Heikki Rytsälä

Functional and Work Disability and Treatment Received by Patients with Major Depressive Disorder

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

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Academic Dissertation

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TIIVISTELMÄ

Tämä tutkimus on osa Kansanterveyslaitoksen Mielenterveyden ja alkoholitutkimuksen osaston ja Helsingin ja Uudenmaan sairaanhoitopiirin Peijaksen sairaalan Psykiatrian tulosyksikön vakavan masennustilan tutkimusta. Tutkimus (Vantaa Depression Study, VDS) koostuu kahdesta osatutkimuksesta, 803 potilaan sairauskertomuksiin perustuvasta osasta ja 269 potilaan seurantatutkimuksesta. Molemmissa tutkimusosioissa potilaat ovat erikoissairaanhoidon avohoito- ja sairaalapotilaita, joilla on todettu sairastuminen uuteen masennusjaksoon.

Tiedot sairauskertomuksiin perustuvaan tutkimukseen on kerätty potilaiden käynti- ja sairaalahoitotiedot sisältävistä tietokannoista. Tutkimukseen valikoitiin kaikki 20-59-vuotiaat depressiopotilaat, joiden diagnoosi oli määritelty tautiluokituksen (ICD-10) mukaan masennustilaksi tai toistuvaksi masennukseksi ja joilla oli vähintään yksi avohoitokäynti tai sairaalahoitopäivä 1.1.1996-31.12.1996 välisenä aikana. Poissulkukriteereinä olivat aiempi skitsofreniadiagnoosi, muu psykoosi tai kaksisuuntainen mielialahäiriö. Myös sellaiset potilaat suljettiin pois, joita oli hoidettu somaattisilla sairaalaosastoilla ja joiden hoidon suhteen oli pyydetty vain psykiatrin konsultaatiota. Tutkimukseen valittiin 290 mies- ja 513 naispotilasta. Näiden kaikkien sairauskertomukset käytiin läpi ja niiden pohjalta täytettiin 57-kohtainen lomake. Potilaiden hoitoa seurattiin hoitojakson loppuun tai enintään vuoden 1997 loppuun.

Useimmat (84%) saivat masennuslääkitystä, joskin pieni osa (11%) selvästi lääkkeen hoitotasoa alemmilla annoksilla. Hoitojakson aikana potilaat pääsivät psykiatrin vastaanotolle harvoin (mediaani kaksi käyntiä), mutta muille työntekijöille selvästi useammin (mediaani seitsemän käyntiä). Kummastakin sukupuolesta viidesosalla oli vähintään yksi sairaalahoitojakso (keskimäärin lähes kaksi) koko seuranta-aikana. Sairaalahoidon keskimääräinen kesto oli kaksi viikkoa.

Masennuslääkkeiden käyttö oli varsin konservatiivista. Ensiksi aloitettu lääke vaihdettiin toiseen vain noin joka viidennellä (22%) ja vain kaksi potilasta sai yhteensä viittä eri masennuslääkettä. Vain 7% masennuslääkettä saaneista sai kahta lääkettä samanaikaisesti. Kukaan ei saanut muuta masennuslääkkeen tehoa parantavaa lääkitystä. Lääkityksestä kieltäytyminen oli tavallisin syy masennuslääkehoidon puuttumiseen.

Hoitojakson aikana 19%:lle niistä, jotka eivät hoidon alussa olleet eläkkeellä, myönnettiin työkyvyttömyyseläke psykiatrisen sairauden perusteella. Nämä potilaat olivat lähes yhdeksän vuotta vanhempia kuin ne, jotka eivät jääneet eläkkeelle. He olivat myös vakavammin sairaita, kävivät selvästi useammin hoitavan henkilön vastaanotolla ja käyttivät merkittävästi enemmän rinnakkaista lääkitystä (unilääkkeitä, rauhoittavia lääkkeitä ja psykoosilääkkeitä) kuin ne, jotka eivät jääneet eläkkeelle.

Seurantatutkimuksessa seulottiin aluksi 806 aikuispotilasta iältään 20 - 59 vuotta mahdollisen uuden masennusjakson varalta. Näistä 542 potilasta haastateltiin kasvotusten puolistrukturoidulla haastattelumenetelmällä (WHO Schedule for Clinical Assessment in Neuropsychiatry [SCAN], Version 2.0). Tutkimuksen poissulkukriteerit olivat vastaavat kuin sairauskertomuspohjaisessa tutkimuksessakin. Näistä 542 potilaasta 269 täytti vakavan masennuksen kriteerit. Tässä tutkimuksessa kiinnitettiin erityisesti huomiota potilaiden huonoon toimintakykyyn, sosiaaliseen sopeutumiseen ja työkyvyttömyyteen (sairauslomalla oloon tai eläköitymiseen) vaikuttaviin tekijöihin.

Hoidon alussa tärkein yksittäinen sosiaaliseen ja toiminnalliseen kyvyttömyyteen vaikuttanut tekijä oli masennuksen vaikeusaste. Muita korkeammalla iällä ja persoonallisuushäiriöillä oli myös merkitystä. Koko masennusjakson kesto ja vaikeusaste, pelko-oireiset ahdistuneisuushäiriöt, alkoholismi ja persoonallisuushäiriöt vaikeuttivat sosiaalista sopeutumista. Työssä olevista lähes puolet (43%) oli sairauslomalla. Sairauslomalla olon riskitekijöinä olivat masennuksen vaikeusaste, aiempien masennusjaksojen määrä, naissukupuoli ja yli 50 vuoden ikä.

Sosiaaliseen ja ammatilliseen toimintakyvyttömyyteen ja sosiaaliseen sopeutumiseen vaikuttavia tekijöitä tutkittiin 18 kuukauden seuranta-aikana. Potilaiden toimintakyvyttömyys ja sosiaalinen sopeutuminen paranivat samanaikaisesti depressiosta toipumisen myötä. Masennuksen vaikeusaste, aiemmat ja hoidon aikaiset uudet masennusjaksot, täyden toipumisen saavuttamattomuus ja masentuneena vietetty aika ennustivat kulloistakin toimintakyvyn ja sosiaalisen sopeutumisen astetta. Samanaikaisilla psyykkisillä häiriöillä, persoonallisuuden piirteillä (neurotisismi) ja koetulla sosiaalisella tuella oli myös vaikutuksensa.

Seuranta-aikana (18 kuukautta) 269 potilaasta 13:lla (5%) potilaalla havaittiin masennuksen muuttuneen kaksisuuntaiseksi mielialahäiriöksi ja 58 (20%) jäi pois tutkimuksesta. Näistä 198:sta 186 ei ollut tutkimuksen alussa eläkkeellä. Heistä 21 jäi seuranta-aikana työkyvyttömyyseläkkeelle. Eläköityneet olivat muita selvästi vanhempia, heillä oli muita harvemmin ammattikoulutus, ja he olivat selvästi useammin sairauslomalla kuin muut. Ryhmät eivät eronneet minkään muiden muuttujien suhteen.

Masennuspotilaat saavat enimmäkseen riittävää masennuslääkitystä, mutta hoidon intensiteetissä ja seurannassa oli ongelmia. On haasteellista löytää suurimmassa toimintakykynsä menettämisvaarassa olevat ja tarjota heille riittävää ja vaikuttavaa hoitoa. Koko yhteiskunta on haasteellisen tehtävän edessä voidakseen tarjota tarvittavat voimavarat riittävän ja vaikuttavan hoidon toteuttamiseen.

Avainsanat: masennustila, sairauskertomuksiin perustuva tutkimus, seurantatutkimus, sosiaalinen sopeutuminen, hoidon laatu, toimintakyvyttömyys, työkyvyttömyyseläke

ABREVIATIONS

ANOVA	Analysis of Variance
APA	American Psychiatric Association
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CBT	Cognitive Behaviour Therapy
CDS	Collaborative Depression Study
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CRH	Corticotrophin Releasing Hormone
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
ECA	Epidemiological Catchment Area Study
ECT	Electroconvulsive therapy
EPI	Eysenck Personality Inventory
ESEMeD	European Study of the Epidemiology of Mental Disorders
GAD	Generalised Anxiety Disorder
Ham-D	Hamilton Rating Scale for Depression
HPA	Hypothalamic-pituitary-adrenal
HS	Beck Hopelessness Scale

ICD-10	International Classification of Diseases, 10th edition
LIFE	Longitudinal interval follow-up evaluation
MinD	Minor Depressive Disorder
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
NaSSA	Noradrenergic and specific serotonergic antidepressant
NCS	National Comorbidity Survey
NCS-R	National Comorbidity Survey Replication
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NIMH	National Institute of Mental Health
NS	Non-significant
ODIN	European Outcomes of Depression International Network Study
OR	Odds ratio
PMCD	Peijas Medical Care District
PSSS-R	Perceived Social Support Scale - Revised
RIMA	Reversible inhibitors of monoamine oxidase
SAS-SR	Social Adjustment Scale-Self Report
SCAN	Schedules for Clinical Assessment of Neuropsychiatry
SCID-II	Structured Clinical Interview for DSM-III-R personality disorders
SD	Standard deviation
SNRI	Serotonin and norepinephrine reuptake inhibitors
SOFAS	Social and Occupational Functioning Assessment Scale for DSM-IV
SPSS	Statistical Package for the Social Sciences for Windows

SSI	Scale for Suicidal Ideation
SSRI	Selective serotonin reuptake inhibitor
SSRIs	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressant
TCAs	Tricyclic antidepressants
UKKI study	Uusikaupunki – Kemijärvi study (Social Psychiatric Investigation of the Social Insurance Institute)
UM-CIDI SF	University of Michigan Composite International Diagnostic Interview Short Form
VDS	Vantaa Depression Study
WHO	World Health Organization

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1. ABSTRACT

This study is one part of a collaborative depression research project, the Vantaa Depression Study (VDS), involving the Department of Mental and Alcohol Research of the National Public Health Institute, Helsinki, and the Department of Psychiatry of the Peijas Medical Care District (PMCD), Vantaa, Finland. The VDS includes two parts, a record-based study consisting of 803 patients, and a prospective, naturalistic cohort study of 269 patients. Both studies include secondary-level care psychiatric out- and inpatients with a new episode of major depressive disorder (MDD).

