary design for human nature, expressed as a developing pattern of (b) dispositional traits, (c) characteristic adaptations, and (d) self-defining life narratives, complexly and differentially situated (e) in culture and social context. The five principles suggest a framework for integrating the model of personality traits with those self-defining features of psychological individuality constructed in response to situated social tasks and the human need to make meaning in culture (McAdams and Pals, 2006). Two widely studied personality dimensions describing negative and positive trait entities, neuroticism, and extroversion have been included in the Five Factor Model together with agreeableness, conscientiousness and openness to new experience (Goldberg, 1993).

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, cooperativeness, and self-transcendence (Cloninger et al., 1993). Personality as the visible aspect of one's character as it impresses others 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). Personality dimensions have been found to influence the propensity for depression. High neuroticism has been regarded as a risk factor for depression (Angst and Clayton, 1986; Hirschfeld et al., 1989; Boyce et al., 1991; Shea

et al., 1996; Fanous et al., 2007). Neuroticism may limit the psychosocial and psychiatric care received (Hopwood et al., 2008). Moreover, extraversion has been reported to have a negative correlation with depressive disorders (Hirschfeld et al., 1989; Cox et al., 2004; Kendler et al., 2006) and to even exert some protective effects against depression (Farmer et al., 2002).

However, the role of extroversion 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 extroversion to be a risk factor. The relationship between personality and affective disorders is complex. Personality features may have a common cause with affective disorders, may predispose an individual to affective disorders, be shaped by repeated episodes of the illness, modify the clinical picture of the illness, be an attenuated expression of the disorder or be state-dependent concomitants of affective disorders (Shea and Yen, 2003; Brandes and Bienvenu, 2006).

2.3.5 Imaging findings in patients with MDD.

Many brain regions have been implicated in regulating emotions and thus also postulated to mediate the symptoms of depression (Nestler et al., 2002). A meta-analysis which analysed studies that used magnetic resonance imaging or x-ray computed tomography showed that MDD was associated with lateral ventricle enlargement; larger cerebrospinal fluid volume; smaller volumes of the basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex, and gyrus rectus. Patients during depressive episodes had significantly smaller hippocampal volume than patients during remission (Martinot and Mana, 2011). In another meta-analysis MDD was associated with reduced rates of deep white matter hyperintensities, increased corpus callosum cross-sectional area, and smaller hippocampus and basal ganglia (Kempton et al., 2011). Recently a meta-analysis showed a relative hypoactivation of the sensorimotor cortices in MDD (Delvecchio et al., 2012). One meta-analysis identified 4 consistent locations of decreased fractional anisotropy in patients with MDD: white matter in the right frontal lobe, right fusiform gyrus, left frontal lobe and right occipital lobe. Fibre tracking showed that the main fascicles involved were the right inferior longitudinal fasciculus, right inferior fronto-occipital fasciculus, right posterior thalamic radiation and interhemispheric fibres running through the genu and body of the corpus callosum (Liao et al., 2012) or involving the superior frontal gyrus, insula and putamen (Tao et al., 2013). MRI and fMRI studies have also revealed decreased white matter volumes in the left anterior cingulated gyrus and right middle frontal gyrus among elderly MDD patients (Tham et al., 2010), and also in middle-aged MDD patients an enlarged middle genu area of corpus callosum has been revealed (Kieseppä et al., 2010). Late-life depression (LLD) has tended to be associated with smaller volumes in circumscribed frontal and subcortical structures with the most robust differences being found

in thalamic volume (Bora et al., 2012). 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; Townsend et al., 2010). 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.

2.3.6 Neurochemical, neurotrophic, and neuroendocrinological findings

Even though depression is associated with a number of biological changes, none of them is now a positive biomarker for depression as MDD is a biologically heterogeneous disorder (Goltser-Dubner et al., 2010; Schneider et al., 2011). The best-known changes are related to the HPA-axis function and immune system activation. Howevwr, according to one Finnish research, depressive symptoms may be partly responsible for inflammatory processes, and inflammatory processes may induce depressive symptoms in men (Elovainio et al., 2009). A recent study from a largest study to date, reported elevated levels of CRP to be associated with increased risk for psychological distress and depression in general population (Wium-Andersen et al., 2012).

Concerning the treatment of depression with antidepressants, it was hypothesized that, in particular brain monoamines (serotonin, norepinephrine and dopamine) activity is disturbed in depressed patients (Thase et al., 2002). This theory was proved to be true at least in part by the use of imaging techniques (Hirvonen et al., 2008). 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 advanced into the direction of a chemical or molecular hypothesis of depression, which suggests 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).

Stress activates the hypothalamic-pituitary-adrenal axis through a complex mechanism. Key elements of the stress response in the brain as a whole are the hippocampus, the prefrontal cortex and amygdala. In general, hippocampus and prefrontal cortex suppress and amygdala stimulates HPA axis activity. Several lines of research point to separate mechanisms, for example, amygdala hyperactivity, hypoactivity in the DLPFC (the dorsolateral prefrontal cortex) and blunted nucleus accumbens response in individuals with depression that increase the salience of negative stimuli and decrease the salience of positive or rewarding stimuli. As a result, a person with depression displays a cognitive bias towards negative informa-

tion and away from positive information, thus contributing to the maintenance of a depressed mood state (Disner et al., 2011). There is a plausible role for cytokines, brain-derived neurotrophic factor (BDNF), and their interaction in major depressive disorders (MDD) etiology. The bidirectional relationship between BDNF and cytokines is therefore discussed. Cytokines affect the synthesis and reuptake of serotonine, dopamine, and glutamate. In addition, they interfere neuroplasticity by disturbing groth factors during chronic stress (Capuron and Miller, 2011). In short-term, dopamine helps to avoid a stressor, but in long-term, chronic stress leads to a reduction in dopamine levels (Cabib and Puglisi-Allegra, 2012). Potential ramifications for MDD treatment that are appraised include use of cytokine biomarkers for identifying specific populations for targeted MDD therapy, the use of medications that directly antagonize the role of inflammatory cytokines, potential indirect modifiers of cytokine activity, and possible downstream intracellular second messenger targets (Lotrich, 2012).

Neuroplasticity may have a key role in the pathophysiology of MDD, a concept supported by experimental studies that found that excessive cortisol secretion and/or excessive production of inflammatory cytokines impair neuronal plasticity and neurogenesis in the hippocampus (Frodl et al., 2012). Antidepressant treatment can lead to a normalization of the elevated cytokine levels that occur when an individual is suffering from major depression. Most antidepressants have also specific anti-inflammatory effects (Maes, 2010; Raedler, 2011).

2.4 Comorbidity of MDD

2.4.1 Definition of the concept

Comorbidity is defined as the occurrence of two or more disorders in a person in a defined period of time (Klerman, 1990). The comorbidity concept was first presented in literature on the epidemiology of medical diseases. In psychiatry the concept of comorbidity has been sustained by DSM-III and DSM-IV with a multixial classification system (APA, 1987). The concept of comorbidity has been discussed, whether it refers to co-occurrence, covariation (Lilienfeld, 2003), or multimorbidity (Kessler et al., 1994).

Comorbidity of depression has been the topic of numerous studies over the years (Angst, 1996; Kessler et al., 2003; Pirkola et al., 2005; Olfson et al., 2012). Comorbid MDD is so common that it is almost exceptional not to have a comorbid disorder in connection with MDD (Kessler et al., 1996). MDD patients have generally at least one comorbid Axis I disorder (Placidi et al., 2000, Melartin et al., 2002; 2004; Merikangas et al., 2003; Alonso et al., 2004; Hasin et al., 2005; Vuorilehto et al., 2005). In NCS-R, the lifetime prevalence was over 70% and the 12-month prevalence ocer 80% of at least one comorbid disorder among MDD patients, including

59% with anxiety disorder, 24% with substance use disorder and 30% with impulse control disorder (Kessler et al., 2003). Half of the subjects with MDD have a current anxiety disorder (Regier et al., 1990; 1998; Kessler et al., 1996b), and about a fifth a current substance use disorder (SUD) (Regier et al., 1990; Grant & Harford, 1995; Kessler et al., 1996a). In a nationally representative sample of 5958 adults, a majority (61.3%) of respondents with MDD reported having sought treatment for depression at some point in their lives (Olfson et al., 2012). In the National Comorbidity Survey Replication (NCS-R) study about 80% of respondents with 12-month DSM-IV MDD had at least one axis I comorbid disorder, with anxiety disorders being the most common (67.8%), followed by substance use disorders (27.1%) (Kessler et al., 2003). 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%). In the Finnish Health 2000 study, 32% of respondents with 12-month DSM-IV MDD had at least one comorbid disorder, with anxiety disorder being the most common (25%), followed by alcohol use disorder (9%) (Pirkola et al., 2005c).

2.4.2 Comorbidity of MDD in clinical samples

In psychiatric cohorts, the reported prevalences of current comorbid disorders among patients with MDD have varied widely. Approximately half of the patients have had a current anxiety disorder and about one fifth a current substance use disorder (Fava et al., 2000; Zimmerman et al., 2000; Melartin et al., 2002). Dysthymia, anxiety disorders, and alcohol use disorders have been significantly more prevalent in subjects with MDD than in subjects without MDD (Verhagen et al., 2008).

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al., 2005), which investigated 1376 outpatients of the total population of 4041, with DSM-IV MDD associated the concurrent comorbidity of MDD with other disorders through a Psychiatric Diagnostic Screening Questionnaire. It was found that 61.8% of cases having at least one comorbid disorder with 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%).

Clinical studies have reported that comorbidity is one of the major factors associated with poor MDD outcome as it increases the risk of relapse or recurrence (Alnaes & Torgersen, 1997), chronicity (Keller et al., 1984; Mueller et al., 1994), residual symptoms (Paykel et al., 1995), suicide (Cheng et al., 1997; Fawcett, 1997; Foster et al., 1999; Hansen et al., 2003) and psychosocial impairment (Rytsälä et al., 2005; Lam et al., 2011).

The reported prevalence of concurrent MDD patients with personality disorders in psychiatric settings has varied greatly (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 with 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 a study with depressed outpatients, a significant proportion (64%) met criteria for at least one co-morbid personality disorder (Fava et al., 2002). 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 of 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 VDS (Melartin et al., 2010) have been similar: the categorical stability of concurrent personality disorder diagnoses assigned when the patient was depressed was relatively poor, but the dimensional stability was moderate.

2.4.3 Physical illnesses comorbidity

MDD increases the risk of developing a number of physical illnesses. The risk is not necessarily related to lifestyle, although depression is associated with elevated prevalence of smoking, alcohol abuse, and lack of physical activity (Herva et al., 2006; de Wit et al., 2010; Pacek et al., 2012). About 60% of excess mortality is due to physical illness (De Hert et al., 2011). Depression increases independently the risk of developing coronary heart disease (Hemingway and Marmot, 1999), stroke (Everson et al., 1998), osteoporosis (Cizza, 2011), type 2 diabetes (Golden et al., 2004), and Alzheimer's disease (Ownby et al., 2006). It will also degrade the prognosis of many diseases.

2.4.4 Nicotine dependence as MDD comorbidity

The mortality rate of MDD sufferers is double the mortality rate compared to the general population (Robson and Gray, 2007). One risk factor is smoking. MDD and nicotine dependence are epidemiologically comorbid. Tobacco smoking is a

risk factor for more than 50 diseases, 20 of which are fatal (Lopez et al., 2006). Smoking has also been associated with recurrence and even suicidal behaviour in depressive subjects (Bronisch et al., 2008). Cigarette smoking and weekly alcohol abuse seems to be risk factors for MDD in the general population (Hämäläinen et al., 2001). The prevalence of smoking among alcohol-dependent people has been found to be 3- to 4-fold that of the general population, at a level of about 80–95% reporting smoking (Joseph et al., 1990). Also, a dose-response relationship between the number of cigarettes smoked and amount alcohol consumed has been reported (Dani and Harris, 2005). In the NESARC study, over one-fifth of patients with current nicotine dependence had concurrent alcohol use disorder, mood disorder, and anxiety disorder, and nearly one-third had a current personality disorder (Grant et al., 2004). In the same study major depression was associated with increased likelihood of nondependent cigarette use (Goodwin et al., 2012). In a Finnish study, the overall prevalence of smoking was 22.2% in the general population, but 47.5% among patients with current alcohol dependence (Pirkola et al., 2006). Substance abuse exacts a considerable toll on society in terms of morbidity and mortality, accounting for 21% of deaths, 23% of years of potential life lost, and 8% of hospitalizations (Single et al., 1999).

2.5 Treatment of MDD

Treating subjects with depression remains a major clinical and public health challenge. Significant treatment advances have been made recently in the areas of pharmacotherapy, psychotherapies, combination of pharmaco- and psychotherapy, electroconvulsive therapy (ECT) and bright light therapy (Cohen and Guthrie, 1997; Schulberg et al., 1998; Crismon et al., 1999; Bauer et al., 2002; Bauer et al., 2002; NICE, 2004; Fochtmann and Gelenberg, 2005; Anderson et al., 2008; Suehs et al., 2008; NICE, 2009; Patten et al., 2009; APA, 2010; Suomen Psykiatriyhdistys, 2010). Other treatments that have been used for MDD are among others exercise (Ernst et al., 2006) and sleep deprivation (Wirz-Justice, 2006). New treatments for MDD currently being evaluated include brain stimulation (transcranial magnetic stimulation, deep brain stimulation and vagus nerve stimulation) (Eitan and Lerer 2006; Ressler and Mayberg 2007) and intravenous injection of ketamine (Zarate et al. 2006).