Data for the record-based part of the study came from a computerised patient database incorporating all outpatient visits as well as treatment periods at the inpatient unit. We included all patients aged 20 to 59 years old who had been assigned a clinical diagnosis of depressive episode or recurrent depressive disorder according to the International Classification of Diseases, 10th edition (ICD-10) criteria and who had at least one outpatient visit or day as an inpatient in the PMCD during the study period January 1, 1996, to December 31, 1996. All those with an earlier diagnosis of schizophrenia, other non-affective psychosis, or bipolar disorder were excluded. Patients treated in the somatic departments of Peijas Hospital and those who had consulted but not received treatment from the psychiatric consultation services were excluded. The study sample comprised 290 male and 513 female patients. All their psychiatric records were reviewed and each patient completed a structured form with 57 items. The treatment provided was reviewed up to the end of the depression episode or to the end of 1997.

Most (84%) of the patients received antidepressants, including a minority (11%) on treatment with clearly subtherapeutic low doses. During the treatment period the depressed patients investigated averaged only a few visits to psychiatrists (median two visits), but more to other health professionals (median seven). One-fifth of both genders were inpatients, with a mean of nearly two inpatient treatment periods during the overall treatment period investigated. The median length of a hospital stay was 2 weeks.

Use of antidepressants was quite conservative: The first antidepressant had been switched to another compound in only about one-fifth (22%) of patients, and only two patients had received up to five antidepressant trials. Only 7% of those prescribed any antidepressant received two antidepressants simultaneously. None of the patients was prescribed any other

augmentation medication. Refusing antidepressant treatment was the most common explanation for receiving no antidepressants.

During the treatment period, 19% of those not already receiving a disability pension were granted one due to psychiatric illness. These patients were nearly nine years older than those not pensioned. They were also more severely ill, made significantly more visits to professionals and received significantly more concomitant medications (hypnotics, anxiolytics, and neuroleptics) than did those receiving no pension.

In the prospective part of the VDS, 806 adult patients were screened (aged 20-59 years) in the PMCD for a possible new episode of DSM-IV MDD. Of these, 542 patients were interviewed face-to-face with the WHO Schedules for Clinical Assessment in Neuro-psychiatry (SCAN), Version 2.0. Exclusion criteria were the same as in the record-based part of the VDS. Of these, 542 269 patients fulfiled the criteria of DSM-IV MDE. This study investigated factors associated with patients' functional disability, social adjustment, and work disability (being on sick-leave or being granted a disability pension).

In the beginning of the treatment the most important single factor associated with overall social and functional disability was found to be severity of depression, but older age and personality disorders also significantly contributed. Total duration and severity of depression, phobic disorders, alcoholism, and personality disorders all independently contributed to poor social adjustment. Of those who were employed, almost half (43%) were on sick-leave. Besides severity and number of episodes of depression, female gender and age over 50 years strongly and independently predicted being on sick-leave.

Factors influencing social and occupational disability and social adjustment among patients with MDD were studied prospectively during an 18-month follow-up period. Patients' functional disability and social adjustment were alleviated during the follow-up concurrently with recovery from depression. The current level of functioning and social adjustment of a patient with depression was predicted by severity of depression, recurrence before baseline and during follow-up, lack of full remission, and time spent depressed. Comorbid psychiatric disorders, personality traits (neuroticism), and perceived social support also had a significant influence.

During the 18-month follow-up period, of the 269, 13 (5%) patients switched to bipolar disorder, and 58 (20%) dropped out. Of the 198, 186 (94%) patients were at baseline not pensioned, and they were investigated. Of them, 21 were granted a disability pension during the follow-up. Those who received a pension were significantly older, more seldom had vocational education, and were more often on sick-leave than those not pensioned, but did not differ with regard to any other sociodemographic or clinical factors.

Patients with MDD received mostly adequate antidepressant treatment, but problems existed in treatment intensity and monitoring. It is challenging to find those at greatest risk for disability and to provide them adequate and efficacious treatment. This includes great challenges to the whole society to provide sufficient resources.

Keywords: major depressive disorder, record-based study, prospective study, social adjustment, social and occupational disability, quality of care, disability pension

2. LIST OF ORIGINAL PUBLICATIONS

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

I Rytsälä HJ, Melartin TK, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET: A Record-Based Analysis of 803 Patients Treated for Depression in Psychiatric Care. J Clin Psychiatry 2001;62: 701-706.

II Rytsälä HJ, Melartin TK, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä E.T. Functional and Work Disability in Major Depressive Disorder. J Nerv Ment Dis 2005;193: 189-195.

III Rytsälä HJ, Melartin TK, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET. Determinants of Functional Disability and Social Adjustment in Major Depressive Disorder: A Prospective Study. J Nerv Ment Dis 2006;194: 570-576..

IV Rytsälä HJ, Melartin TK, Leskelä US, Sokero, TP, Lestelä-Mielonen PS, Isometsä ET. Predictors of Long-Term Work Disability in Major Depressive Disorder: A Prospective Study. Acta Psychiatr Scand (in press). Published online: 23-Aug-2006.

3. INTRODUCTION

Major depressive disorder (MDD) is one of the worlds' most common mental disorders. About 6% of the Finnish population is suffering from it, and from milder depressive symptoms many times more. Patients suffering from MDD have several symptoms including either depressive mood or loss of interest or pleasure, difficulties in sleeping, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate or make decisions, and thoughts of death or suicide attempts. Depression has a strong tendency towards recurrence and chronicity.

The Global Burden of Disease Study estimated in the 1990's that MDD is worldwide the fourth leading cause of functional impairment, disability, and days lost from work (Murray and Lopez, 1997a). Depending on the different statistical conventions in developed vs. developing countries it is possible that many cases of depression have remained unrecognisable. Murray and Lopez (1997b) estimated that depression will be by the year 2020 the second major cause of functional disability. Patients with MDD have difficulties in physical, social, and role functioning. Even those suffering from relatively mild depressive symptoms appear to function significantly worse than do inpatients with several other chronic medical illnesses. Depression or depressive symptoms are also strongly associated with increased service utilisation and social morbidity (Johnson et al., 1992). The presence of comorbid somatic diseases or mental disorders leads to disability associated with depression.

Effective MDD treatments have been available for decades. During the last 50 years effective medicines have been found and developed to treat depression. Different types of psychotherapy and electroconvulsive therapy have been in use far longer. There have, however, been repeated reports of severe problems in the availability, adequacy, intensity, and monitoring of treatment (Lehtinen et al., 1990b; Brugha & Bebbington, 1992; Isometsä et al., 2000; Demyttenaere et al., 2004).

As a cause of work disability, MDD has become increasingly more important. During the last decade in Finland (Salminen et al., 1997; Sorvaniemi et al., 2003; Karpansalo et al., 2005) much attention has been paid to work disability pensions granted for depression. The number of pensions has increased threefold in Finland between the 1987 and 1994 (Salminen et al., 1997). These numbers include both permanent and temporary pensions, and some patients may return to work after temporary pensions. The increase in pensions has been remarkable, despite the creation of new, effective medicines with a favourable side-effect profile and the development of new psychotherapy strategies. Studies related to increased disability and number of pensions have not for the present been able to scrutinise these problems thoroughly.

The present thesis includes a record-based and a prospective study in which treatment received and predictors affecting social adjustment and functional and work disability could be examined.

4. REVIEW OF THE LITERATURE

4.1 Major depressive disorder (MDD)

4.1.1 Definition of depression

Depressive affects belong to normal human life. These can be seen as a normal response to an unpleasant event or situation or to a psychological or concrete loss. Normal 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 from those normal feelings. Mood disorders are either unipolar (depressive disorder, dysthymia) or bipolar (bipolar affective disorder, cyclothymia) which are defined by given criteria. Even though strict boundaries between normal affect and depressive disorder do not exist, diagnosed disorders have a similar course, risks, and outcome. The differential diagnosis of unipolar - bipolar is an important one, as the course and treatment of bipolar affective disorder differ significantly from those of unipolar depression.

4.1.2 Diagnosis of depression

In diagnostic classifications, mood disorders are defined as "illnesses characterised by a distinct constellation of several co-occurring symptoms for a defined period of time contributing to significant psychosocial impairment" (WHO 1992; 1993; APA 1987; 1994).

The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines (WHO 1992; 1993) are in use in Finland. Diagnosis of a major depressive episode (MDE) in both classifications requires a 2-week period of at least one of the symptoms either 1) depressive mood or 2) loss of interest or pleasure. In the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), which has been used in this thesis, these must be accompanied by at least four (i.e., a total of at least five vs. ICD-10 requires symptoms totalling at least four) associated with symptoms existing nearly every day, such as 3) significant weight change (loss or gain), 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness or excessive or inappropriate guilt, 8) diminished ability to think or concentrate or make decisions, and 9) suicidal thinking, recurrent suicidal ideation with or without a specific plan for committing suicide.

These symptoms do not meet criteria for a mixed episode of the bipolar disorder. The symptoms cause clinically significant distress or impairment in important areas of functioning, and are not caused by physiological effects of a medication or an illness. The symptoms are not caused by loss of an important loved one (The ICD-10 does not exclude this), they last longer than two months or include obvious functional

impairment, feelings of worthlessness, suicidal thoughts, psychotic symptoms, or psychomotor retardation (APA, 1987; 1994). The MDD diagnosis includes one or more MDEs which are not accounted for by schizophrenia or schizophrenia, or other psychotic disorders, and there has never been a manic, mixed, or hypomanic episode. The DSM-IV also lists three levels of severity of MDD. Severity may be mild, moderate or severe (with or without psychotic features) based on the number and severity of the diagnostic criteria, and the degree of functional disability and distress. Psychotic MDE includes delusions or hallucinations, whether the psychotic features are mood congruent or mood incongruent. Depression can also include a few depressive symptoms diagnosed as minor depressive disorder (MinD). Those patients have never met the criteria of MDE or manic episode (DSM-IV).

4.2 Epidemiology of MDD

4.2.1 Incidence of MDD

Although the epidemiology of depression has been studied widely, studies regarding incidence of depression have remained quite few. The two recent epidemiological studies in Finland, the Finnish Uusikaupunki – Kemijärvi study (UKKI study; Lehtinen et al., 1996)) and the Finnish sub-sample of the European Outcomes of Depression International Network study (ODIN) (Lehtinen et al., 2005) differ significantly by their methods and results. The first-mentioned study consists of populations randomly drawn from two small Finnish areas, southern and northern, and the second one of populations randomly drawn from two large southern urban (Turku) and rural (Koski tl, Marttila and Tarvasjoki) areas. Studies differed also from each other in with their diagnostic tools and diagnostic classifications. In the UKKI study, the annual incidence of neurotic depression was calculated as 2.0 per 1000 in men and 2.7 per women for the whole 16-year follow-up period (Lehtinen et al., 1996). The ODIN study comprised 2999 inhabitants aged 18 to 64. In this study, the annual incidence for the first-time episode of depressive disorder (according to ICD-10) was 20.5 per 1000 and recurrent episodes 8.0 per 1000. Significant differences between results of these studies may be explained by the differences in their methods.

4.2.2 Prevalence of MDD

In contrast to studies concerning incidence of depression, several studies estimate the prevalence of depressive disorders in the general population. Those indicate that depression is a highly prevalent disorder (Kessler et al 1994; 2005), with a recurrent or chronic course, and often characterised by comorbidity with Axis I or II disorders or other somatic illnesses. Estimates are that as much as one-fifth of the population (Kessler et al 1994; 2003) will suffer from clinical MDE at some point in their lives. Depression seems to be more common in women than in men, and its recurrence rate

has been estimated as up to 60 to 87% (Mueller et al., 1999; Keller & Boland, 1998) depending on follow-up time.

Variation in the prevalence of mood disorders (including bipolar I and II disorders, dysthymia, and major depressive disorder) has been estimated as quite small among developed countries, but greater between the developed and less-developed countries (Demyttenaere et al. 2004). Differences in resources in treatment and possible validation problems in diagnostic methodology may explain some part of this.

In the USA, the National Comorbidity Survey Replication has estimated that in adults the lifetime prevalence of unipolar major depression in the general population is 16.2%, and the 12-month prevalence 6.6 to 6.7% (Kessler et al., 2003; 2005). The comprehensive National Epidemiologic Survey on Alcoholism and Related Conditions was conducted from 2001 through 2002 by the National Institute on Alcohol Abuse and Alcoholism (Bethesda, MD) in the USA (including Alaska and Hawaii) (Hasin et al. 2005). The target population was the civilian, non-institutionalised population aged 18 years and older. This study comprised 43 093 respondents in face-to-face interviews. The prevalence of 12-month DSM-IV MDD was 5.28% and lifetime 13.23%. In Australia, Andrews et al. (2001) found, in their study comprising non-institutionalised adults aged 18 or older, nearly the same proportion as in the USA, depending on the diagnostic system used (ICD-10, 6.7%; DSM-IV, 6.3%).

Several European studies have estimated the epidemiology of MDD in their countries, showing prevalences of depression quite similar to those in the USA and Australia. In the Netherlands Mental Health Survey and Incidence Study (NEMESIS; Bijl et al., 1998) in 1996, the prevalence of psychiatric disorders in the Dutch population aged 18-64 found (by interviewing 7076 members of the general population) a lifetime MDD prevalence of 15.4% (in women 20.1% and men 10.9%) and a 12-month prevalence of 5.8% (7.5% and 4.1%) (Bijl et al 1998). The European Study of the Epidemiology of Mental Disorders (ESEMeD), conducted between January 2001 and August 2003 in a non-institutionalised population in Belgium, France, Germany, Italy, the Netherlands, and Spain aged 18 or older (n=21 425), described the 12-month and lifetime prevalence rates of mood, anxiety, and alcohol disorders. In this comprehensive study, lifetime prevalence of MDD was around 13% and the 12-month around 4% (Alonso et al. 2004a).

In Finland, the Mini-Finland Health Survey, an extensive epidemiological study of the Finnish population aged 30 years and over, conducted from 1978 through 1980 (Lehtinen et al. 1990a) found in their large sample of the Finnish population aged 30 or more (n=8000) a one-month prevalence of 4.6% for neurotic depression. Another study comprising a total of 2293 of the Finnish general population in 1994 with a telephone survey and utilising the UM-CIDI Short Form found a 6-month prevalence of major depressive episode of 4.1% (Isometsä et al. 1997). The national Finnish Health Care Survey (FINHCS ‘96) monitored the health of the general population and evaluated the use of and need for health services. The data were collected between April 5 and June

21, 1996 from non-institutionalized Finnish individuals aged 15 to 75 (N=5993) by interviewing personally the reference person and other household members aged 15 and over. The 12-month prevalence of MDE was 9.3%, and the age-adjusted prevalences for females and males were 10.9% and 7.2%. After adjustment for age, factors associated with MDE were urban residency, smoking, alcohol intoxication, and chronic medical conditions (Lindeman et al. 2000).

The most recent epidemiological, comprehensive, and multidisciplinary study in Finland, the Health 2000, interviewed a representative sample (6005) of the Finnish general adult population (≥ 30 years), in the period 2000–2001 with the CIDI for the presence of DSM-IV mental disorders during the last 12 months. MDD prevalence was 4.9% (males 3.4%, females 6.3%) and any depressive disorder 6.5% (4.5% and 8.2%). In the Health 2000 study, depressive disorders were most usual in the middle-aged, in residents of the Oulu region, among men separated or divorced, and among the unemployed (Pirkola et al., 2005). Differences between the prevalence figures may be explained by differences in the diagnostic tools used (in the former study UM-CIDI SF vs. CIDI in the latter).

In conclusion, prevalence of depression seems to be fairly comparable in western industrialised countries. Differences in prevalences between males and females seem to hold, while taking into account design, sampling, and other methodological differences between studies.

4.2.3 Use of health care services for MDD

The high burden of depression makes great demands upon the mental health services provided. Although effective treatments exist, treatment-related studies have shown that many patients with MDD remain untreated or undertreated (Demyttenaere et al. 2004; Shen et al. 2006). The big question is: Has the patient any contact with the health service system, and if so, what kind of treatment is that patient receiving? The median treatment gap has, among psychiatric disorders, been found to be one of the greatest for depression (56.3%; Kohn et al. 2004).

The ESEMeD project (Alonso J et al. 2004b) found that only 36.5% of patients with mood disorders had consulted formal health services. The Mini-Finland Health Survey (Lehtinen et al. 1990b) assessed, besides the epidemiology of diseases and disorders, also the met and unmet need for mental health care. In this comprehensive study, about 60% of those patients in need of care received no treatment, and half the treatment received was inadequate. Of the depressive subjects, only one-third received some kind of treatment. Two of five suffering even the most severe MDE did not use the health services for depression. However, 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).

Patients seeking treatment have problems in recognizing their depression. Vuorilehto et al. (2005) reported that only one-third of the depressed primary care patients perceived

a need for treatment for psychological reasons. The Finnish Health Care Survey, conducted in 1996 and consisting of a random population sample of 5993 Finns aged 15 to 75 years, found that only 13% of subjects suffering from MDE reported use of antidepressants during the preceding 12 months.