2.5.1 Psychosocial Therapies

In the acute phase, a specific, effective psychotherapy (cognitive, psychodynamic, behavioural, interpersonal, may be provided as an initial treatment for patients with mild to moderate MDD (APA, 2010; Suomen Psykiatriyhdistys, 2010). Clinical features that may suggest the use of psychotherapeutic interventions include

the presence of psychosocial stressors, intrapsychic conflict/interpersonal difficulties, or comorbid axis II disorder (APA, 2010). There is increasing evidence to support the use of a specific psychotherapy in the continuation and maintenance phases to prevent recurrences (Nierenberg et al., 2003; APA, 2010; Suomen Psykiatriyhdistys, 2010). Frequency of visits usually decreases in the maintenance phase (APA, 2010; Suomen Psykiatriyhdistys, 2010). The lack of several randomized, controlled clinical trials of long-term cognitive or psychodynamic psychotherapies, or of psychoanalysis makes it difficult to estimate their effectiveness in the treatment of depression. The Canadian CANMAT guideline states that cognitive therapy (CT), cognitive behavioural therapy (CBT), and interpersonal therapy (IPT) have efficacy 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. Poor adherence to treatments may also warrant a combination of treatment modalities (APA, 2010). In a systematic review Pampallona et al. concluded that combined antidepressant therapy and psychosocial treatment is associated with a higher improvement rate than pharmacotherapy alone (Pampallona et al., 2004).

2.5.2 Antidepressant treatment

There are three phases of treatment: the acute, continuation and maintenance phases. In the acute phase, the aim of the treatment is full remission, in the continuation phase, the prevention of relapse, and in the maintenance phase, the prevention of recurrence (Suomen Psykiatriyhdistys 2010). The most common methods of treatments for MDD in Finland are antidepressant treatment with or without augmenting and adjunctive medications; psychotherapy and ECT.

Modern effective antidepressant treatment (ADM) has been in use since 1957 (Ban, 2001) with then the development of new antidepressants being based on the monoamine theory. Some types of medication were monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). More recently developed treatments include agents that block the reuptake of serotonin, noradrenalin or dopamine, their names refer to the neurotransmitter systems that they are believed to affect the mind the most. The efficacy of ADM has been established in literally thousands of placebo-controlled clinical trials (Depression Guideline Panel, 1993). Suitable antidepressant treatment of MDD consists of three phases: 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, 2010; Suomen Psykiatriyhdistys, 2010). The more severe the depression is, the more important the antidepressants are for the treatment of MDD. In severe or psychotic depres-

sion 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 a combination of antidepressants and antipsychotics is recommended (Psykiatriyhdistys, 2010). The NICE guideline from UK does not recommend antidepressants for mild depression unless other treatments have failed (NICE, 2009).

2.5.3 Acute phase treatment and continuation phase treatment

Antidepressant medication is effective in the treatment of the acute depressive episode and is preventive so long as its use is maintained (APA, 2010). Acute phase pharmacotherapy is effective for all severities of MDE. In mild to moderate depression, psychotherapy alone or combined with medication is helpful. The more severe the depression, the more important is the role of adequate medication. According to recommendations, adequate dosage of an antidepressant is equivalent to imipramine 150–300 mg per day (NICE, 2004) Acute phase treatment lasts for weeks or months until remission is reached. The continuation phase should generally last four to nine 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 (Suomen Psykiatriyhdistys 2010).

2.5.4 Maintenance phase treatment

MDD is often a recurrent disease and practice guidelines recommend maintenance treatment for MDD for most patients with a history of three or more major depressive episodes, comorbid conditions, residual symptoms between episodes, severe disability, suicidal behavior or psychotic features (Depression Guideline Panel, 1993; APA, 2010; Suomen Psykiatriyhdistys, 2010). Maintenance treatment is an effective tertiary preventive intervention (Geddes et al., 2003). Maintenance treatment should be nearly the same treatment (antidepressant at full dose, psychotherapy perhaps at a lowered frequency) that was effective during acute depression and should continue preferably at least for 5 years to prevent further recurrences, or in some cases to rest of the life (Depression Guideline Panel, 1993; APA, 2010; Suomen Psykiatriyhdistys, 2010). APA defines an indication for maintenance treatment to exist after a major depressive episode among patients having already had more than three lifetime episodes but then achieving full remission for more than 2 months. Treatment should commence 4 months after the achievement of full remission (APA, 2010).

2.5.5 Other treatment methods

Electroconvulsive therapy (ECT) is the oldest of the modern ways to treat depression. ECT was first developed 70 years ago as a treatment for psychoses. It has been found to be an effective form 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, 2010). New treatments for MDD currently being evaluated include other neurostimulation therapies, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), and vagal nerve stimulation (VNS) (Rush et al., 2005; Rossi et al., 2009; Hansen et al., 2011). 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 (Zarate et al., 2006), 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).

2.5.6 Effects of treatment on brain circuitry

Both cognitive therapy (CT) and antidepressant medication (ADM) probably affect limbic and prefrontal circuitry, while their proximal mechanisms of action might differ (DeRubeis et al., 2008; Disner et al., 2011). The neurobiological underpinnings of a blunted response to positive stimuli, a key feature of depression, has been shown in functional MRI results indicating that nucleus accumbens and prefrontal cortex (PFC) activity decreased more dramatically in individuals with depression than in healthy controls groups during the period following positive stimulus presentation (Wager et al., 2008; Heller et al., 2009). A primary goal of CT is to replace automatic emotional reactivity with more-controlled processing (Rush et al., 1982; Heller et al., 2009). ADM might target limbic regions directly rather than relying on inhibition though the prefrontal cortex. SSRIs increase the availability of serotonin at the synapse, which could lead to inhibition of amygdala as well as of other ventral limbic regions, as has been observed in resting-state neuroimaging studies (Mayberg et al., 2000; Fu et al., 2004; Anand et al., 2005; Dunlop et al., 2012). Treatment likely modifies the effects of illness, e.g. the previously decreased volume of amygdala increases with treatment for depression (Fu et al., 2004). CT normalizes amygdala and dorsolateral prefrontal cortex (DLPFC) activity in individuals with depression (DeRubeis et al., 2008). In addition, antidepressant medication may prevent the reduction of hippocampal volume among patients with major depression (Sheline et al., 2003). Using deep brain stimulation to reduce hy-

peractivity in the subgenual cingulate cortex, thereby reducing bottom-up influence to some extent, seems to be a promising treatment for depression (Mayberg et al., 2005). The evidence shows that CT is as efficacious as antidepressant treatment, and that its effects are more enduring. Indeed, it has been proposed that CT helps patients learn to recruit prefrontal regulatory brain mechanisms – a skill that these patients could continue to use long after treatment ends (Nemeroff et al., 2003; Fu et al., 2008).

2.5.7 Treatment attitudes and adherence

Practice guidelines suggest that psychiatrists should recognize patients' non-adherence, and encourage them to discuss any concerns regarding adherence (APA, 2010). Understanding factors influencing attitudes and adherence is important to better involve patients in treatment and advance their prognosis. The term "adherence" denotes the relationship between patient and medical treatment and advice (Hansen and Kessing, 2007) and has been defined as patient acceptance of recommended health behaviours (Wright, 1993). The literature (Frank et al., 1992; Lingam & Scott, 2002; Nemeroff, 2003) tends to prefer the term adherence instead of compliance as it may also remind clinicians to form a good therapeutic alliance with the patient, and emphasizes active rather than passive participation of the patient in this process. Part of this neglect is explained by the unresolved confusion about terminology, and highly variable methods (i.e. prescription counts, pill counts, appointments kept, drug/metabolite plasma concentrations) used in measuring non-adherence (Demyttenaere et al., 2001; Lingam & Scott, 2002; Pampallona et al., 2002; Demyttenaere, 2003). Problems of adherence to pharmacotherapy appear similar in both primary care and psychiatric settings, but generalizability of findings from one setting to another remains uncertain, and adherence to psychosocial treatments is largely uninvestigated.

Medication non-adherence is common; estimates of non-adherence for affective disorders range from 10% to 60%, with a median of 40% (Lingam & Scott, 2002). Few studies have investigated the extent to which treatment recommendations, especially after the immediate acute phase, are followed by psychiatric patients with depression (Simon et al., 2001; Cuffel et al., 2003; ten Doesschate et al., 2009). Several primary care studies (Katon et al., 1995; Demyttenaere and Haddad, 2000; Lin et al., 2003; Åkerblad et al., 2006) have reported frequent shortcomings such as inadequate follow-up of dosage or monitoring of antidepressant treatment. Large register-based studies of primary care patients (Melfi et al., 1998; Claxton et al., 2000) also document the marked adverse influence of poor adherence on risk of relapse or recurrence.

However, research on adherence and premature termination of treatment has been rare in psychiatric settings. About one-third of depressive patients discontinue their antidepressant treatment during the first month, and nearly one-half by

the third month (Olfson et al., 2006); possibly only a quarter of patients use antidepressant medication as recommended by international guidelines (Bockting et al., 2008).

Intervention studies have shown that psychoeducation is an effective way to enhance treatment adherence by offering structured and detailed information to patients about their treatments (Demyttenaere & Haddad, 2000; Lin et al., 2003; Vergouwen et al., 2003). Non-adherence undermines optimal treatment and may pose a risk for suicidal individuals (Meehan et al., 2006).

Attitude describes the patient's subjective opinion of treatment, and is one, but not the only, factor influencing adherence. The components of communication to patients that have been shown to improve adherence include reminding them of when and how often to take the medicine, the need for at least 2-4 weeks before beneficial effects may be noticed, the need to take medication even after feeling better, the need to consult with the doctor before discontinuing medication, and what to do if problems arise (APA, 2010).

2.6 Disability in MDD

2.6.1 Level of functional disability in MDD

Functional disability has been defined as limitations in performing social and family roles and tasks (Nagi, 1976), or restricted ability to perform the most basic activities. Lack on social adjustment is a part of functional disability. Problems in it seem to be difficulties in the patient´s role performance, interpersonal relationships, and work and leisure satisfaction (Weissman and Bothwell, 1976).

2.6.2 Work disability in MDD

Work disability is a specific form of impairment, defined as inability to work at a job or business, and receiving social security benefits in the form of a disability pension on that basis. Major depression (MD) is one of the most prevalent psychiatric disorders and a leading cause of loss in work productivity. The risk of disability is almost five-fold compared to non-depressive individuals (Kessler et al., 1999). Moreover, high costs are incurred by employees and employers alike (Stewart et al., 2003; Katon et al., 2008) and by society as a whole (Kessler et al., 1999; Simon et al., 2000). Despite this link to public health and the economic importance, only a few studies have specifically focused on the granting of such pensions and long sick leave to patients with depression (Karpansalo et al., 2005; Bultmann et al., 2008; Doshi et al., 2008; Korkeila et al., 2010). Of these, most were either record-based (Rytsälä et al., 2001; Sorvaniemi et al., 2003; Bultmann et al., 2008) or retro-

spective (Isometsä et al., 2000) and seldom longitudinal (Karpansalo et al., 2005; Korkeila et al., 2010).

In previous studies from general population and primary care settings, disability pension has been predicted by older age (Karpansalo et al., 2005; Doshi et al., 2008), severity of depression (Bultmann et al., 2008), psychiatric comorbidity (Korkeila et al., 2010), medical comorbidity (Karpansalo et al., 2005) and personality disorder (Korkeila et al., 2010). Shortcomings in treatment of depression and poor adherence to treatment (Katon et al., 1995; Lingam and Scott, 2002) have been reported to affect recovery from depression, and thus contribute to functional and work disability(Von Korff et al., 2003). The longitudinal and recurrent nature of MDD makes the need for investigation of long-term predictors obvious. However, remarkably few prospective, comprehensive clinical studies on long-term work disability in psychiatric or primary care exist.

2.6.3 Work disability pension due to MDD

Depression is the most prevalent mental disorder causing sickness absence from work on the grounds of illness (Wells et al., 1989; Hensing et al., 2000), and the growing number of disability pensions granted for this reason is a major concern. Major depressive disorder (MDD) is one of 10 leading diseases in the global burden of disease (Lopez et al., 2006), and by 2030 it is projected to be the main cause of disability (WHO, 2004). In many Western countries, disability compensations granted for depressive disorders have markedly increased since the 1990s (Järvisalo et al., Finland; 2005). The risk of disability is almost five-fold compared to asymptomatic individuals (Kessler et al., 1999). Moreover, high costs are incurred by employees and employers alike (Stewart et al., 2003; Katon et al., 2008) and by society as a whole (Kessler et al., 1999; Simon et al., 2000). In Finland, almost half of the disability pensions were granted due to depression in 2005 (Source of information: Finnish Centre for Pensions, 2006).

The scarcity of previous studies on predictors for a disability pension renders comparison with previous findings difficult. Although predictors for short-term sick leave are not necessarily the same as those disability pension, medium-term studies of absenteeism due to illness have reported mostly convergent findings. Severity of depression has been associated with work disability, and working people with vulnerable personalities (neuroticism) have a greater risk of impaired work functioning, independent of the risk from any mental disorder they may have (Kruijshaar et al., 2003; Michon et al., 2008).

3 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 in a 5-year prospective follow-up study of psychiatric patients with major depressive disorder the prevalence, duration and predictors of maintenance treatment.

II
To investigate patients´ attitudes and adherence towards pharmacotherapy and psychotherapeutic treatments at baseline, 6 months, 18 months and 5 years.

III
To investigate factors predicting the granting of a long-term disability pension among psychiatric patients with MDD.

IV
To compare the characteristics of smoking and non-smoking psychiatric MDD patients and to investigate whether depression and smoking behaviour covary or have an independent course.

4 Materials and methods

4.1 General study design

The Vantaa Depression Study (VDS) is a collaborative depression project between the Department of Mental Health and Substance Abuse Services, Mood, Depression, and Suicidal Behaviour Unit of the National Institute for Health and Welfare, Helsinki (the former Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki), and the Department of Psychiatry of Helsinki University Central Hospital (HUCH), and Peijas Hospital, Vantaa, Finland. The Department of Psychiatry at Peijas Hospital (PMCD) provides secondary care psychiatric services to all residents of Vantaa (169 000 inhabitants in 1997), and provides psychiatric services to all Vantaa citizens. The Ethics Committee of Peijas Hospital approved the study on 2nd December 1996 and the 5-year follow-up study on 23rd January 2002.

4.2 Screening

The first phase of patient sampling for the VDS cohort involved screening all patients in the PMCD with a possible new episode of DSM-IV-TR MDD between 1st February 1997 and 31st May 1998. During that period, every patient (N=806) aged 20–59 years 1) seeking treatment, 2) being referred, or 3) already receiving care and now showing signs of deteriorating clinical state in the Department of Psychiatry but without a clinical diagnosis of ICD-10 schizophrenia or bipolar I disorder, was screened for the presence of depressive symptoms. 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 identify 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 requested to sign an informed consent document. Of the 703 eligible patients, 161 (22.9%) refused to participate in the study, but 542 (77.1%) agreed and gave written informed consent. Those who withheld consent did not differ significantly ($P>.05$) by age or gender from those who consented.