4.3 Aetiology of MDD

Depression is an etiologically complex disorder influenced by risk factors from multiple domains that are interrelated through developmental pathways (Kendler et al. 1993; 2003; 2006b). The main domains of risk factors associated with the development of depression are, basically, genetic, biological, developmental, and environmental (Caspi et al. 2003; Kendler et al. 2001; 2002; 2004; 2006b). By these means, development of depression is likely mediated by the interaction of genetic and environmental factors.

4.3.1 Heritability of MDD

MDD is inevitably a familial disorder (Lieb et al., 2002; Weissman et al., 2005) and its familiality results mostly or entirely from genetic influences (Sullivan et al., 2000). In family studies it is impossible to distinguish genetic influences from environmental risk factors, which also are familial. However, the current literature has estimated that heritability of depression is lower than that of schizophrenia or alcoholism (True et al., 1996; Kendler et al., 1992). Studies have reported different estimates of depression heritability, percentages usually ranging between 20 and 45% (Sullivan et al., 2000; Kendler et al., 2002; 2004; 2006b), but higher have also been reported (54-70%) (Torgersen, 1986; Lesch, 2004). Sullivan et al (2000) reported in their meta-analysis strong evidence for an association between major depression in the proband and major depression in first-degree relatives. Although several epidemiological studies have demonstrated a clear environmental component in the aetiology of MDD, especially twin studies have demonstrated the presence of genetic factors. Kendler et al. (2006a) demonstrated that the heritability of major depression is higher in women than in men and that some genetic risk factors for major depression are gender-specific in their effect.

Recent genetic studies have identified genetic markers that may indicate susceptibility to depressive disorders. Monoamine transporter genetic variation has been found to have linkage and association with psychiatric and other complex disorders (Hahn & Blakely, 2002). It has been suggested that this polymorphism, especially in the promoter region of the serotonin transporter (5-HTT) gene, also is related to stress vulnerability (Caspi et al. 2003). Other studies of depression neurobiology hypothesise that neurotoxic effects of hypercortisolemia may damage hippocampal cells, contributing to depression. Supporting this, Sheline et al. (2003) showed that hippocampal volume was significantly predicted by duration of untreated depression, whereas no relationship was detectable between cumulative time treated with

antidepressants during depression. They suggested that antidepressants may have a neuroprotective effect during depression. Hippocampal volume loss during untreated depression has been thought to be mediated by deficient function of neuroprotective peptides. Genetic factors may underlie this, acting by altering the balance of neurotoxic and neuroprotective responses to stress. Antidepressants have been shown to enhance neuroprotective effects (Manji et al., 2001; Castrén, 2005) in animal experiments.

4.3.2 Developmental and psychosocial factors

Genetic factors explain a great part of the entire aetiology of MDD. It is undoubtedly a clinically heterogeneous disorder thought to result from multiple genes interacting with environmental and developmental components modifying the patient's mental state. Such would be: maternal stress during pregnancy (Essex et al., 2002; O'Connor et al., 2002; Oates, 2002), parental depression (Lieb et al., 2002), traumatic childhood experiences (Tennant, 1988; Heim et al., 2000), predisposing comorbidity (Caspi et al., 1996; Young et al., 2004), lack of social support from family or friends, or stressful life events (Brown & Harris, 1978; Miller et al., 1986; Cooper & Paykel, 1994; Paykel et al., 1969; Kendler et al., 2004). Stressful life events with a combination of humiliation and loss, which directly devaluate the individual, are clearly depressogenic (Kendler et al., 2003). However, especially in women, emotionally supportive social relationships seem to have a protective effect against depression (Kendler et al. 2005). Neuroticism has been shown to modify the risk for depressive episodes in the context of stressful life events (Kendler et al. 2004). Kendler et al. (2002) constructed a developmental model to predict depressive episodes in the year before the most recent interview. They considered eighteen risk factors in five developmental tiers: firstly, childhood traumas and genetic factors, secondly, personality development in early adolescence, thirdly, possible traumas, substance abuse, and other factors in late adolescence fourthly, adulthood traumas and major depression history, and fifthly, difficulties during the last year.

4.3.3 Hormonal, neurochemical, physiological and structural findings in depression

Hormonal changes have a clear connection with major depression (Birzniece et al., 2006; Keller et al., 2006; Young & Veldhuis 2006; Young et al., 2000). The hypothalamic-pituitary-adrenal (HPA) system is an important factor as a stress-responsive system. In stressful events, the HPA axis is activated, and the hypothalamus secretes the corticotropin-releasing hormone (CRH), which causes increased corticotropin release in the pituitary. Corticotropin stimulates in the adrenal cortex the production and release of cortisol, which is the adrenal glucocorticoid stress hormone secreted in humans. The production and release of hypothalamic CRH and corticotropin are regulated by the circulating glucocorticoids through negative feedback loops to the hypothalamus and pituitary. Enhanced cortisol activity is related to depression, its

severity, and the interaction of depressive and psychotic symptoms (Arborelius et al., 1999; Sapolsky, 2000; Keller et al., 2006).

The cytokines have been suggested to play an important role in the mediation of the pathophysiological characteristics of major depression (Maes 1995). This model implies that MDD is related to activation of the inflammatory response system. In the depressive disorders, one of the actions of the cytokines may be that they cause HPA axis hyperactivity (Schiepers et al. 2005).

The newest studies support the network hypothesis of depression, which is based on the dynamics of the central nervous system (Hua & Smith, 2004¸ Buzsaki, 2004). These networks are thought to develop through interactions with the environment, and the neuronal structure of and neurotransmission in these networks are constantly being refined through activity-dependent synaptic plasticity to optimally process and store relevant information (Katz & Shanz, 1996; Castrén, 2005). The best support for this network hypothesis is the recent observation that long-lasting antidepressant treatment leads to increased production of new neurons in the rat hippocampus (Malberg et al., 2000). On the other hand depression duration predicts hippocampal volume-loss in women with recurrent depression. This loss may be the cause of cognitive impairment in these patients (Sheline et al., 1999). Goldapple et al. (2004) showed that in patients treated with cognitive behaviour therapy (CBT) the treatment response was associated with significant metabolic changes: increases in the hippocampus and dorsal cingulate and decreases in the dorsal, ventral, and medial frontal cortex. These changes were associated with patients' clinical recovery by their modulation of the functioning of specific sites in limbic and cortical regions. As these changes were distinct from those found after paroxetine treatment, they therefore concluded that like other antidepressant treatments, CBT seems to affect clinical recovery by modulating the functioning of specific sites in limbic and cortical regions. Unique directional changes in frontal cortex, cingulate, and hippocampus with CBT relative to paroxetine may reflect modality-specific effects with implications for understanding mechanisms underlying different treatment strategies.

Most recently, changes in depressive patients vs. healthy controls have been observed in magnetoencephalography (Linkenkaer-Hansen et al., 2005), and EEG changes in depressive patients have been found (Fingelkurts et al., Published Online: 15 Jun 2006). Both findings are possibly linked to the findings of the abnormal structural changes (Campbell et al. 2004; Lloyd et al. 2004; Milak et al. 2005; Neumeister et al., 2005; Videbech et al., 2004) in MDD.

4.4 Course and outcome of MDE

4.4.1 Duration of MDE and course of MDD

Data on the duration of MDE differs notably among studies, mostly dependent on the population studied. Eaton et al. (1997) calculated its duration in the general population in the Epidemiological Catchment Area Study (ECA) as about 12 weeks and also estimated that the duration of the first episode was longer than that of recurrent episodes. Spijker et al. (2002) observed the median of depression duration as nearly the same; meanwhile, Hämäläinen et al. (2004) estimated the length of the depression episode depending on severity as 4, 5, or 9 weeks. Kessler et al. (2003) estimated the episode length to be 16 weeks. Hasin et al. (2005) reported the median episode length to be 24.3 weeks in the general population in the USA. This variation in results may be explained by the different definitions of the episode. Studies indicate that in psychiatric care MDE endures longer (Solomon et al., 1997; Melartin et al. 2004).

Depression is a life-long, recurrent, and disabling disorder. The high recurrence rate and a tendency towards chronicity have been demonstrated strongly. Even during the two-year follow-up after their first MDE, about one third suffer at least one more. During five years nearly 60%, during 10 years about three-fourths, and after 15 to 25 years about 85% (Angst 1986; Brodaty et al. 2001; Keller & Boland, 1998; Mueller et al 1999) suffer at least one more episode. Subsyndromal, minor depression, or dysthymia dominate the course of unipolar MDD (Judd et al. 1998). Because of the chronic course of depression disability is pervasive and increases with the increment of the symptom severity. During the recovery from MDE disability decreases (Mintz et al., 1992) or disappears (Judd et al., 2000a) but it seems clear that after a severe recurrent episode disability does not return to its premorbid level after depression remission (Ormel et al. 2004).

4.5 Comorbidity of MDD

Axis I and II comorbid diagnoses may be difficult to make accurately in depressed patients, who may unconsciously exaggerate their symptoms or feelings and thus fulfil the criteria of some other mental disorder that, when in remission, they do not suffer from.

4.5.1 Axis I comorbidity in MDD

Comorbidity in depression has been widely studied. Patients suffering from unipolar depression usually have at least one comorbid Axis I disorder (Placidi et al., 2000; Melartin et al., 2002; 2004; Merikangas et al., 2003; Alonso et al., 2004c; Hasin et al., 2005; Vuorilehto et al., 2005). The frequency of comorbid disorders depends on the population studied. About 50% of primary-care MDD patients suffer from anxiety

disorders (social and simple phobias 23%, panic disorder 9%, generalised anxiety disorder (GAD) 20%, and other anxiety disorders 8%), those with alcohol or substance-use disorder had 16% (Vuorilehto et al., 2005). Alcohol-use disorders (Melartin et al., 2002; Hasin et al., 2005; Vuorilehto et al., 2005) are relatively usual. The frequency of MDD in dysthymic patients (double depression clinical populations) is about 12% (Melartin et al., 2002; Vuorilehto et al., 2005).

4.5.2 Axis II comorbidity in MDD

Frequently the question has been: Is it possible to assess personality disorders simultaneously when a patient is depressed (Stuart et al. 1992)? In diagnostic classification this has been considered possible (DSM-IV, Multiaxial Evaluation). Only a few studies have assessed both depression and Axis II disorders in the same population (Sato et al., 1996; Melartin et al., 2002; Hasin et al., 2005). The most usual personality disorders in depression seem to be avoidant, borderline, and paranoid personality disorder (Melartin et al., 2002; Markowitz et al., 2005). As a personality trait, neuroticism (Eysenck & Eysenck, 1964) has been strongly connected with MDD (Lyness et al., 1998; Mulder, 2002; Kendler et al., 2004).

4.5.3 Axis III comorbidity in MDD

In depressive patients, somatic diseases are common (Katon & Sullivan, 1990; Isometsä et al., 2000; Vuorilehto et al., 2005), often chronic ones (Moldin et al. 1993; Oslin et al., 2002). Of primary care MDD patients, 47% have been found to suffer from chronic medical illnesses (Vuorilehto et al., 2005).

4.6 Treatment of MDD

Effective treatments of depression, such as antidepressants, different psychotherapies, ECT, and combinations of these, have been in use for decades. Despite the treatments available, problems have been reported in the treatment provided and its efficacy all over the world (Lehtinen et al. 1990b; Brugha & Bebbington, 1992; Salminen et al., 1999; Laukkala et al., 2001; Kohn et al., 2004; Starkes et al., 2005; Wittchen & Jacobi, 2005; Shen et al., 2006). For this reason there have been developed several treatment guidelines to improve treatment of depression (APA 1993; 2000; Schulberg et al., 1998; Bauer et al., 2002; NICE, 2004; Depressio: Käypä hoito -suositus, 2004).

4.6.1 Psychosocial treatment

The several psychotherapy types in use in the treatment and rehabilitation of depression are cognitive-behavioural approaches, brief, interpersonal therapy, structured psychodynamic short-term therapy, and psychodynamic therapy. Psychotherapy even alone is recommended for mild to moderate depression (APA, 2000; Depressio: Käypä

hoito-suositus, 2004). The outcome of psychotherapeutic treatment is influenced both by factors specific for each type of psychotherapy and by unspecific factors. A typical therapy visit lasts 45 minutes. Time-limited psychotherapies involve a variable number of therapy sessions; usually the number ranges from a few to up to 20 to 30 weekly sessions. In brief therapies, 10 to 20 weekly therapy sessions usually are sufficient. Long-term individual therapies typically involve from one up to three weekly sessions lasting from one to several years. Research on the efficacy of the different psychotherapy types has focused on time-limited therapies. The lack of several randomised, 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 (Isometsä et al., 2003).

4.6.2 Antidepressant treatment

Modern effective antidepressants have been in use since 1957 (Ban, 2001), and since then the development of new antidepressants has been intensely based on the monoamine theory. The four main types of antidepressants are serotonin reuptake inhibitors, noradrenaline reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and monoamine oxidase inhibitors. Antidepressant treatment of MDD consists of three phases: an acute, a continuation, and a maintenance phase.

4.6.2.1 Acute phase treatment

Acute phase pharmacotherapy is effective for all severities of MDE. In mild to moderate depression, psychotherapy alone or combined with medication is helpful. While medication is part of the treatment, it must be integrated with the psychiatric management and any other treatments provided. The more severe the depression, the more important is the role of adequate medication. All antidepressants available are shown to be equally effective, and differences are mostly related to their adverse effects. The dosage of the antidepressant must be adequate as defined in the treatment guidelines (APA 1993; 2000; Depressio: Käypä hoito -suositus, 2004) (Table 1.). The goal of the treatment is always full remission in order to restore the patient's functional ability and prevent relapses (Judd et al., 2000b; Papakostas et al., 2004; Pintor et al., 2004).

4.6.2.2 Continuation phase treatment

When the full remission has been attained, antidepressant treatment has to continue at its full dosage from 4 to 9 consecutive months. After sustained remission the need should be considered for maintenance treatment to prevent more relapses or recurrences. (APA 1993; 2000; Depressio: Käypä hoito -suositus, 2004).

4.6.2.3 Maintenance phase treatment

Antidepressant treatment clearly reduces the risk for relapse in depressive disorder, and many patients with recurrent depressive disorder will benefit from continued treatment with antidepressants. The treatment benefit for an individual patient will depend on his or her absolute risk for relapse, with greater benefits for those at higher risk. Maintenance treatment should be considered if a patient has a third at least moderate depression episode, has had comorbid conditions, residual symptoms between episodes, severe disability, suicidal behaviour or psychotic features. Nearly the same treatment (antidepressant at full dose, psychotherapy perhaps at a lowered frequency) that was effective during acute depression and should continue preferably for years to prevent further recurrences (APA 2000; Geddes et al., 2003; Depressio: Käypä hoito-suositus, 2004).

Table 1. Antidepressants available in Finland in 2006. Based on Duodecim, Käypä hoito, 2004, and updated with a new antidepressant.

Generic name		Starting dose (mg/day)	Usual dose (mg/day)
Tricyclics (TCA)			
	amitriptyline	25 – 50	75 - 300
	clomipramine	25 – 50	75 - 300
	doxepin	25 – 50	75 - 300
	nortriptyline	25 – 50	50 - 200
	trimipramine	25 – 30	75 - 300
Selective serotonin reuptake inhibitors (SSRI)			
	citalopram	20	20 - 60
	escitalopram	10	10 - 20
	fluoxetine	20	20 - 80
	fluvoxamine	50	100 - 300
	paroxetine	20	20 - 50
	sertraline	50	50 - 200
Other antidepressants			
	duloxetine	60	60
	mianserin	30	30 - 120
	milnacipran	50	100
	mirtazapine	15 – 30	30 - 60
	moclobemide	300	300 - 900
	reboxetine	8	8 - 10
	trazodone	50 – 100	150 - 500
	venlafaxine	75	75 - 375

4.6.3 Electroconvulsive therapy (ECT)

Electroconvulsive therapy is the oldest modern treatment of depression. It has been in use since the late 1930's, first as treatment for psychoses. Its action has not been entirely understood, but different hypotheses exist, such as HPA axis normalisation (Yuuki et al., 2005). It is an effective short-term treatment for depression and is probably more effective than drug therapy. Bilateral ECT is moderately more effective than unilateral ECT, and high-dose ECT is more effective than low-dose ECT (The UK ECT review group, 2003). ECT should be considered if antidepressants fail to resolve depression, in patients with a high severity of symptoms, or those who are suicidal, or have other life-threatening symptoms, or when antidepressant treatment is precluded because of somatic illness (APA, 2000; Depressio: Käypä hoito-suositus, 2004).

4.6.4 Treatment of refractory depression

Combined treatment by psychotherapy and pharmacotherapy is associated with better outcome than is either treatment alone (Hirschfeld et al., 2002; Pampallona et al., 2004). Antidepressant combination may be more favourable in some cases than is one drug alone (Nelson et al., 1991; Nutt, 2002). Combining of drugs is intended to combine mechanisms of action, not just of drugs to promote pharmacological synergy and tolerability and to use important synergies within the serotonin, noradrenaline, or even dopamine monoaminergic system. In refractory depressions, whereas two consecutive antidepressant trials have not been favourable at adequate doses and durations, combination or augmentation strategies may be effective. The usual augmentation agents are lithium (Dinan & Barry, 1989), buspirone (Appelberg et al., 2001) and triiodothyronine (Lifschytz et al. 2004). Antidepressants combined with neuroleptics are needed in psychotic depression (Depressio: Käypä hoito-suositus, 2004). ECT combined with antidepressant therapy may be useful in patients with severe depression (Hirschfeld, 1999).

4.7 Disability

4.7.1 Functional and work disability

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 of social adjustment is a part of functional disability. Problems in it may seem to be difficulties in the patient's role performance, interpersonal relationships, and work and leisure satisfaction (Weissman & Bothwell, 1976). Work disability is a specific form of impairment, defined as inability to work at a job or business, and receiving social security benefits or disability pension on that basis (MMWR, 2000).