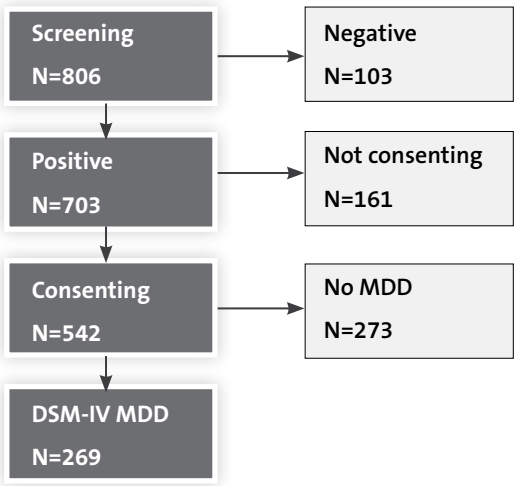


FIGURE 1. Flow-chart of the screening process in the Vantaa Depression Study.

4.3 Baseline evaluation

4.3.1 Diagnostic measures

In the second phase of sampling, the 542 participating patients were interviewed face-to-face by a researcher using the WHO SCAN 2.0 by interviewers who had all received relevant training by a WHO certified training centre. They inspected whether or not the current mood episode fulfilled the criteria for (unipolar) DSM-IV-TR 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 examined using 20 videotaped diagnostic interviews; the kappa coefficient for MDD was 0.86 [0.58-1.0] with a 95% observed agreement rate.

The decision to include the patient in the study cohort was made by the researcher during the interview, after which the entire SCAN interview (Wing et al., 1990) 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; Spitzer et al., 1989) was used to assess diagnoses on axis II. Current axis III diseases were measured 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.

4.3.2 Exclusion criteria

All patients who had earlier received a diagnosis of DSM-IV-TR bipolar I or II disorder, schizoaffective disorder, schizophrenia or another psychotic disorder, organic or substance-induced mood disorder were excluded from the study, even though they fulfilled the symptom criteria of current MDE. Also, patients with a history of MDD, not fulfilling the criteria of the disorder in the current episode were excluded.

4.3.3 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), 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).

4.4 Follow-up procedure

4.4.1 Study participants

Of the 269 patients with current MDD initially included in the study (Melartin et al., 2002), 229 participated in the 6-month, 207 in the 18-month 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 (I.A.K.H. or K.M.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 the 18 month mark, 13 patients' diagnoses had been changed 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])

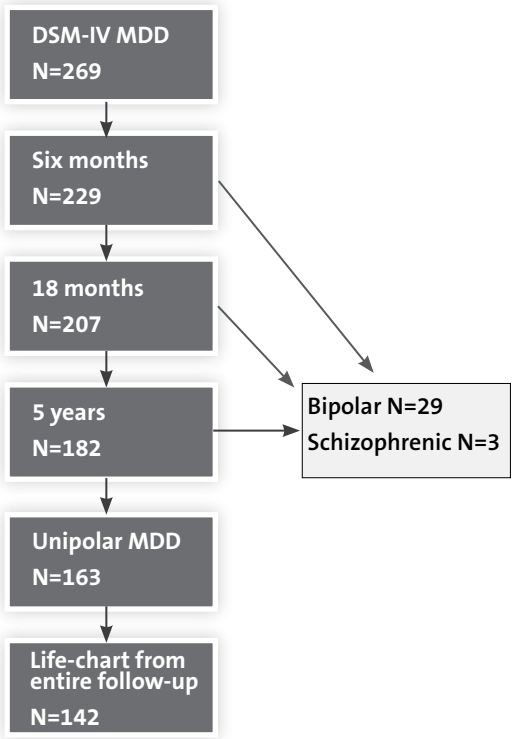


FIGURE 2. Flow-chart of the follow-up process in the Vantaa Depression Study.

remained for the analyses, and 65 patients dropped out. Life-chart information on 142 of the 163 patients was available for the entire follow-up period.

At baseline, the majority of the 269 patients in the cohort were outpatients (83%), females (73%), half (50%) were married or cohabited, and 60% employed with a mean age of 39.6 years (SD=11.1). More than a third (35%) was experiencing their first MDD. The patients' mean Ham-D value was 19.5 (SD=5.9), and BDI 27.7 (SD=8.6). A majority (79%) suffered from at least one comorbid disorder, and over half (54%) had 2 or more. Over half (57%) suffered from a comorbid anxiety disorder, a quarter (25%) from alcohol abuse or dependence, and almost half (44%) from at least one personality disorder (Melartin et al., 2002) (Table 1).

At five years, a majority of the patients (N=163) were females, outpatients, over half married or cohabited, two thirds employed, two thirds had a comorbid axis I disorder, and two fifths an axis II disorder (Table 1). The median 17-item Ham-D score was 23.0 for those currently in an MDE. At 5 years, half of the followed-up subjects (49.7%, 81/163) were in full remission, i.e. without any significant depressive symptoms, and one-fourth (23.9%, 39/163) were currently in the midst of MDE.

TABLE 1. Baseline characteristics of patients participating to the 5-year follow-up of the Vantaa Depression Study (n=163)

Characteristic	N	(%)
Sosiodemographic factors		
Sex		
Female	127	(77.9)
Married or cohabiting	93	(57.1)
Professional education	60	(36.8)
Employed	105	(64.4)
Low income	64	(39.3)
Recidential area (east Vantaa)	62	(38.0)
	Mean	**(SD)**
Sosiodemographic factors		
Age (years)	40.7	(11.3)
Clinical factors		
Age at onset	33.0	(12.7)
Ham-D	18.6	(5.8)
BDI	27.0	(8.6)
BAI	21.3	(10.6)
SOFAS	53.5	(9.4)
Hopelessness (HS)	10.2	(4.7)
Psychosocial and personality factors		
Neuroticism [a]	17.2	(3.7)
Extraversion [a]	9.8	(4.5)
Size of social network	7.8	(3.6)
Perceived social support (PSSS-R)	39.1	(12.7)
Negative life events[b]	4.0	(11.0)
Clinical factors		
Suicidal ideation (SSI)	25th	0.0
	50th	0.0
	75th	12.0
Number of previous MDEs	0.0	
	50th	1.0
	75th	2.0
	n	**%**
Outpatient	143	(87.7)
MDD subtype		
Melancholic	51	(31.3)
Atypical	18	(11.0)
Psychotic	7	(4.3)
Axis I comorbidity	104	(63.8)
Dysthymia	17	(10.4)

	n	%
Comorbid disorders		
Anxiety disorders	89	(54.6)
Phobic/ Nonphobic	60	(36.8)
Panic disorder	24	
with/	9	(5.5)
without agoraphobia	15	(9.2)
Agoraphobia without panic	16	(9.8)
Specific phobia	43	(26.4)
Social phobia	22	(13.5)
OCD	7	(4.3)
GAD	26	(16.0)
Alcohol use disorders	29	(17.8)
Dependence	11	(6.7)
Abuse	18	(11.0)
Axis II comorbidity		
Personality disorders	66	(40.5)
Cluster A	26	(16.0)
Cluster B	21	(12.9)
Cluster C	46	(28.2)
	Mean	**(SD)**
No. of psychiatric disorders		(1.6)
Axis III comorbidity		
No. of current somatic diseases		(1.2)

[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 Scale, BAI = Beck Anxiety Scale, 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.

4.4.2 Study drop-outs

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

In Cox´s proportional hazards analysis, all the information available for different lengths of follow-up time was used. In this case, only patients not participating to any of the follow-up interviews were dropped from the study (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), 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 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), had more antisocial personality disorder symptoms (z=–2.73, p=.006), reported less perceived 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).

4.4.3 Life-chart methodology

The careful duration of the index episode and the timing of possible relapses/recurrences were examined by gathering all available data, which were then combined into the form of a graphical life chart. This was created at the six- and 18-month interviews after reviewing with the patient all the information from the follow-up period. The life-chart was based on DSM-IV criteria and definitions. 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). Patients were considered to have achieved full remission if they had spent at least two consecutive months in the state of full remission, and partial remission if they had spent at least two months in the state of partial remission. Relapse was defined as a 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 symp-

toms sufficiently severe to satisfy criteria for an MDE after at least two consecutive months of partial or full remission.

4.4.4 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 at follow-up assessments. All available medical and psychiatric records were used to complete and check the interview information. The diagnoses and timing of depressive episodes were based on the structured interviews as well as patient records.

4.4.5 Treatment received

All available data from interviews and medical records was used in analyses including psychopharmacological treatment, number of visits to psychiatrists and other health professionals, inpatient treatment, and acceptance or refusal of antidepressant treatment. All antidepressant trials and their doses were recorded as well as the adequacy of the antidepressant treatment trials and their doses. Other medications, like antipsychotics, anxiolytics, hypnotics, and possible augmentation medications, and received electroconvulsive therapy were recorded. Psychosocial treatment was investigated regarding its type, length, and the number of visits.

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 patients (98%) received psychotherapeutic support in the early acute phase, but only few had weekly psychotherapy (16%) (Melartin et al., 2005).

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.

4.4.6 Patients' attitudes towards treatments

Attitudes towards antidepressant and psychotherapeutic treatments at baseline were assessed separately by interview and rated on an ordinal scale with the following items: patient 1) actively wants treatment, 2) passively accepts treatment, 3) has reservations about treatment, 4) definitely has negative attitudes towards treatment, or 5) could not answer. At the follow-ups, patients were interviewed with scales comprised of the following items: attitudes are 1) very positive, 2) positive, 3) neutral, 4) negative, 5) very negative towards treatment, or 6) could not answer. Patients with reservations about, or definitely negative attitudes towards treatments were also asked their subjective reasons for these attitudes, with the following alternatives: 1) generally negative attitudes toward treatment, 2) fear of side-effects (antidepressants) / not wanting to confide in a stranger (psychotherapeutic treatments), 3) fear of dependence, 4) not knowing enough about treatment, 5) patient's / other's negative earlier experiences of treatment, 6) negative information from the media, 7) no belief that treatment will help, 8) treatment too expensive, or 9) could not answer.

4.4.7 Self-reported treatment adherence

Self-reported treatment adherence concerning the treatments provided was investigated by repeatedly interviewing patients at the follow-ups using an ordinal scale with the following response items: has the patient come to sessions/been on antidepressants 1) regularly, treatment compliance adequate with respect to treatment goals, 2) somewhat irregularly, it is unclear whether this would affect treatment goals, 3) very irregularly, the treatment did not proceed according to plan, and 4) not at all, the provided treatment could not be implemented.

4.4.8 Sosio-demographic characteristics and work status

Patients' age, gender, marital status, occupational status, work status and both the beginning and at the end of the treatment period were noted and especially work disability pensions. Current work status and length of sick-leave (granted by a physician) were recorded at every interview point. These were based on patients' self-reports and the medical records in use at interview.

4.4.9 Information on disability pensions

Information on disability pensions granted to subjects belonging to the VDS population was obtained from interviews, patient records, and registers of the Social Insurance Institution of Finland for the 2002–2007 period. Based on all available information, dates on the granted pension events were recorded in the patient's

life-chart. When this research was carried out, in Finland, sick leaves due to depression and lasting over two months were mostly granted by psychiatrists. These usually occur as several consecutive sick leave periods during treatment, if the patient is considered incapable of working. Medical certificates issued by a psychiatrist for work disability allowances are referred to and granted by the Social Insurance Institution of Finland. After receiving this daily allowance from sickness insurance for 300 days (calculated on the basis of a six-day working week), employees aged 63 to 65 years become eligible for a disability pension. Medical certificates are referred to and pensions granted by the pertinent insurance company with which the person in question is entitled to pension insurance benefits. The information on a possible disability pension from the Social Insurance Institution of Finland was obtained for the whole study population cohort, except for two subjects who withdrew their consent regarding pension register information.

4.4.10 Smoking behavior

The information on smoking behaviour was studied on self-reported material at the follow-up interviews, using a scale with the following response items: the patient 1) has never smoked, 2) has quit smoking, 3) has smoked occasionally, or 4) has smoked regularly. The number of cigarettes per day was recorded. We required that information on smoking status from at least three follow-up interviews would be available. Thus, information on 214/269 patients (79.6%) was included in the analyses of smoking behaviour and depression. Those dropped from the study were subjects who did not participate in any follow-up (n=20) or for whom information on smoking was available from only one or two time-points.

4.5 Statistical methods

Study I

Chi-square test (with Yates` correction), Fisher`s exact, Mann-Whitney and Kruskal-Wallis tests, and the two-sample t-test were used when appropriate. Logistic regression was used to investigate predictors for receiving maintenance treatment from a predetermined set of twelve predictors covering different domains. The nonsignificant variables were eliminated from the final model, but in it age, gender and length of maintenance indication (months) were taken into account.

Study II

Friedman´s and Cochran´s tests were used for analyses of changes in attitudes and adherences during the follow-up. Univariate and multivariate logistic regression models were used to evaluate attitude and adherence to treatment in the final follow-up interview; positive and negative outcome values were compared. Responses of "not having received the treatment" or "not being able to answer" were excluded from the analyses. In these analyses, censored data included subjects who left the study before any follow-up interview. The baseline attitude towards treatment was added to the model when analysing adherence.

Study III

Normally distributed continuous variables were analysed by the two-sample t-test or by ANOVA test, and non-normally distributed variables were analysed using the Mann-Whitney and the Kruskal-Wallis tests. Kaplan-Meier survival curves were used to estimate the probability of a granted disability pension during the 5-year follow-up. Cox proportional hazards models were used for univariate and multivariate analyses to predict the interval time to the date the pension was granted. Subjects were eliminated from the survival analysis at the time they discontinued the study, i.e. either at the time of the last interview or due to change of diagnosis.