4.7.1.1 Functional disability in MDD

Disability associated with unipolar MDD is pervasive, affecting most areas of everyday life, and varying as a function of depressive symptom severity. The level of disability seems to correspond to the level of depressive symptomatology, and decreases (Mintz et al., 1992) or disappears (Judd et al., 2000a) when the patient is asymptomatic. It is unclear how simultaneously occur the recovery from depression and the disappearance of disability symptoms. This is a problem worth further research. Persons with major depression are at an almost five times greater risk for disability than are the asymptomatic (Broadhead et al., 1990).

4.7.1.2 Work disability in MDD

Work disability may appear both as decreased ability to work or as days lost from work, and unipolar depression is its fourth leading cause worldwide (Murray & Lopez, 1997). Even diminished ability to work affects work productivity considerably. Depression itself causes severe human suffering to the individual and leads to reduced performance while at work and work absence, both causing enormous costs to the employee, employer, and to society, as lack of income. Additional to this are costs of the treatment of depression, with costs being the higher the more severe the depression (Simon, 2003). Improvement of depression is associated with the possibility that patients are able to maintain their paid employment. Their treatment costs also diminish some in the future (Simon et al., 2000).

4.7.1.3 Work disability pensions due to MDD

Depression is the most prevalent mental disorder causing sickness absence from work (Wells et al., 1989; Hensing et al., 2000), and the increasing number of disability pensions granted for major depression is a major concern. During the last two decades, especially in Finland, new disability pensions granted due to mental disorders have increased markedly, including both permanent and temporary pensions (Salminen et al., 1997, Finnish Centre for Pensions, 2006; Figure 1). Nearly half the disability in 2005 received their pension due to mental disorders (Figure 2), and over three-fifths of those granted a new disability pension due to mental disorders in 2005 received it due to mood disorders (Figure 3).

Predictive factors for being granted a disability pension have been examined in a few studies, despite depression's human and economic significance. Salminen et al. (1997) hypothesised that the deep economic recession in the early 1990's, changes in the diagnostic system, and better recognition of affective disorders may be factors contributing to this development. Isometsä et al. (2000) found in their study of a random representative sample of 277 subjects drawn from the Disability Pension Register of the Social Insurance Institution that comorbid mental or physical disorders had the most significant effect on being granted a disability pension Sorvaniemi et al.

(2003) found, in their retrospective document-based cohort study of 213 adult psychiatricoutpatients, that greater age, comorbidity, and lowered self-esteem were strongly associated with being granted a pension. It is notable that only a few in this study received adequate antidepressant treatment.These studies were done by quite different methods, and a comprehensive, prospective, naturalistic cohort study focusing on the whole comorbidity, social, functional and work disability is lacking.

Figure 1. New work disablity pensions in the Finnish private sector granted from 1986 to 2005. Source of data: Finnish Centre for Pensions, 2006.

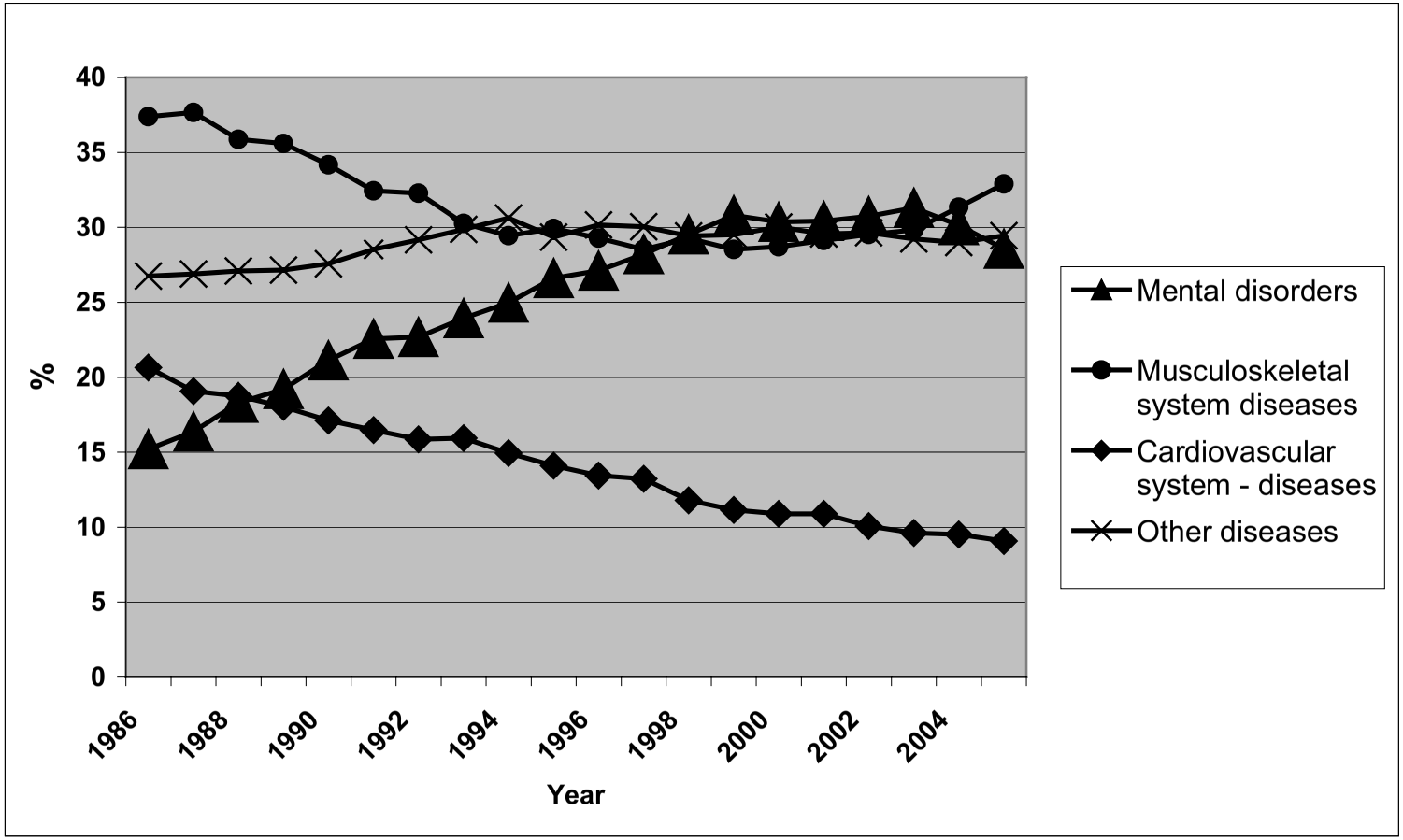


Figure 2. All disability pensions in 2005 due to mental disorders in the private sector. Source of information: Finnish Centre for Pensions, 2006 (F20-F29 Psychoses, F30-F33 Mood disorders).

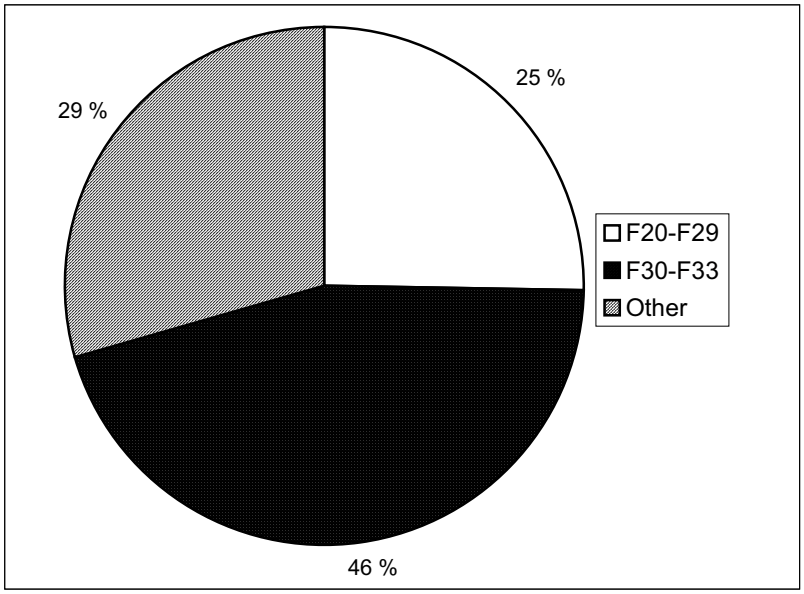
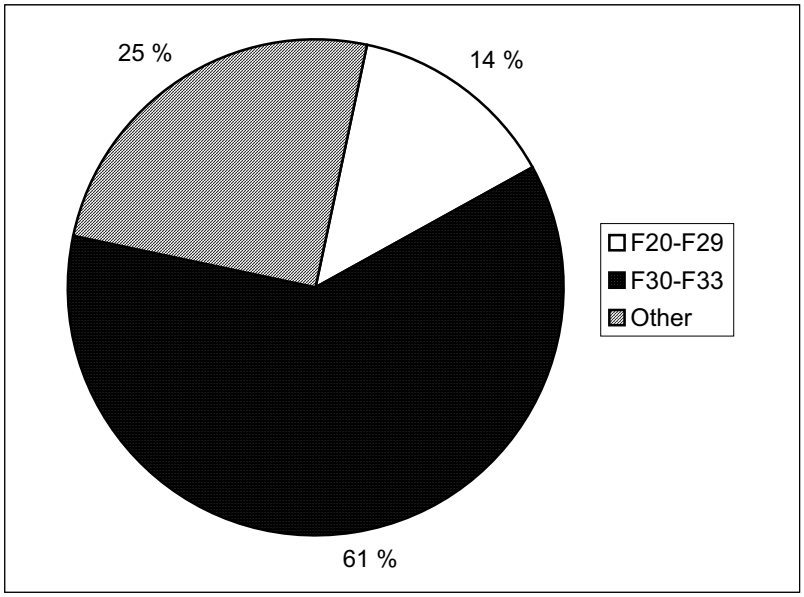


Figure 3. New work disability pensions granted in 2005 due to mental disorders in the Finnish private sector. Source of information: Finnish Centre for Pensions, 2006 (F20-F29: Psychoses, F30-F33: Mood disorders).