Study IV

Multivariate methods were used to control for possible confounding factors, and these analyses constitute our main findings. Discriminant analyses were used for a linear combination of predictor variables that would maximally separate two groups of interest (never smoked, has smoked) from one another. Smoking was similarly operationalized in logistic model as a three-category ordinal variable at each time point (does not smoke, smokes occasionally, smokes regularly). For discriminant analyses, a predictor "number cigarettes per day" was used. Whenever the predicted variable in a regression equation was categorical (smoking, alcohol use disorder), the relationship between the predictor and the predicted variable was to be interpreted as a logistic regression. When the Ham-D measure for depression was used, this path was interpreted as a classical regression path. Mplus 5.21 was used to estimate the models (Muthén and Muthén, 1998–2010).

5 Results

5.1 Maintenance pharmacotherapy in MDD (Study I)

5.1.1 Maintenance treatment received

Figure 3 summarizes the maintenance treatment patients received up to the 5-year follow-up. Only about half of the patients (57.0%, 49/86) received the treatment indicated by their diagnosis and only for 15.9% (SD ±43.7) (of all patients with indication) of the total time (2961.4 patient months) with indication, for a mean of once (SD ±0.71). Median time with indication was 22.7 months (SD±17.7), and median duration of maintenance treatment received was only 2.8 months (SD±14.8). Patients receiving maintenance treatment visited physicians more often than those not receiving such treatment (median 4.0 [SD±5.72] vs. 2.0 [SD±2.78], z=-2.65, p=0.008), among whom in two thirds of cases (64.9%, 24/37) contact with secondary care services had ended prior to the onset of indication.

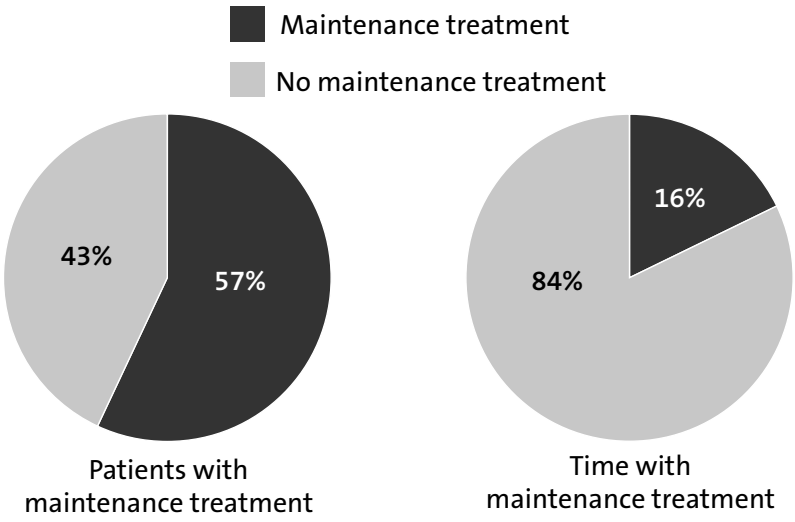


FIGURE 3. Proportion of patients and time with maintenance antidepressant treatment during five-year follow-up of Vantaa Depression Study (VDS).

5.1.2 Predictors for maintenance treatment received

Maintenance treatment associated significantly with numbers of previous episodes, of comorbid Axis I-III disorders and mental disorders, severity of anxiety, anxiety disorders, panic disorder, social phobia, avoidant personality disorder, positive medication attitude, good adherence during the acute phase, and higher income level (Table 2). However, in multivariate logistic regression analyses, only good antidepressant adherence in the acute phase (OR=3.18; 95% CI 1.12 – 9.03, p=0.030) independently predicted maintenance treatment.

5.2 Treatment attitudes and adherence in MDD (Study II)

5.2.1 The general features of treatment attitudes and adherence during follow-up

During follow-up, treatment adherence was reportedly good, and the overall attitudes to both antidepressant medication and psychosocial treatment were positive. Among study cohort patients, attitudes to antidepressant medication became less positive during the follow-up (χ^2=14.9, df=3, P=0.002), but adherence to medication did not change significantly. Attitudes to psychosocial treatment also changed to less positive during follow-up (χ^2=13.1, df=3, P=0.004), but adherence improved significantly (χ^2=6.87, df=2, P=0.032) (Figures 4 a and 4 b).

5.2.2 Attitudes towards treatments

During follow-up, nearly four-fifths (78.7%, n=237/187), had a positive attitude towards medication and the majority (90.7%, n=227/206) had a positive attitude towards psychosocial treatment. Patients with negative attitudes to medication were significantly more often female, had fewer previous MDEs, less social phobia, less alcohol dependence, fewer cluster C personality disorder symptoms and less comorbid psychiatric disorders, and were more often employed. In multivariate logistic regression models, the predetermined covariates consisted of age, gender, time at risk, number of previous episodes, Ham-D, BAI, SSI, SOFAS, axis I disorders, personality disorders, melancholic depression, professional education, employment situation, negative life events and neuroticism. Only employment at baseline predicted a positive attitude (Table 3).

TABLE 2. Characteristics of major depressive disorder (MDD) patients in the Vantaa Depression Study with an indication of maintenance antidepressant treatment.

	Maintenance (n=49)		No maintenance (n=37)		Total (n=86)			
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**χ2**	**p-value**
Sociodemographic features								
Female	36	73.5	26	70.3	62	72.1	0.11	0.740
Outpatient status at baseline	40	81.6	31	83.8	71	82.6	0.07	0.800
Married or cohabiting	33	67.3	18	48.6	51	59.3	3.05	0.081
Comorbid disorders								
Axis I disorders	36	73.5	22	59.5	58	67.4	1.88	0.170
Anxiety disorders	33	67.3	17	45.9	50	58.1	3.97	0.046
Alcohol use disorders	12	24.5	8	21.6	20	23.3	0.97	0.755
Axis II disorders	27	55.1	16	43.2	43	50.0	1.19	0.280
MDD subtype features								
Melancholic	20	40.8	14	37.8	34	39.5	0.08	0.780
Psychotic	3	6.1	3	8.1	6	7.0	0.13	0.720
Treatment-related factors								
Positive attitude towards antidepressants	38	77.6	19	51.4	57	66.3	6.48	0.011
Good adherence to antidepressants[a]	33	71.7	14	45.2	47	61.0	5.50	0.019
	mean	**SD**	**mean**	**SD**	**mean**	**SD**	**t/z**	**p-value**
Sociodemographic features								
Age	40.1	10.9	37.7	11.5	39.1	11.2	-0.98	0.329
Clinical features of MDD								
Age at onset	27.3	12.8	26.9	12.3	27.1	12.6	-0.14	0.888
Number of previous episodes	3.1	3.1	2.5	3.6	2.9	3.3	-2.04	0.041
Ham-D	19.1	5.8	18.9	5.9	19.1	5.8	0.18	0.859
BDI, mean	27.3	7.1	29.0	8.4	28.0	7.7	1.04	0.302
BAI, mean	23.8	10.7	18.9	9.4	21.7	10.4	-2.23	0.029
SOFAS, mean	52.7	9.9	49.6	10.6	51.3	10.3	-1.40	0.166
Comorbid disorders								
No. of psychiatric disorders	3.7	2.1	2.9	1.7	3.3	2.0	-1.91	0.059
No. of current somatic diseases	0.8	1.4	0.4	1.0	0.6	1.1	-1.73	0.084
No. of all axis I-III disorders	4.5	2.5	3.2	1.9	3.9	2.3	-2.58	0.012
Psychosocial factors								
Size of social network	7.8	3.7	6.5	3.4	7.3	3.6	-1.66	0.100
Family net income/month (FIM)	9 681	6 029	7 192	4 091	8 692	5 453	-2.01	0.048
Treatment-related factors								
Length of maintenance indication	40.2	18.1	26.7	20.2	34.4	20.1	-3.25	0.002

Chi square-, t- and Mann-Whitney U-tests.
[a]Investigated at 6 months (n=77 due to nine patients missing this interview)

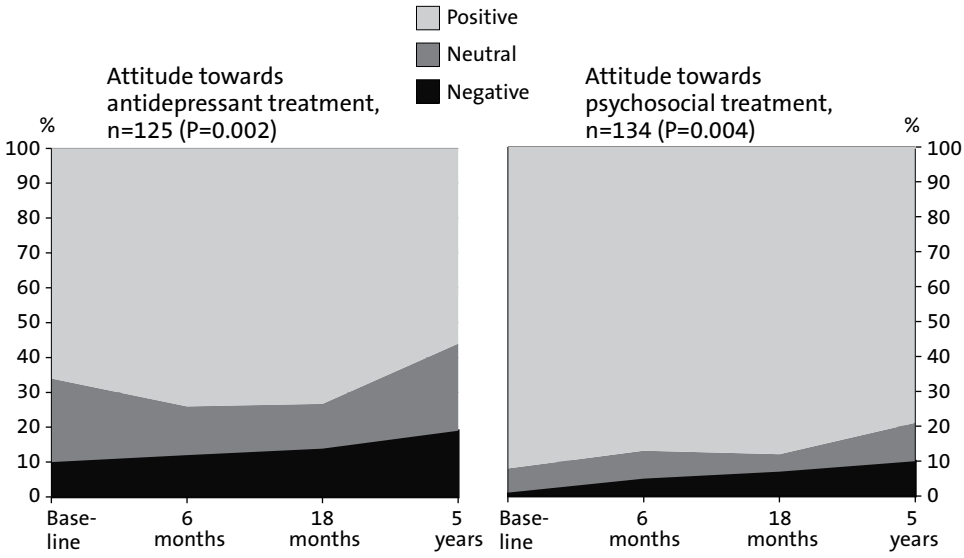


FIGURE 4 a. Change of attitudes towards treatment during five-year follow-up in the Vantaa Depression Study.

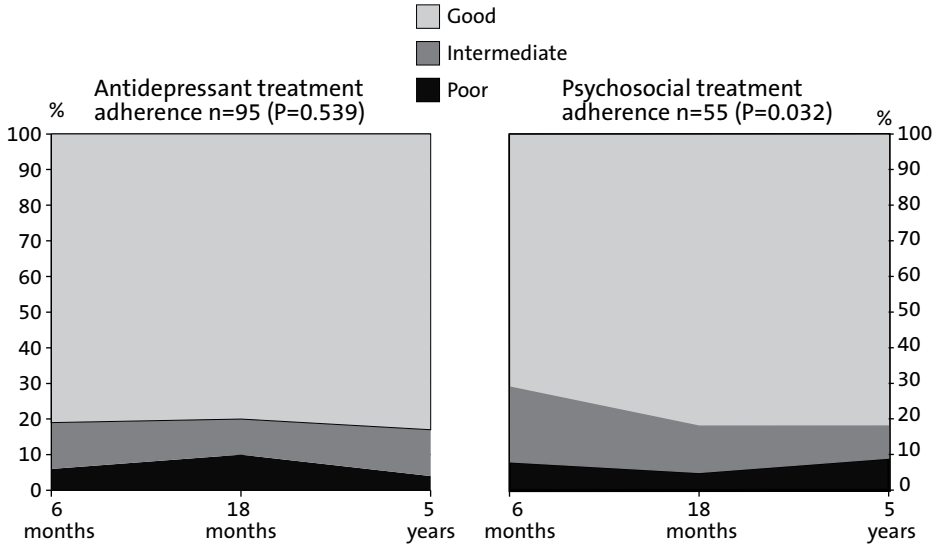


FIGURE 4 b. Change of treatment adherence during five-year follow-up in the Vantaa Depression Study.

TABLE 3. Predictors of positive vs. negative treatment attitudes and good vs. poor adherence at last follow-up interview of the Vantaa Depression Study (VDS)

Predictors	OR	95% CI	p
Attitude to antidepressants			
Employed	1.97	1.01 – 3.83	0.046
Pharmacotherapy adherence			
Size of social network	1.11	1.00 – 1.23	0.042
Attitude to psychosocial treatment			
No. of cluster B personality disorder symptoms	0.82	0.70 – 0.96	0.012
No. of cluster C personality disorder symptoms	1.30	1.09 – 1.54	0.003
Psychosocial treatment adherence			
No. of cluster B personality disorder symptoms	0.83	0.72 – 0.95	0.007
Living alone	3.13	1.10 – 9.09	0.032

Multivariate logistic regression models, adjusted for sex and age.

During the 5-year follow-up, nine-tenths, the majority of patients (n=206, 90.7%), had at their last follow-up a positive attitude towards psychosocial treatment. Negative attitudes towards psychosocial treatment were significantly associated with phobia, panic disorder without agoraphobia, cluster C personality disorder symptoms, comorbid axis I-III disorders and neuroticism. In multivariate logistic regression models, predetermined covariates included were age, gender, time at risk, number of previous MDEs, comorbid axis I-III disorders, Ham-D, melancholic depression, employment situation, income level and neuroticism. In the models, a higher number of cluster C symptoms predicted a positive attitude and a higher number of cluster B disorder symptoms predicted a negative attitude (Table 3).

5.2.3 Adherence to treatment

During the 5-year follow-up, the majority (73.6%, 173/128) of patients reported good adherence to medication, and to psychosocial treatment (81.1%, 163/133). The factors explaining poor adherence to antidepressant medication were economic reasons (n=4, 10%), a generally negative attitude towards pharmacotherapy (n=5, 12.5%), lack of motivation for pharmacotherapy (n=19, 47.5%), side-effects (n=7, 17.5%) and other reasons (n=5, 12.5%) such as fear of addiction, memory difficulties and alcohol-related problems (subjects could report several reasons). Subjects with poor medication adherence had significantly fewer previous MDEs, more often melancholic depressive features, and a smaller social network and at baseline a more negative attitude towards medication. According to multivariate logistic regression models, the predetermined covariates consisted of age, gender,

time at risk, attitude at baseline, number of previous episodes, Ham-D, BAI, SSI, SOFAS, axis I disorders, personality disorders, melancholic depression, size of social network and employment situation. In the analyses, only a larger social network at baseline predicted good adherence (Table 3).

The factors explaining poor adherence to psychosocial treatment were as follows: a generally negative attitude towards this treatment form (n=2, 10.5%), a lack of motivation (n=9, 47.4%), a practical excuse (n=3, 15.8%) and other reasons (n=5, 26.3%), e.g. poor cooperation or conflict with the therapist. Patients with poor psychosocial treatment adherence had significantly more alcohol use disorders and cluster B personality disorders and symptoms. In multivariate logistic regression analyses, the included covariates consisted of age, gender, time at risk, negative attitude at baseline, number of previous episodes, Ham-D, BAI, axis I disorders, personality disorders, melancholic depression, size of social network, marital status and employment situation. A large number of cluster B personality disorder symptoms predicted poor adherence and living alone good adherence (Table 3).

5.3 MDD and work disability (Study III)

The information of 230 patients belonging to the labour force at baseline was included in the analyses. During the 5-year follow-up, 20 per cent of the patients were granted disability pension, and nearly all of them, (95.7%, [44/46]) on the grounds of major depression as the primary diagnosis. One patient had depression as a secondary diagnosis, and one a physical condition (low back pain) as the primary diagnosis.

5.3.1 Differences between patients with and without a disability pension

Those patients who were granted a disability pension were significantly older, had received vocational education less often, had higher introversion and less perceived less social support compared to those not superannuated. They also were older at the onset of depression, had more severe anxiety (in BAI), more comorbid somatic disorders, and spent a longer time in MDEs during follow-up than individuals who were not granted pension. In addition, they had lower levels of overall social and occupational functioning (SOFAS), and were concurrently on sick leave and perceived themselves to be unable to work markedly more often than their non-pensioned counterparts (Table 4).

Numerous other variables also individually predicted the granting of a disability pension. These included sociodemographic factors (lack of vocational education), clinical and depression-related factors (longer time in MDE prior to entry,

TABLE 4.
Characteristics of subjects pensioned (N=46) or not pensioned (N=184) in the Vantaa Depression Study, 5-year follow-up

Characteristic	Not pensioned n (%)	Pensioned n (%)	Total n (%)	p
Sociodemographic characteristics				
Female	136 (73.9)	36 (78.3)	172 (74.8)	0.544
Married or cohabiting	90 (48.9)	0 (65.2)	120 (52.2)	0.048
Vocational education	120 (65.2)	0 (43.5)	140 (60.9)	0.007
Employed	119 (65.4)	6 (57.8)	145 (63.9)	0.342
Low income	80 (47.6)	3 (34.2)	93 (45,1)	0.134
Clinical characteristics				
Outpatient	155 (84.2)	38 (82.6)	193 (83.9)	0.788
Melancholic	67 (36.4)	17 (37.0)	84 (36.5)	0.945
Atypical	17 (9.2)	3 (6.5)	20 (8.9)	0.559
Psychotic	16 (8.7)	3 (6.5)	19 (8.3)	0.632
Axis I comorbidity				
Any axis I comorbidity	128 (69.6)	28 (60.9	156 (67.8)	0.259
Dysthymia	15 (8.2)	6 (13.0)	21 (9.1)	0.303
Any anxiety disorder	107 (58.2)	24 (52.2)	131 (57.0)	0.464
Any alcohol use disorder	47 (25.5)	8 (17.4)	55 (23.9)	0.246
Axis II comorbidity				
Any personality disorder	76 (41.3)	24 (52.2)	100 (43.5)	0.183
Cluster A	35 (19.0)	8 (17.4)	43 (18.7)	0.800
Cluster B	26 (14.1)	7 (15.2)	33 (14.3)	0.851
Cluster C	55 (29.9)	19 (14.3)	74 (32.2)	0.138
Perceived work ability				
Good	25 (13.7)	12 (4.4)	27 (11.9)	0.001
Impaired	111 (61.0)	19 (42.2)	130 (57.3)	
Unable to work	46 (25.3)	24 (53.3)	70 (30.8)	
Sick leave at baseline	34 (27.9)	22 (51.2)	56 (33.9)	0.006
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**p**
Sociodemographic characteristics				
Age (years)	37.5 (10.4)	46.3 (10.3)	39.3 (10.9)	<0.001
Clinical characteristics				
Age at onset	30.2 (12.0)	36.9 (13.2)	31.6 (12.5)	0.001
Number of episodes prior to baseline	1.4 (2.5)	2.2 (3.6)	1.6 (2.7)	0.194
Ham-D	19.0 (6.5)	20.8 (4.5)	19.4 (6.2)	0.087
BDI	27.2 (8.6)	28.7 (8.5)	27.5 (8.6)	0.281
BAI	21.8 (11.0)	25.3 (10.2)	22.5 (10.9)	0.050
Hopelessness (HS)	9.9 (4.9)	10.6 (4.4)	10.1 (4.8)	0.346
Suicidal ideation (SSI)	6.1 (8.0)	5.7 (7.7)	6.0 (7.9)	0.767
SOFAS	53.1 (11.2)	49.8 (9.6)	52.5 (10.9)	0.070
Neuroticism*	12.6 (5.6)	16.4 (4.3)	13.5 (5.6)	0.835
Extraversion*	12.3 (4.5)	9.0 (3.1)	11.5 (4.5)	0.003
No. of comorbid psychiatric disorders	3.0 (1.7)	3.2 (2.1)	3.1 (1.8)	0.538
No. of comorbid somatic disorders	0.4 (0.8)	1.1 (1.7)	0.6 (1.1)	0.018
No. of comorbid psychiatric and somatic disorders	3.5 (1.9)	4.3 (2.7)	3.6 (2.1)	0.053
Body mass index	24.4 (4.8)	25.8 (5.2)	24.7 (4.8)	0.082
Proportion of time spent in MDE during follow-up	0.2 (0.3)	0.4 (0.4)	0.3 (0.3)	<0.001
Sociodemographic characteristics				
Perceived social support	40.7 (12.2)	36.4 (12.3)	39.9 (12.3)	0.031
Size of social network	7.8 (3.5)	7.2 (3.5)	7.6 (3.5)	0.297

* Eysenck Personality Inventory, neuroticism and extraversion at lowest Ham-D during the follow-up

Abbreviations: MDE = Major Depressive Episode, Ham-D = Hamilton Rating Scale for Depression, BDI= Beck Depression Scale, BAI = Beck Anxiety Scale, SOFAS = Social and Occupational Functioning Assessment Scale.

severity of depression and anxiety, lower levels of social and occupational functioning), comorbidity (number of comorbid psychiatric and somatic disorders), personality (neuroticism, introversion), and psychosocial factors (lack of perceived social support). However, besides older age only a perceived lack of work ability and greater introversion persisted as independent robust predictors in the multivariate analyses. When the proportion of time spent depressed during the follow-up was added to the model, it was a robust strong predictor together with older age, number of comorbid somatic disorders, and lack of vocational education (Table 5).

A patient's age had a great effect on the risk of being superannuated: an effect which was considerably greater in older age groups. One half (23/45, 51.1%) of patients > 50 years were granted a disability pension, compared to only one eighth (23/185, 12.4%) of those ≤ 50; the relationship between age and risk of being superannuated was nonlinear (Figure 5). Those over 50 did not differ in regard to the duration or severity of depression or for the overall level of functioning compared to younger age groups.

TABLE 5. Baseline and 5-years follow-up predictors of granted work disability pension for employed patients with major depressive disorder (MDD) in the Vantaa depression study.

Baseline predictors*	***HR***	***95% CI***	***P***
Age over 50	3.91	2.02–7.52	<0.001
Gender (Female)	1.37	0.66–2.83	0.400
Lower perceived work ability	2.14	1.22–3.76	0.008
Intraversion **	1.08	1.00–1.16	0.049
Predictors by follow-up***	***OR***	***95% CI***	***P***
Age over 50	6.25	2.71–14.3	<0.001
Gender (Female)	1.01	0.41–2.50	0.988
Proportion of time spent depressed	14.6	4.43–48.4	<0.001
Number of comorbid somatic disorders	1.47	1.08–2.00	0.013
Lack of vocational education	2.38	1.08–5.2	0.032

*Cox proportional hazards models; analyses adjusted for gender; hazard reported for decreasing time to event.
** Eysenck Personality Inventory at baseline.
***Logistic regression models

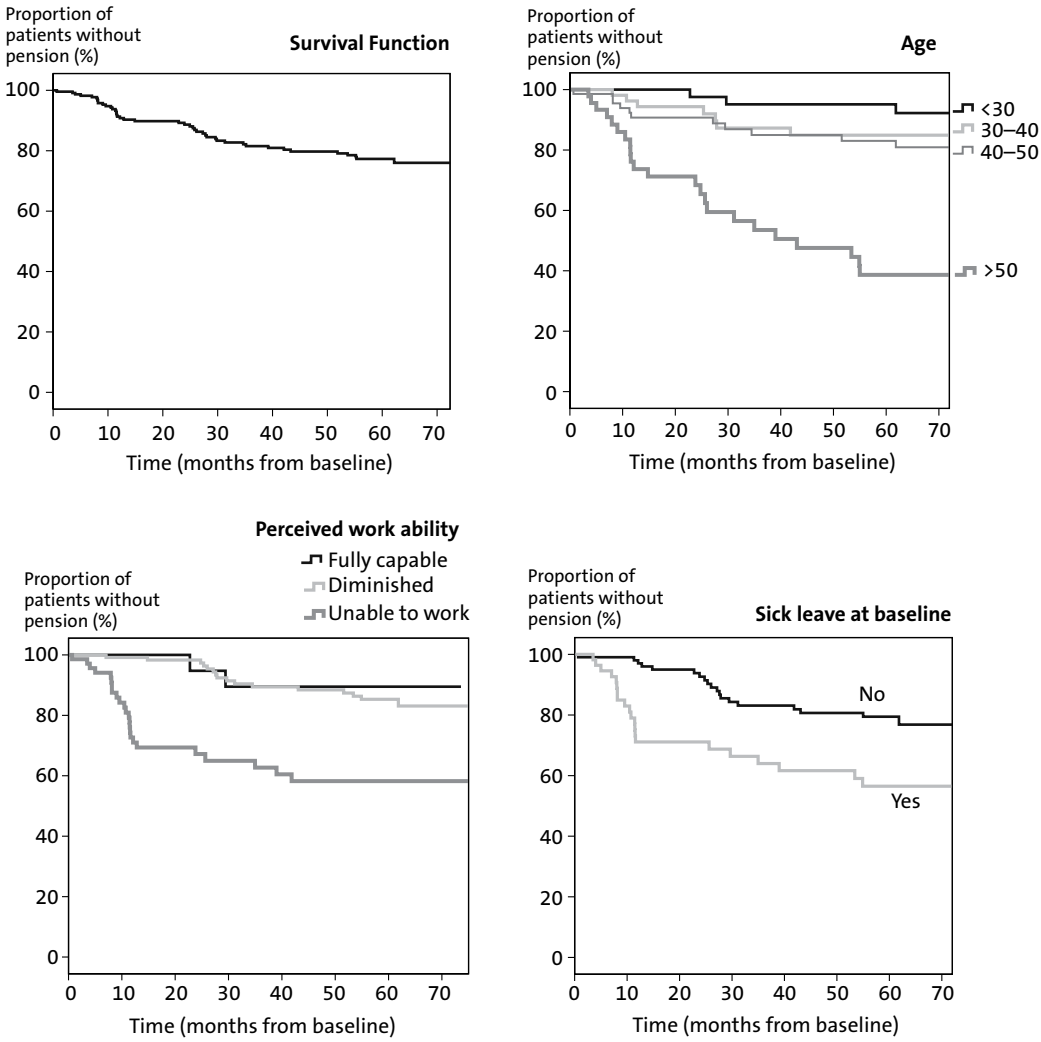


FIGURE 5. Proportion of patients with granted disability pension in relation to age, perceived work ability, and being on sick leave at baseline in the Vantaa Depression Study, 5-year follow-up.

5.4 MDD and smoking (Study IV)

5.4.1 Prevalence of smoking

Information on 214 (79.6%) of the 269 patients was included in the analyses. Over the 5-year follow-up, 31.3% (67/214) of the patients smoked regularly, 41.1% (88/214) had intermittent smoking behaviour, and 27.6% (59/214) had never smoked. Of the patients not smoking at baseline (50.9%, 109/214), ten (9.2%, 10/109) began to smoke, and of patients initially smoking regularly (39.7%, 85/214), ten (11.8%, 10/85) quit smoking during the follow-up.

5.4.2 Clinical and socio-demographic characteristic of the sample

Compared with non-smoking patients, patients smoking regularly had more often comorbid alcohol use disorders and a lower age at onset, Cluster B and C personality disorder symptoms, higher Ham-D score, higher SOFAS score, lower perceived social support, smaller social network, higher neuroticism, and had more often attempted suicide prior to baseline. In addition, there was a non-significant tendency to be younger (Table 6).

TABLE 6. Baseline patient characteristics and smoking status in the Vantaa Depression Study during 5-year follow-up (n=214)

Smoking status	Never smoked	Intermittent smoking	Regular smoking	
	n (%)	n (%)	n (%)	P
	59 (27.6)	88 (41.1)	67 (31.3)	
Characteristic				
Sociodemographic factors				
Female	46 (78.0)	62 (70.5)	50 (74.6)	0.588
Married or cohabiting	31 (52.5)	49 (55.7)	36 (53.7)	0.928
Employed	32 (56.1)	61 (70.1)	39 (60.9)	0.207
Professional education	23 (39.0)	36 (40.9)	25 (37.3)	0.901
Low income	27 (51.9)	48 (59.3)	32 (52.5)	0.622
Outpatient	49 (83.1)	79 (89.8)	51 (76.1)	0.074
MDD subtype				
Melancholic	20 (33.9)	32 (36.4)	27 (40.3)	0.751
Atypical	5 (8.5)	11 (12.5)	4 (6.0)	0.370
Psychotic	4 (6.8)	6 (6.8)	4 (6.0)	0.974
Axis I comorbidity				
Dysthymia	6 (10.2)	7 (8.0)	9 (13.4)	0.538
Any anxiety disorder	35 (59.3)	51 (58.0)	33 (49.3)	0.444
Alcohol use disorder	5 (8.5)	19 (21.6)	24 (35.8)	0.001
abuse	3 (5.1)	11 (12.5)	7 (10.4)	0.326
dependence	2 (3.4)	8 (9.1)	17 (25.4)	<0.001

TABLE 6.