4.7.1.4 Conclusions of the present literature

Studies conducted in the 1980s (Keller et al., 1982; 1986; Kocsis et al., 1988; Brugha & Bebbington, 1992) showed that patients receiving no specific treatment for depression, or inadequate treatment, seemed to have been the rule, even among patients attending psychiatric facilities. Problems in the treatment of depression are closely connected to the patient's level of disability; level of disability corresponds to the level of depressive symptomatology, and is alleviated when the patient is asymptomatic (Judd et al. 2000a). Some other studies have shown that disability recovery is slower than symptom remission (Mintz et al. 1992).

Many cross-sectional studies have reported that MDD with comorbid mental disorders is associated with more impairment than is pure MDD alone (Isometsä et al. 2000; McDermut et al. 2001). The personality trait neuroticism (Lyness et al. 1998) and poor social support (Hays et al. 2001), seem to be associated with functional disability among older adults with MDD. Among patients of working age, poor family functioning (Keitner and Miller, 1990) and low satisfaction with one's social support (Ezquiaga et al. 1999) may predict a less favourable course of MDD.

In Finland has been noticed during the last two decades a rapid increase in long-term work disability pensions due to depression. Salminen et al. (1997) noted the rapid increase in number of long-term work disability pensions, temporary and permanent, between 1987 and 1994, raising the issue how and why the functional capacity of depressive patients could have markedly deteriorated despite new drugs and other treatments that had become available. Isometsä et al. (2000) investigated in their representative record-based study has been investigated the quality and intensity of treatment provided for patients with clinically diagnosed depression who were granted a disability pension in Finland in 1993.

On the basis of the present literature, current information on the intensity and quality of treatment is limited. Poor or insufficient treatment cannot influence recovery from depression and thus reduce disability, and factors associated with patients' characteristic features are not well known. Another major issue little investigated is to what extent the present functioning of the patient reflects the patient's present state, or includes the accumulated burden of the earlier illness history. Overall, given the high human and economic costs of long-term disability, continuous evaluation of quality of treatment provided to those disabled due to depression is warranted.

5. AIMS OF THE STUDY

This study investigated the treatment received in a record-based study of 803 secondary care patients and predictors affecting psychosocial and work disability at baseline and during follow-up in the prospective part of the VDS consisting of 269 patients. This thesis consists of four original publications, the aims of which are:

I To investigate the adequacy of the antidepressant and quality of the psychosocial treatment for depression in 1996 in a psychiatric secondary care setting providing treatment for a well-defined catchment area.

II To investigate in the follow-up study baseline predictors of psychosocial disability and current work disability in a large sample of patients with MDD.

III To prospectively investigate in our cohort of patients with MDD during the 18-month follow-up predictors of functional and psychosocial disability.

IV To prospectively investigate, during the 18-month follow-up, factors predicting long-term work disability resulting in work disability retirement among patients with MDD.

6. METHODS

6.1 General study design

The Vantaa Depression Study (VDS) is a collaborative depression research project in cooperation with the Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki, Finland, and the Department of Psychiatry of the Peijas Medical Care District (PMCD), Vantaa, Finland. The catchment area of the project comprises the city of Vantaa (population 169 000 in 1997). The PMCD Department of Psychiatry offers secondary care psychiatric services to all Vantaa citizens. These include a psychiatric inpatient unit, a general hospital outpatient clinic, six community mental health care centres, and two day hospitals.

6.2 Design of the record-based study (Study I)

Data for this study were collected from a computerized patient database incorporating all outpatient visits as well as treatment periods at the inpatient unit.

6.2.1 Inclusion criteria

Inclusion criteria in this study incorporated all patients aged 20 to 59 years who had been assigned a clinical diagnosis of Depressive Episode (F32.xx) or Recurrent Depressive Disorder (F33.xx) according to the ICD-10, and who had at least one outpatient visit or day as an inpatient in the Peijas Medical Care District during the study period January 1, 1996, to December 31, 1996.

6.2.2 Exclusion criteria

We excluded all patients who had earlier received a diagnosis of schizophrenia, other non-affective psychosis, or bipolar disorder. Exclusion criteria also applied to patients treated in the somatic departments of Peijas hospital, or who had only consulted but were not treated by the psychiatric consultation services.

6.2.3 Data collection

In the computerized database were found 972 patients initially fulfiling inclusion criteria in the register of visits to outpatient clinics or hospital stays. In the patient records, 169 of these had diagnoses fulfiling the exclusion criteria, and the remaining 803 patient records were examined thoroughly. A structured form with 57 items was filled in including a) sociodemographic and clinical characteristics of the patients, and b) treatment received during the whole treatment period in the PMCD, irrespective of

the year it began. Treatment provided was reviewed up to the end of 1997 if continued. Patients treated at the PMCD inpatient unit at least once were classified as inpatients. There were no possibilities to record Axis I and II comorbidity, except alcohol misuse, because only the first diagnosis was known. Diagnoses were clinical and were made by the treating psychiatrist according to the ICD-10. Possible alcohol misuse was noted if the patient him- or herself or the treating personnel considered it to be a problem. The number of antidepressant trials was calculated, and medicine combinations including both antidepressants and neuroleptics and augmentations were recorded. The adequacy of any antidepressant dose was defined as the usual adult dose in the APA Practice Guidelines (APA, 2000); the length of treatment with antidepressants and switching strategies for it were recorded. Changes in work disability and pensioning were analysed.

6.2.4 Validity of the diagnoses

In the computerised database were all outpatient visits and hospital stays with first diagnosis found. From this database were selected those having at least once a ICD-10 clinical diagnosis of F32.x or F33.x. The medical records ensured that each patient's diagnosis fulfiled the criteria of MDE. Of the 972 eligible patients, 169 had an earlier or current diagnosis of schizophrenia, other non-affective psychosis, or bipolar disorder, and these were excluded. The severity of depression as classified in the clinical ICD-10 diagnosis was shown in the database. Its validity in the beginning of the treatment period was estimated by selecting randomly 181 patients' diagnoses, and the author estimated the severity based on the description of each patient's status in the medical records. The author estimated 4.4% (8 of 181) of diagnoses differently than did the treating psychiatrist. Possible alcohol misuse was stated in the medical records either as the patient's or health professional's opinion or both.

6.2.5 Outpatient visits and hospital stays

All outpatient visits and hospital stays were found in the computerized database. All visits for the current episode were calculated; patients with at least one hospital stay during the current episode were treated as inpatients, and the lengths of the hospital stays were calculated.

6.2.6 Sociodemographic characteristics and work status

Patients' age, gender, marital status, occupational status, and work status at both the beginning and at the end of the treatment period were recorded, and especially work disability pensions.

6.2.7 Treatment received

In the database and medical records were available all data including psychopharmacological treatment, number of visits to psychiatrists and other health

professionals, inpatient treatment, and acceptance or refusal of antidepressant treatment. All antidepressant treatment trials and their doses were recorded as well as the adequacy of the antidepressants received. Other medication, like neuroleptics, anxiolytics, hypnotics, and possible augmentation medications, were recorded, and use of electroconvulsive therapy was analysed.

6.3 Design of the VDS cohort study (Studies II-IV)

6.3.1 Patient screening

In the first phase of the study, psychiatric patients were screened for the presence of depressive symptoms during a 16-month period starting from February first 1997. During that period, 806 patients were screened at the ages of 20 to 59 years if they were: 1) seeking treatment at the Department of Psychiatry, 2) being referred there, or 3) already receiving care and now showing signs of deteriorating in their clinical state there, but without a clinical diagnosis of ICD-10 schizophrenia or bipolar I or II disorders. These were screened by the personnel 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). These questions were: 1. “Have you felt yourself depressed during the past month?” 2. “Have you often cried during the past month?” 3. “Do you no longer positively enjoy things usually felt to be enjoyable?” 4. The interviewer estimates possible “masked” depression, 5. “Have you thought of harming yourself?”. The final question was been specified by five additional questions according to the Scale for Suicidal Ideation (SSI) (Beck et al., 1979) to identify cases with moderate to severe suicidal ideation or plans. After either 1) a positive response to any of the SCAN screening questions or 2) a score of six or more on the SSI, irrespective of the presence of depressive symptoms, the patient was fully informed about the study project, and written informed consent requested. Of the 703 eligible patients, 161 (22.9%) refused to participate in the study, but 542 (77.1%) agreed and gave their written informed consent after the procedure was fully explained. Those refusing patients did not significantly differ from those participating in age or gender. The Ethics Committee of Peijas Hospital approved the study in December 1996.