Smoking status	Never smoked	Intermittent smoking	Regular smoking	
	n (%)	n (%)	n (%)	P
Axis II comorbidity				
Any personality disorder	19 (32.2)	43 (48.9)	31 (46.3)	0.116
Cluster A	8 (13.6)	20 (22.7)	12 (17.9)	0.369
Cluster B	3 (5.1)	14 (15.9)	13 (19.4)	0.056
Cluster C	12 (20.3)	35 (39.8)	21 (31.3)	0.046
Clinical factors				
Suicide attempt prior to baseline	13 (22.0)	26 (29.5)	40 (52.2)	0.001
Suicide attempt during follow-up	8 (13.6)	10 (11.4)	12 (17.9)	0.505
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**P**
Sociodemographic factors				
Age	43.7 (11.4)	39.3 (11.5)	40.2 (9.6)	0.052
Clinical factors				
Age at onset	36.6 (13.5)	30.9 (12.4)	30.4 (11.8)	0.006
No. of episodes prior to baseline	1.9 (3.4)	1.6 (2.4)	1.8 (2.9)	0.838
Ham-D	18.7 (6.4)	18.4 (6.0)	20.9 (5.6)	0.027
BDI	25.5 (8.8)	27.6 (7.7)	28.8 (8.3)	0.083
BAI	20.2 (10.3)	22.7 (10.1)	22.3 (11.5)	0.360
Hopelessness	9.1 (4.4)	10.6 (4.7)	10.2 (4.5)	0.147
Suicide ideation (SSI)	5.3 (7.8)	6.3 (7.5)	6.5 (8.3)	0.639
SOFAS	52.1 (10.9)	54.2 (10.3)	49.7 (10.5)	0.032
No. of recurrences	1.6 (1.5)	1.8 (1.8)	1.9 (1.8)	0.665
Time spent in MDEs	9.4 (11.9)	12.0 (15.2)	9.7 (11.3)	0.443
Comorbidity				
Cluster A symptoms	1.9 (2.3)	2.5 (2.9)	2.8 (2.5)	0.195
Cluster B symptoms	2.3 (2.6)	3.4 (3.3)	4.6 (4.1)	0.001
Cluster C symptoms	4.6 (3.5)	6.7 (5.0)	6.4 (4.2)	0.016
No. of psychiatric disorders	2.6 (1.6)	3.2 (1.8)	3.2 (1.9)	0.122
No. of somatic disorders	0.9 (1.5)	0.6 (1.1)	0.3 (0.5)	0.014
Psychosocial and personality factors				
Perceived social support	42.9 (11.3)	37.5 (13.1)	38.9 (13.0)	0.040
Size of social network	8.7 (3.7)	8.0 (3.6)	6.2 (3.0)	<0.001
Neuroticism[a]	12.2 (4.9)	15.0 (5.4)	13.0 (5.7)	0.010
Extraversion[a]	10.9 (4.2)	11.3 (5.7)	11.9 (4.3)	0.412
Adverse life events[b]	7.7 (4.6)	8.1 (4.7)	9.2 (4.5)	0.163

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.
For continuous variables: ANOVA for normal distribution, and Mann-Whitney and Kruskal-Wallis tests for non-normal distribution.

[a]Eysenck Personality Inventory: for dimensions of neuroticism and extraversion (at lowest Ham-D),
[b]Interview for Recent Life Events: objective measure of negative impact of adverse life events.

Abbreviations: MDE = Major Depressive Episode, Ham-D = Hamilton Rating Scale for Depression, BDI= Beck Depression Scale, BAI = Beck Anxiety Scale, SOFAS = Social and Occupational Functioning Assessment Scal

5.4.3 Comparison of smoking and non-smoking patients during the follow-up (Discriminant analyses)

We compared the characteristics of patients who had never smoked with those who had smoked at some point (regular or intermittent smokers) in discriminant analyses. According to these analyses, smoking patients were younger, more likely to suffer from an alcohol disorder at baseline, exhibited a greater number of Cluster B and C symptoms, had a higher frequency of lifetime suicide attempts, higher neuroticism, smaller networks, and lower perceived social support than non-smokers. All of these variables had at least a moderate correlation in the discriminant function, but alcohol disorder at baseline and Cluster B and C personality disorders had the highest correlations (Table 7). Predicting group membership based on the discriminant function correctly classified 66.5% of the cases.

5.4.4 Covariation of level of depression and smoking

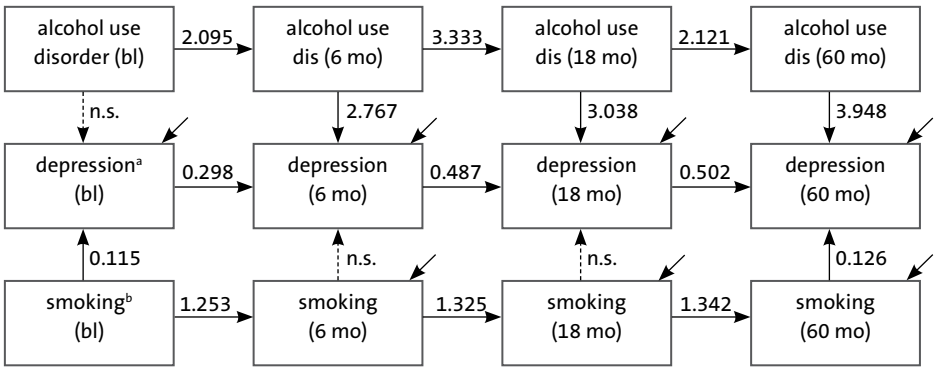
Smoking and depression had only limited covariation (Figure 6). According to autoregressive models, level of depression, smoking, and also alcohol use disorders all exhibited a strong autoregressive component; depressive symptoms, alcohol use disorders, and smoking at t+1 were each best predicted by the respective variable at t.

In the analyses at six months path from alcohol use disorder (alco6) to severity level of depression (depr6) was significant. Depr6 variable explained alco6 variable in addition to smoking status (smoking6). A packet of cigarettes a day and substance abuse reflected in the relative sizes of the same effects of topical depression symptoms: 2 points and 3 points. In addition at five years the path from smoking status (smoking5v) to severity of depression (depr5v) became clear. In additional analyses categorical smoking status was replaced with the variable "number of cigarettes per day". Error term arrows were added to those endogenous variables that have one (depression and smoking). The equations where alcohol use disorder was used as a dependent variable were logistic regressions, which did not have an error term (Figure 6). While depression and smoking had limited covariation, that of smoking and alcohol use disorders needed to be elaborated. At baseline, about 70% (35/54) of patients with alcohol use disorder were regular smokers, compared with 33% (59/177) of patients without an alcohol problem. The contemporaneous correlations of alcohol use disorders and smoking at baseline were significant, but just moderately (0.25). From the point of view of estimating model parameters, this correlation (not the percentages) was more relevant. This is true not just for the baseline, but also for the other time-points. Thus, the contemporaneous correlation between smoking and alcohol use disorders did not create any notable problems in the analyses.

TABLE 7. Multivariate discriminate analysis of smoking status during the 5-year follow-up (n=214).

Variable	Coefficient[a]	Correlation[b]
Age	-.406	-432
Alcohol use disorder	.400	.544
No. of Cluster B personality disorder symptoms	.188	.534
No. of Cluster C personality disorder symptoms	.168	.508
Lifetime suicide attempt	.289	.422
Neuroticism (at lowest Ham-D)	.196	.301
Size of social network	-.234	-.473
Perceived social support	-.309	-.422

[a]Standardized canonical discriminant function coefficients
[b]Overall correlations with the discriminant function in descending order



[a] Hamilton rating scale for depression score
[b] Number of cigarettes per day (zero or a positive integer, modelled in the Mplus analysis as a continuous variable censored from below)
Unstardardized coeffiencts are shown (standardized coefficients are not available, because there are categorical endogenous variables)

FIGURE 6. Autoregressive path model of depression, smoking, and alcohol use disorder.

6 Discussion

6.1 Main findings

The most important finding in the first study was that only 57% patients received indicated maintenance treatment, and only for 16% of the time indicated; good adherence to pharmacotherapy in the acute phase independently predicted maintenance treatment. The tertiary preventive impact of maintenance treatment may remain limited, as many MDD patients either do not receive it, or receive it for a too short period.

Most patients reported positive attitudes towards pharmacotherapy and psychosocial treatments, and good adherence during the follow-up. While attitudes became somewhat more critical over time, adherence to psychosocial treatment improved, but remained unchanged for pharmacotherapy. Employment predicted positive attitude, and larger social network good adherence to pharmacotherapy at the last follow-up. Cluster B personality disorder symptoms predicted a negative attitude and poor adherence, but cluster C symptoms positive attitude, and living alone good adherence to psychosocial treatment.

Factors associated with work disability were: age ≥ 50 years at baseline, subjective experience of inability to work, and introversion. When follow-up variables were included, the predictors were age over 50, proportion of time spent depressed, number of comorbid somatic disorders and lack of vocational education. Within five years, 20% of the patients belonging to the labour force at baseline were granted a disability pension.

The main findings of the last study are the differences between smokers and non-smokers. A third of the patients smoked regularly, less than half intermittently, and a fifth never. Compared with non-smokers, smokers were younger, had more alcohol use disorders, a greater number of Cluster B and C personality disorder symptoms, a higher frequency of lifetime suicide attempts, higher neuroticism, smaller social networks, and lower perceived social support. Smoking and depression did not co-vary longitudinally. In contrast, depression, smoking, and alcohol use disorders all exhibited strong autoregressive tendencies predicting expecially the disorders themselves during follow-up.

6.2 Methods

6.2.1 Representativeness of the sample

The major strength of this present naturalistic study is that it was based on a relatively large (N=269) 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 and maintenance treatment recommendations in the period 1997–1999 within a community psychiatric setting. On the basis of an epidemiological survey, two-thirds of all depressed subjects in the city of Vantaa were treated (within the facilities investigated) at the time of the study (Rytsälä et al., 2001).

The different diagnostic criteria, availability of only tricyclic antidepressants, and lack of recommendations for widespread maintenance phase treatments are all major changes that undermine the generalizability of earlier findings to current practice. 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 study (I–IV) is from the modern era in terms of the use of DSM-IV-TR diagnoses and definitions, modern antidepressants, and maintenance treatment recommendations. We used structured and semi-structured measures, both objective and subjective, and investigating a broad range of factors from several other domains; socio-demographic factors, work disability factors, clinical variables (including axis I, II and III disorders), and temperamental, and psychosocial factors (perceived social support, size of social network and negative life events). We used a life-chart methodology, which enabled us to investigate maintenance treatment endorsements, work ability changes, attitude and adherence to treatment, the stability of nicotine dependence and the outcome of MDD over time.

6.2.2 Diagnostic measures and life chart methodology

The diagnoses of MDD and comorbid disorders were made using structured and 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. Because of this, it was also used in the 5-year follow-up interviews. 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 inclu-

sion 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 observed.

Perhaps one of the most influential measurements in this study was the use of a life-chart. The longitudinal Interval Follow-up Evaluation (LIFE), a semi-structured interview and rating system for assessing the longitudinal course of psychiatric disorders in sufficient detail to provide the basis for calculating length of episodes and time to remission, was used for the first time used to investigate the outcome of depression in the NIMH-CDS (Keller et al., 1987). In the VDS we used a graphical life chart, which is similar, but not identical, to the LIFE method. Unlike the latter, patients' follow-up time was classified into periods of DSM-IV-TR MDE, or partial remission (1–4 criteria symptoms) or full remission (no symptoms).

This is the first long-term prospective study to investigate treatment attitudes and adherence among psychiatric patients with MDD. In addition, no prospective studies exist on attitude and adherence to psychosocial treatment. Unlike previous studies, we were able to investigate the role of a wide variety of variables from different domains as predictors for treatment attitudes and adherence.

The information on granted disability pensions was based on registers of the Social Insurance Institute of Finland, patient records and interviews. The level of attrition was low, as 91.3% (230/252) of those in the labour force at baseline contributed to this prospective study. Furthermore, dates of granting the respective pensions were granted were recorded in the patient's life-chart. The clinical characteristics of patients in the VDS cohort have been reviewed earlier (Melartin et al., 2002; Melartin et al., 2004) and are unlikely to differ greatly from those found in other studies on psychiatric MDD outpatients. Our findings can probably be generalized to those countries with similar health services and disability pension systems as in Finland. Treatment and a statement by a psychiatrist are usually required for disability pension to be granted to a MDD patient in Finland. Thus, the coverage with regard to all disability pensions in the study area is likely to be good (Isometsä et al., 2000; Sorvaniemi et al., 2003; Honkonen et al., 2007; Raitasalo et al., 2010). The SOFAS scale was used to measure global level of functioning at the time of evaluation. This scale just measures the level of social and occupational functioning, without taking symptoms into account.

To our knowledge, no previous long-term clinical study has investigated variations in the prevalence of smoking behaviour in MDD patients or the co-variation of tobacco smoking and MDD. We examined the aforementioned, also accounting for co-variation with comorbid alcohol use disorder, a major confounding factor. There are few long-term (up to 5 years) prospective studies of cohorts of patients with MDD and even fewer representative cohorts of outpatients (83% in our

study). For all patients, information on smoking was available from three or four phases of the longitudinal follow-up. The level of attrition was fairly low, as 79.6% (214/269) of the initial cohort contributed to this prospective study. Our evaluation methods included a wide range of predictors; we investigated associations of smoking with factors from different domains, including sociodemographic, clinical, comorbidity Axis I-III, and temperamental/personality factors, and we also had information on the duration and outcome of depression.

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, any anxiety disorder 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). In VDS approximately half of the patients have had a current anxiety disorder and about one fifth a current substance use disorder (Melartin et al., 2002).

6.2.3 Study limitations

Two-thirds of the patients participated in the five-year interview, and we had prospective information obtained from patients of varying lengths of follow-up. One limitation of the study includes the fact that there was a long interval between the last two interviews (3.5 years) and this may have affected the accuracy of information regarding longitudinal outcome of maintenance indication (Study I) and the information on treatment adherence (Study II). The recurrence rate (and thus onset of maintenance indication) may have been slightly underestimated during this period. The critical question here is the degree to which adherence during temporally distant periods could actually differ from temporally close periods. We cannot exclude the possibility of a recall bias, but are not aware of any reason why adherence would significantly differ between these periods, in particular as it otherwise appears relatively constant during the five-year follow-up. In order to complement and check the interview information, we also had access to patient records. With regard to measure points, we have only four measure-points in analyses of attitude and only three measure-points in analyses of adherence. Minor inaccuracies may also exist regarding treatment information. Subjects may also not always have recalled information on treatment precisely or reported adherence honestly. However, data from both subjects themselves and their records were carefully compared and synthesized. We defined the indication for maintenance pharmacotherapy to begin after three lifetime MDEs, and a different threshold could change the findings. However, setting it to lifetime fourth or fifth episodes in sensitivity analyses resulted in quite similar proportions of patients having received maintenance treatment (61.5 and 62.9%, respectively).

In the second study, the proportion of patients who dropped out of all prospective phases was 11.5% those eligible with 28.5% dropping out of the 5-year follow-up. The drop-outs differed significantly from those participating in terms of some socio-demographic characteristics (age, marital status, income) and comorbid psychiatric disorders (dysthymia, panic disorder with agoraphobia, alcohol dependence, cluster A and B personality disorder symptoms, and somatic disorders). Some of these features were associated with negative, others in turn with positive attitude or adherence among those remaining in the cohort. Overall, the drop-outs did not differ in terms of baseline attitudes to antidepressant medication or psychosocial treatment.

Thus, variations in attitudes or adherence could have occurred between interviews. Also, patients could perceive or report their adherence as sufficient even if the treatment was implemented poorly. Estimates of adherence were based on patients´ own accounts, albeit evaluated by the interviewer. In addition, we did not inquire about physicians' attitudes towards medication treatment, which is also important (Demyttenaere, 2003). Lastly, we used self-developed repeated interviews/questionnaires, possibly affecting the comparison of our results with those of others. However, while the variety of interview measures is a problem in this field, our strength was that we asked the same questions repeatedly over time. There were some factors that we did not investigate. Evidence suggests that establishing a good doctor-patient relationship has an important role in increasing adherence (Fawcett, 1995; Paykel, 1995). A clinician´s initial communication style influences a patient´s beliefs about and understanding of antidepressants, and subjects with more positive beliefs are more engaged in and satisfied with their treatment (Bultman and Svarstad, 2000).

In the third study, despite a low level of attrition, we had prospective information obtained from patients of varying lengths of follow-up. The main measure of functional ability, the Social and Occupational Functioning Assessment Scale of DSM-IV (SOFAS), includes the ability to work as one of the factors of functioning, and may thus cause some degree of circularity when used as a predictor for a future disability pension. In addition, we did not investigate work motivation, work circumstances (Sanderson et al., 2007), work functioning (Sanderson et al., 2007; Lagerveld et al., 2010), or patient's cognitive capacity (Raitasalo et al., 2010) which could be of importance. Finally, it is to be noted that in order to prospectively analyse predictors, we excluded 17 cases that had already received disability pension at baseline. The total proportion of patients who were known to have been granted a disability pension was one quarter (25%) of the total cohort (including patients whose diagnoses were changed).

In the fourth study, smoking behavior is also a limitation as it was ascertained by means of self-reported information. The cohort consisted of depressive psychiatric patients, mostly outpatients, all suffering from MDD at baseline, which influ-

ences the generalizability of our findings. We did not use Fagerström`s questionnaire (Fagerstrom and Schneider, 1989) on nicotine dependence, nor did we have information on plasma cotinine concentrations. However, we did collect information of smoking behaviour, including number of cigarettes smoked, at three to four time-points during the follow-up. In our view, a regular smoker was very likely to have true nicotine dependence. Finally, our investigation of co-variation and autoregression was limited to three factors, and co-variation with other possible confounding factors was not investigated.

6.3 Maintenance pharmacotherapy in MDD (Study I)

This study investigated the duration, prevalence and predictors of maintenance treatment. MDD is a commonly occurring and burdensome disorder and one of the most important mental disorders in terms of public health impact. Maintenance therapy is an effective tertiary preventive intervention. National practice guidelines recommend maintenance treatment for tertiary prevention of depressive recurrences (APA, 2010; Schaffer et al., 2012) may deny need for treatment fear facing their illness as a chronic condition. However, untreated and prolonged depression involves a marked risk of functional disability and days lost from work and adversely affect interpersonal relationships. Indeed, it has been shown that MDD involves a marked risk of functional disability (Lopez et al., 2006; Rytsälä et al., 2006; Holma et al., 2011) and adversely affects interpersonal relationships (Wade and Cairney, 2000). Suicide attempts among patients with MDD are strongly associated with the presence and severity of depressive symptoms (Holma et al., 2010).

To my knowledge, no previous secondary care long time study has investigated whether these recommendations have been implemented. In this prospective naturalistic 5-year follow-up study, only about half of the subjects with the indication received the indicated maintenance treatment, and only for about one-sixth of the time indicated. Maintenance treatment was best predicted by good medication adherence during the acute phase. A third of patients who did not receive indicated maintenance treatment, had a negative attitude towards longlasting medication. The main reason for discontinued antidepressant treatment, was a generally negative attitude towards medication.

6.4 Treatment attitudes and adherence of MDD (Study II)

Poor adherence to treatment for depression is likely to be common, and an important limit for what can be realized by treatment. In this prospective long-term study, the aim was to investigate temporal patterns of attitudes and adherence towards treatments, and factors influencing these patterns among psychiatric MDD subjects.

Depressive patients attitudes towards pharmacotherapy and psychosocial treatments were mostly positive during follow up. However, while the attitudes towards medication and psychosocial treatment became slightly less positive, adherence to treatments either improved or remained similar over time**.** Attitudes and adherence were associated with both psychiatric and psychosocial factors. Employment predicted a positive attitude towards antidepressants, and a larger social network good adherence. Attitudes and adherence to psychosocial treatments were associated with type of personality disorders; cluster B personality features predicted a negative attitude and poor adherence, while cluster C features predicted a positive attitude.

In earlier 6- and 18-month studies of VDS negative treatment attitudes at baseline were more common towards antidepressants than psychotherapeutic treatments, but in 82% of cases these attitudes become positive during the treatment. At baseline, negative attitudes towards treatment were associated with younger age, lower anxiety level (BAI), lower depression level (Ham-D), longer duration of MDE prior to entry and no current comorbid alcohol use disorder (Melartin et al., 2005). In the long-term, the majority of subjects (78.7%) reported a positive attitude at their last follow-up, but became slightly less positive over a longer period. A positive attitude towards medication was associated only with employment, not other socio-demographic factors or psychiatric factors. It is important that at baseline many patients had no previous treatment experience; during the follow-up, their personal experiences of treatments received could have increasingly contributed to their attitudes.

In the present study, only a larger social network to be independently associated with good pharmacotherapy adherence. In a Swedish 2-year study, a finding that non-adherent patients were observed to more often be living alone (Akerblad et al., 2006) was the same as that in the present study. In previous primary care studies substance abuse, coexisting personality disorder and unemployment were associated with poor medication adherence. Personality pathology is thought of as behaviour patterns characterized by limited adaptive capability (American Psychiatric Association, 2003). In this study, alcohol dependence and a cluster of C symptoms were associated with a positive attitude towards medication, but not antidepressant adherence. Extroversion was associated with non-adherence in a short-term antidepressant medication compliance study (Cohen et al., 2004). Association be-

tween lower rates of narcissistic-histrionic personality disorders was also found to be associated with better adherence in one secondary care study (Tedlow et al., 1996; Tedlow et al., 2002). In one recent secondary study authors found the predictors for non-adherence to antidepressant continuation and maintenance treatment in recurrently depressed patients to be a higher level of personality pathology and, somewhat surprisingly and a higher level of education (ten Doesschate et al., 2009). In this present study, better adherence was independently associated with only larger social network. Surprise, the attitude was not a major predictor of compliance with anti-depressants.

In the present study attitudes towards psychosocial treatment became slightly less positive and were associated with psychiatric disorders. A positive attitude towards psychosocial treatment was found to be associated with cluster C personality disorder, while cluster B personality disorder was associated with a negative attitude. It is probable that the trait of fearfulness characteristic of patients with cluster C features can increase positive attitudes. This is because patients with cluster C personality have a smaller social network. After all, they are fearful and have a lower perceived social support, which obviously makes it difficult for them to establish and maintain relationships like marriages. Indeed, persons lacking marital support may be more motivated to adhere to psychosocial treatment, perhaps in lieu of other social contacts. Some of the factors that were important at baseline such as male gender and dysthymia did not remain as important after baseline. Some factors such as the number of psychiatric disorders, the axis of the number I-III disorders, phobic anxiety, panic disorder without agoraphobia and neuroticism were associated with attitudes in univariate analyzes, but not in multivariate analyzes. In the present study, only psychiatric features affected attitudes towards psychosocial treatment, while psychosocial situation, gender, age, outpatient status or clinical features of MDD did not.

Patients' adherence to psychosocial treatment tended to improve or remained similar over time. Cluster B personality disorders were associated with poor adherence and living alone with good adherence. This sounds logical; unstable people make unlikely long-term patients as they are not capable of committing to long-term treatment. Alcohol dependence was a predictor in univariate analyses, but not in logistic regression analyses. As well as diagnostic clinical features and psychosocial factors were associated with treatment behaviour. Poor adherence was associated with psychosocial treatment. Some socio-demographic factors (gender, age of onset, functional ability), and clinical factors (suicidal ideation, hopelessness) were associated with adherence as trends in univariate analyses, but not in multivariate logistic regression models.

6.5 MDD and work disability (Study III)

Disability pension was granted on the grounds of MDD would independently be predicted by patients' age, severity of depression, proportion of time depressed during follow-up, baseline level of functioning and sick leave. To the best of my knowledge, there are only a few earlier prospective long-term clinical studies that exist on disability pensions granted for MDD patients. Accordingly, the factors predicting disability pensions among psychiatric MDD patients are not well known. Current study strengthens the view on MDD being an illness with a potentially poor prognosis in terms of working ability, as one fifth of patients were granted a disability pension.

The lack of previous studies on predictors on factors that predict the granting of a disability pension renders comparison with previous findings difficult. Although predictors for short-term sick leave are not necessarily the same as those that predict the granting of a disability pension, medium-term studies of sickness absence or work functioning have reported mostly congruent results (Druss et al., 2000; Kruijshaar et al., 2003; Lerner et al., 2004; Michon et al., 2008).

In a recent large register-based Finnish study (Korkeila et al., 2010) it was found that comprised psychiatric inpatients or outpatients selected for psychotherapeutic rehabilitation reported comparable rates of being granted a disability pension as those among patients with depression. That study also found patients with a principal diagnosis of personality disorder to have a similar risk of having to take a disability pension, whereas those with anxiety disorder had a lower risk compared with patients who had depression alone. In this study, of comorbid anxiety disorders only GAD was a predictor for a disability pension. The study did not find any comorbid personality disorder to significantly influence the risk of getting a disability pension. In previously study were reported that introverted patients also have lesser social networks, and their subjective social support resumes along with recovery from depression to a smaller extent, than among more extroverted patients (Leskelä et al., 2009). In an earlier phase of the VDS study, Rytsälä and co-workers reported that severity and preceding duration of depression among MDD's patients are the major determinants of overall functional ability (SOFAS), which probably mediates their influence on the risk of getting a disability pension (Rytsälä et al., 2007). The associations between the level of social and occupational functioning and sick leave and perceived (subjective) ability to work with objective work disability are unavoidably somewhat circular. These variables overlap conceptually and are statistically correlated, thus presenting both potential problems of multicollinearity in multivariate models, as well as difficulties in interpreting the findings. When comparing these objective predictors and subjective view on work ability, perceived work ability was in our model the strongest independent predictor followed by sick leave at baseline, and SOFAS. However, these differ-

ences may also be influenced by methodological factors, and thus should be interpreted cautiously and replicated in future studies. Being on sick leave at baseline appears to markedly increase the risk of becoming superannuated even after adjusting for the other major predictors; thus it cannot be excluded that the possibility that prolonged sick leave for some patients may decrease rather than increase their probability of returning to work. The risk of being granted a disability pension was greatest during the first year of follow-up. However, t this probably also reflects the pension system in Finland as a disability pension in Finland is granted only after 300 days of sick leave.

In VDS previous 18-month follow-up, disability pension was predicted by older age, longer time being in a depressed state, sense of hopelessness, and lower level of social and occupational functioning at baseline (Rytsälå et al., 2007). The longitudinal and recurrent nature of MDD makes the need for investigation of long-term predictors obvious. However, remarkably few prospective, comprehensive clinical studies on long-term work disability in psychiatric or primary care exist.

Many socio-demographic and clinical factors clearly predict long-term work disability among psychiatric patients with MDD even after adjusting for clinical variables, age, introversion, perception of being unable to work at baseline, lack of vocational education, and higher number of comorbid somatic disorders as independent predictors for the granting of future disability pensions. Depression-related clinical factors were also important, in particular the time spent in depressive episodes during the follow-up. In this study, of comorbid anxiety disorders only GAD significantly predicted the granting of a disability pension in univariate analyses. The personality dimension of introversion was a predictor. It is highly correlated with cluster C personality disorders and social phobia (Jylhä et al., 2010) and increased the risks of chronicity and recurrence of MDD. A recent Finnish study also found that obsessive-compulsive personality disorder is common among occupational health care clients with depression (Raiskila et al., 2013). In addition, a previously report shows that introverted patients also have smaller social networks, and their subjective social support increases along with recovery from depression to a lesser extent, than among more extroverted patients (Leskelä et al., 2009). Such findings may also partly explain the difficulties introvert subjects have in regaining their ability to work. Nevertheless, being older than 50 was the most robust predictor for the granting of a disability pension. Indeed, one half of those older than 50 years were granted a disability pension, compared to only one eighth of those younger than 50. The proportion of those superannuated was broadly similar to that reported by two previous studies, one of which was a general population study and the other a psychiatric outpatient study (Sorvaniemi et al., 2003; Doshi et al., 2008). In previous studies, including our own medium-term study, older age also predicted work disability among psychiatric MDD patients (Dewa and Lin, 2000; Dewa et al., 2002; Sorvaniemi et al., 2003; Rytsälä et al., 2005; Rytsälä et al., 2007;

Sanderson et al., 2007; Doshi et al., 2008; Lerner and Henke, 2008; Raitasalo et al., 2010). Those over 50 did not differ in regard to the duration or severity of depression or for the overall level of functioning compared to younger age groups. Thus, differences in clinical characteristics are unlikely to explain fully the difference in risk between age groups.

6.6 MDD and smoking (Study IV)

Depressed persons smoke a lot, and it must be acknowledged that insuffient attention is paid to it in psychiatry as it is a serious health risk. In this study, our aim was to compare the characteristics of smoking psychiatric MDD patients, and to investigate whether depression and smoking behavior covary or have an independent course. Smoking is very common in this study.

People start smoking before they reach adult age, for which reason we did not investigate any cause – effect relationships in our research. This question has been studied in adult psychiatric population. Smoking was very common in patients of this study, only a fifth of them have never smoked, two-fifth of smokers have intermittently, one-third smoked regular during follow-up. This prevalence is even higher than in the general Finnish population, which is 22.2% (Pirkola et al., 2006). Compared with non-smokers, regularly smoking patients had over four times more often alcohol use disorders at baseline. Regularly smoking patients were on average three years younger, had higher neuroticism, smaller social networks, and lower perceived social support than non-smokers. Of those factors alcohol use disorder at baseline and Cluster B and C personality disorders had the highest correlations with smoking. Previous studies are in line with these findings. The link found between alcohol use disorders and cigarette smoking for both MDD patients and the general population alike is likely due at least in part to common genetic mechanisms (Madden et al., 2004). Mood, anxiety, personality and illicit substance use disorders were associated with significantly increased risk of persistent nicotine dependence. Persistent nicotine dependence was more common among unmarried, younger females with lower income levels and lower educational attainment (Goodwin et al., 2011). Current smokers have generally had higher levels of negative emotionality and less behavioural consistency than former smokers and those who have never smoked (Kahler et al., 2009). Previous studies have also demonstrated a connection between smoking and higher neuroticism, lower extraversion, aggression, and lower sociability and constraint (Kubicka et al., 2001; Etter et al., 2003; Munafo et al., 2007). In an early general study, the prevalence of personality disorders among smoking individuals has also been observed to be high (Grant et al., 2004). In this study were found a similar strong association between smoking and personality traits or disorders among patients with depression; Cluster C

personality disorders have been associated with a more chronic outcome of MDD (Holma et al., 2008) and Cluster B personality disorders also with alcohol use disorders. A decision to smoke may also have serious consequences on the outcome of depression. In the present study, compared with non-smokers, regularly smoking patients had attempted suicide 2.3 times more often prior to follow-up, and the lifetime suicide attempts were significantly associated with smoking status. According to a previous 5-year follow-up report the incidence rate of suicide attempts was 21-fold during time depressed and fourfold during time in partial remission compared with time in full remission (Holma et al., 2010). Smoking patients also had a higher frequency of lifetime suicide attempts. Previous reports have shown a positive association between suicide and smoking status (Tanskanen et al., 2000; Hemmingsson and Kriebel, 2003; Breslau et al., 2005; Bronisch et al., 2008). However, in our earlier study investigating risk factors for suicidal behaviour, we found no independent association with smoking (Sokero et al., 2003).

Smoking and depression are significant public health problems with multiple etiological dimensions and outcomes. Although each condition is important in itself, they are also important because they often potentiate each other. However, no previous clinical study has investigated this long-term covariation between depression and smoking. Among patients who are initially depressed, smoking itself does not seem to increase their probability of remaining depressive in the future. Thus, the idea of smoking itself being depressogenic is not supported by our results, at least not in subjects who, for whatever reason, are already depressed. Only a small number of patients, less than 10% started smoking during the study period and a similar number had quit smoking, so the proportion of smoking patients did not increase during follow-up. Smoking and depression had only limited covariation; the level of depression and smoking did not go hand in hand during follow-up. Thus, our findings do not support the self-medication hypothesis. According to autoregressive models, level of depression, smoking, and also alcohol use disorders exhibited strong autoregressive tendencies, each having an independent course over time. Overall, our findings provide support for neither smoking causing depression nor depression causing smoking, but are consistent with other factors causing their co-occurrence.

Smoking patients differed from non-smoking patients with regard to age, alcohol use disorders, personality disorders, lifetime suicide attempts, personality factors, and social support. The level of depression and smoking did not go hand in hand during the follow-up; they both had an independent course.

6.7 General Discussion

The realization of treatment and its consequences do not depend solely on the treatment offered but also on individual autonomic decisions. People have the power of self-determination; they make their own decisions regarding treatment and whether or not they follow recommendations. However, these decisions have important consequences. We can influence people by presenting the practical consequences of various decisions, the probability of the recurrence of depression or premature retirement if their current depressive state is not treated effectively or actively. A patient is an active subject, and not merely an object of treatment. Cooperation is a key issue for realization of a beneficial treatment, and psychoeducation is of importance as well.

Adherence to treatment during the acute phase predicted the realization of indicated maintenance treatment. Many depressive patients in our 18-month study reported having taken an active, autonomous role in the decision to terminate antidepressants. A patient´s individual decision was a more common reason than perceived side-effects of antidepressants, poor response, or subjectively perceived recovery. In the present 5-year study, premature termination of antidepressants was predicted by negative attitudes at entry. Despite expectations, attitude was not a major predictor of adherence, and predictors of adherence to psychosocial treatment and antidepressants were different. Attitudes towards psychosocial treatment also changed to less positive during follow-up, but adherence improved significantly. However, treatment adherence was reportedly good, and the overall attitudes to both antidepressant medication and psychosocial treatment were positive. Attitudes to antidepressant medication became less positive during the follow-up, but adherence to medication did not change significantly. Discontinuation of psychotherapeutic treatments was associated with more severe and more prolonged depressive symptoms. Noteworthy was also that about a third (32%) of the patients not achieving full remission during the follow-up were without any psychosocial treatment at 18 months (Melartin et al., 2005). In the 18 month follow-up study less than a fifth (16%) of the patients and only 9.2% at the 5 year follow-up study received weekly psychotherapy. At the 5 year mark one fourth (24.5%) were currently receiving any psychosocial treatment, and nearly half (44.8%) were currently using an antidepressant (Holma et al., 2008). Younger age, less severe and longer-lasting depression, and milder anxiety symptoms were also associated with negative treatment attitudes (Melartin et al., 2005). The patients who received psychotherapy were either those able to form a good treatment alliance, and thus probably more able to benefit from therapy, or suicidal patients who needed more intensive treatment in the acute phase and therefore also received it more promptly. Despite recommendations in practice guidelines (NICE, 2009; APA, 2010; Suomen Psykiatriyhdistys, 2010; Schaffer et al., 2012) for more intensive treatment, patients with personality disorders were the least likely to receive weekly psychotherapy.

Non-adherence is rarely an "on-off" phenomenon. Treatments may occur more or less irregularly, and it may be unclear whether this significantly affects the achievement of treatment goals or not. In contrast to the hypotheses those with continued self-reported non-adherence to antidepressants were more often those without comorbidity, especially without anxiety and avoidant personality disorders (Melartin et al., 2005). It seems that the presence of perceived distress is also a major factor that drives the continuation of treatment.

We found that during the five-year follow-up period one fifth of the cohort of psychiatric patients with MDD belonging to the labour force at baseline was eventually granted a disability pension. Individuals who were granted a disability pension also spent more time depressed than non-pensioned patients. In addition, they had a more subjective understanding of themselves as being unable to work markedly more often than their non-pensioned counterparts. Importantly, subjective perception of work ability at baseline was a more significant predictor of later retirement over many other possible predictors emphasizing the autonomic nature of this outcome, and may reflect the motivation, strengths, or coping abilities of an individual. However, age was the major predictor despite similar severity of depression compared to non-pensioned patients. It is possible that the threshold for seeking or being granted a disability pension is lower for older subjects, perhaps due to the fewer remaining working years and lower total costs of pensions. In any case, aging alone is an insufficient explanation. Also the personality structure may be important. In previous studies, introversion as a personality dimension is highly correlated with cluster C personality disorders and social phobia (Jylhä et al., 2010), both of which increased the risks of chronicity and recurrence within our study population (Holma et al., 2008). A contradictory finding was that cluster C personality disorders were associated with a weaker outcome, but a more positive attitude to treatment. This may reflect the difficulties common among these patients to express dissatisfaction. A Canadian study found that personality disorders did not affect the results of psychotherapy or medication treatment, but treatment by the same psychiatrist leaded to similar outcomes (De Bolle et al., 2011). Longer time in MDE prior to entry, severity of depression and anxiety, lower levels of social and occupational functioning, comorbidity; all these findings support the idea that patients should receive effective treatment in order to more likely maintain their working ablity. With aging, these factors are likely to be even more important.

Smoking was very common among depressive patients as only a fifth of them have never smoked. Rather than depression or smoking co-varying or predicting each other, depression, smoking, and alcohol use disorders each have strong autoregressive tendencies, and predicted themselves during follow-up. These findings are more consistent with common factors causing their epidemiological association than depression resulting in increased smoking or smoking inducing depression. Smoking initiation is also a person's autonomous decision, as well as initiation into alcohol use. In this study baseline alcohol use disorder is important, but

not as important a prognostic factor as the strength of the depression. While depression and smoking had limited covariation, that of smoking and alcohol use disorders needed to be elaborated. Compared with non-smokers, regularly smoking patients had over four times more often alcohol use disorders at baseline. At baseline, nearly 70% of patients with alcohol use disorder were regular smokers compared with 33% of patients without an alcohol problem. As smoking in MDD patients is strongly associated with several clinically significant characteristics that are associated with a negative outcome, there is substantial risk that this will affect the findings and lead to false attributions.

7 Conclusions and future implications

7.1 Conclusions

In conclusion, in secondary care, maintenance treatment is received by those able to adhere with their treatments, a finding which highlights the interactive nature of continuity of treatment. The tertiary preventive impact of maintenance treatment for MDD seems currently limited, as many MDD patients may either not receive it or receive it for too short a period. To ensure generalizability, replication of these findings is necessary.

Depressive psychiatric patients followed up for five years reported attitudes and treatment adherence to be mostly positive and good. Even though patients accumulated personal experience of various treatments, attitudes and adherence changed relatively little over time. However, they were significantly associated with both clinical personality disorders and psychosocial factors. Despite expectations, attitude was not a major predictor of adherence, and predictors of adherence to psychosocial treatment and antidepressants may be different. Attention to adherence of those with cluster B personality disorders or poor social support and those who are unemployed may be needed.

Of psychiatric patients with depression, one fifth was granted a disability pension within five years. Future disability pension can be predicted by baseline older age, especially older than 50 years, personality factors, functional disability, lack of vocational education, and comorbid somatic disorders. Longitudinally, accumulation of time spent depressed also appears a decisive factor.

Among psychiatric MDD patients, smoking is associated with several clinical characteristics (particularly substance use disorders) and personality factors (personality disorders and neuroticism), which may markedly confound research on the impact of smoking. Rather than depression or smoking co-varying or predicting each other, depression, smoking, and alcohol use disorders each have strong autoregressive tendencies. These findings are reliable with common factors causing their epidemiological association.

7.2 Clinical and research implications

In depression secondary care, maintenance treatment is received by those able to adhere with their treatments, a finding which highlights the interactive nature of continuity of treatment. Our findings are important from a public health perspective. To ensure generalizability, replication of these discoveries is necessary. The tertiary preventive impact of maintenance treatment for MDD seems currently

limited as many MDD patients may either not receive it or receive it for too short a period.

The provision of psychoeducation to all depressive patients (and their families) seems important. This should include information on antidepressants - not only their side-effects but also their non-addictiveness, and mechanisms of action. As the patient's personal motivation for the implementation of the treatment proved important in this study, it is essential to carefully and without judgement find out the patient´s own reasons to discontinuation of a medication, and ensure that the patient´s view is taken into account, and targeted information given. This might prove an effective way to improve continuity of treatments and outcome of depression. Moreover, it is important to motivate patients at least to try antidepressants, and to regularly ask about their treatment attitudes in order to recognize those at risk of non-adherence.

More research should be conducted on the background to non-adherence and discontinuity of treatments in order to better identify patients at specific risk. Future research should also include intervention studies and investigations of perceived interaction between patients and the persons administering treatment in order to clarify these dimensions of adherence. Special attention should be directed at improving treatment adherence among those who are unemployed, have had unless social support or B personality disorders. Information about treatment adherence and attitude 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 urgently needed on specific psychotherapies. In addition, prospective studies should be performed to investigate the effects of treatment adherence to outcome of MDD.

Factors associated with functional and specifically long-term work disability have been researched surprisingly seldom. When one takes into account especially the huge costs connected with depression treatment and the disability it causes, this is disturbing. Each year about 4,000 Finns go on disability pension because of depression. Pension expenditures for people on disability pension for depression have roughly tripled in ten years, and depression as a reason for the granting of a disability pension has gradually become more common. Recognition of depression and specifically the risk factors associated with functional and work disability such as older age, personality factors, objective and subjective functional disability, lack of vocational education and somatic comorbidity are key factors in avoiding the necessity to superannuate individuals. Research is needed on treatment to better identify those special treatment methods that help high risk patients. Time spent depressed appears to be decisive factor that has had a special effect on work disability. Thus, early commencement of treatment and sufficiency of treatment resources are necessary despite the current shortage of psychiatrists. Reducing time spent depressed by optimal treatment is one of the most important ways to reduce long-term disability, otherwise prolonged sick-leave or even work disability pensions are

possible results. Problems in the intensity and monitoring of treatment stand in the way of patients' rapid recovery and thus restoration of their functional and work disability. Perceived ability to work is also a predicting factor, suggesting that that factors related to the working environment should be investigated in the future.

Rather than depression or smoking co-varying or predicting each other, depression, smoking, and alcohol use disorders each have strong autoregressive tendencies. These findings are more consistent with common factors causing their epidemiological association than depression resulting in increased smoking or smoking inducing depression.

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