6.3.2 Diagnostic process

All interviewers had received relevant training by a WHO-certified training centre on use of the SCAN, Version 2.0 (Wing et al., 1990) diagnostic tool. Patients were interviewed face-to-face by one of the researchers (U.L., P.L-M., T.M., H.R., or P.S.). They examined whether or not the current mood episode fulfiled the criteria for (unipolar) DSM-IV Major depressive disorder. All psychiatric and medical records in the PMCD, including a standardised set of laboratory tests, were also available at the interview. On this basis, all 269 patients diagnosed with DSM-IV MDD were included

in the MDD Cohort Study. Diagnostic reliability was found to be excellent (kappa for MDD 0.86 [0.58-1.0]; Melartin et al., 2002). All patients included in the study cohort were interviewed with the entire SCAN to give a full picture of Axis I comorbid disorders, and with the Structured Clinical Interview for DSM-III-R personality disorders (SCID-II) (Spitzer et al., 1987) to assess diagnoses on Axis II. Current and past axis III diseases were assessed via a self-report checklist with 44 items (corresponding to ICD-10 diagnoses) and medical records. However, the study included only axis III diseases diagnosed by a physician and currently being treated.

6.3.3 Exclusion criteria

We excluded all patients who had earlier received a diagnosis of schizophrenia, other non-affective psychosis, or bipolar disorder even if they currently fulfiled MDE criteria. Currently alcohol-abusing patients with less than two to three weeks of abstinence were excluded.

6.3.4 Self-report and observer scales

For assessment of the severity of MDE, the patient completed the 21-item Beck Depression Inventory (BDI; Beck et al., 1961) and as the observer scale we used the 17-item Hamilton Rating Scale for Depression (Ham-D; Hamilton, 1960). Current functional disability was assessed by the Social and Occupational Functioning Assessment Scale of DSM-IV (SOFAS; Goldman et al., 1992) as an observer scale. This differs from the Global Assessment of Functioning (GAF; APA, 1987) in measuring purely the level of social and occupational functioning, without taking symptoms into account. Its validity has been found to be good (Hilsenroth et al., 2000; Hay et al., 2003).

In measuring patients' social and work adjustment we used the Social Adjustment Scale-Self Report (SAS-SR; Weissman & Bothwell, 1976). In contrast to SOFAS, SAS-SR is a subjective self-rated scale. The lowest score of 1 indicates optimal functioning and 5 the worst functioning for each of the 54 questions. The internal consistency of our translation of the SAS-SR was moderate to good, with Cronbach's Alpha for the subscale work outside home 0.73, work at home 0.69, work as a student 0.82, social and leisure 0.69, extended family 0.53, marital 0.63, parental 0.67, and family unit 0.62. The economic subscale contains only one question. We calculated mean values for all subscales related to the patient's work and family relationships, and the overall score for every patient.

Social support given by the family, friends, and significant others was measured by the Perceived Social Support Scale – Revised (PSSS-R; Blumenthal et al., 1987) the shortened version with a 1–5 scale for each of 12 questions. Although both SAS-SR and PSSS-R in part measure family relations, SAS-SR items focus on social adjustment and functioning, PSSS-R on perceptions of relations with family and significant others. The Beck Anxiety Inventory (BAI; Beck et al 1988) includes mainly somatic symptoms; it

focuses the patient's attention to those which weaken the patient's functioning. The Beck Hopelessness Scale (HS; Beck et al 1974) is also a self-report scale providing data concerning patients' hopelessness about their future. The Eysenck Personality Inventory (EPI; Eysenck & Eysenck, 1964) is a self-report scale of personality traits, i.e., neuroticism and intro- and extraversion. The number of days from baseline spent ill in bed (over 50% of the time spent awake) due to depression were recorded both in 6- and in 18-month follow-up interviews.

6.3.5 Treatment received

Psychosocial treatment was analysed: its type, length, and the number of visits both to psychiatrist and medical personnel. Patients' antidepressant treatment was carefully recorded at both follow-up points. Its length, dosage, any switch to another medicine, additional medication (somatic medicines, neuroleptics, anxiolytics, hypnotics), possible augmentation medications and use of electroconvulsive therapy (ECT) were recorded.

6.3.6 Work status

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.

6.3.7 Follow-up

6.3.7.1 Follow-up cohorts

At baseline, all VDS subjects (269) with current MDD were included Study I. At the 6-month follow-up point, 40 subjects were missing (n=229). Some of these were participating in the study again at the 18-month follow-up (n=207). Only 13% (35/269) dropped out of both follow-up interviews. Of the 269 subjects at baseline, 13 (5%) patients' diagnoses switched to bipolar disorder during the 18-month follow-up. They were censored from the analyses, and 8 patients died during follow-up. The median time points to follow-up interviews were 6.5 and 18.8 months. Of the remaining 198 patients prospectively followed up, those were analysed in Study III who had at every interview data from SOFAS (191) and SAS-SR (N=192) and the number of days ill in bed (N=193). This cohort of 193 patients included those who also had all the data from SOFAS and SAS-SR mentioned above. For Study IV, of the 198 patients prospectively followed up, we excluded those already pensioned at baseline. The remaining 186 patients were classified into two groups as follows; 1) those who at 18 months were still in the labour force (n=99) or were unemployed (n=29), on sick-leave (n=14), were students (n=13) or others (n=10), and 2) those who were granted a long-term work disability pension due to MDD during follow-up (n=21). The majority of subjects in the cohort were women (134, 72%), and the overall mean age was 42.1 (SD 10.8).

6.3.7.2 Follow-up process

After baseline, patients were investigated at 6 and 18 months from baseline with the life chart methodology of depression severity and the scales mentioned above. The life-chart methodology was based on DSM-IV criteria and definitions. Time after the first baseline interview was examined, divided into three periods: 1) state of full remission, 2) state of partial remission, or 3) state of MDE. Full or partial remission was defined as at least two consecutive months during which the patient did not fulfil the MDE criteria (full=0, partial=1-4 of the 9 symptoms) according to the DSM-IV. Relapse was defined as return of symptoms fulfiling the MDE criteria for more than 2 weeks, but less than 2 months, after a period of more than 2 weeks, but less than 2 months spent below the MDE threshold. Recurrence was defined as a return of symptoms fulfiling the criteria of MDE after at least 2 consecutive months of partial or full remission.

We employed a Likert scale to investigate patients' self-reported treatment adherence with the following response items: 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. Hospital treatment periods during follow-up were ascertained in the medical records.

6.3.8 Statistical analyses

The record-based study employed logistic regression models, using stepwise backward elimination with the likelihood ratio test as the criterion for removal to control for age, gender, and other possible confounding factors. The chi-square test was used with Yates correction in all four studies. Variables were dichotomized if needed. The Kruskal-Wallis test and one-way analysis of variance (ANOVA) were also used.

In Study II, the Mann-Whitney and Kruskal-Wallis tests were employed in comparisons of continuous variables not normally distributed, and the two-sample t-test was used for variables normally distributed. Because SOFAS and SAS-SR scales were normally distributed, we employed multivariate linear regression models. The multivariate models included linear regression models, with SOFAS score as the dependent variable. In analysing SAS-SR subscales and overall scores a linear regression model was employed, with the independent factors of gender, age, total duration of depression including prodromal time and duration of depression prior to baseline Ham-D, phobic disorders including agoraphobia, specific and social phobia, alcoholism, and any personality disorder. Factors associated with sick-leave were analysed by logistic regression models including gender, age, Ham-D, and number of previous episodes (classified as none, one, and two or more) as the independent variables.

In Study III, the bivariate correlations of SOFAS and SAS-SR were calculated by Pearson Correlation. Univariate statistical analyses of SOFAS and SAS-SR employed

ANOVA. Overall scores of SAS-SR and SOFAS values were analysed by a linear regression model, with the independent factors at 6 months being gender, age, marital status, Ham-D, and phobic disorders including agoraphobia, specific and social phobia, alcoholism, any personality disorder, any somatic disease for which patients were receiving medical treatment, and BAI and PSSS-R. In analysing factors associated with disability at 18 months, independent variables were those mentioned, and in addition time spent in full remission, in partial remission, or fulfiling the criteria of MDE, and in addition having a relapse or recurrence the during follow-up time or not. Dependent variables too skewed for linear regression were dichotomized by the median of the variable.

In Study IV, Fisher's exact test was used instead of the chi-square analysis in some analyses, where some cell(s) contained less than five cases. ANOVA served for comparisons of continuous variables. In all analyses, item 7 in the Ham-D and item 15 in the BDI, capacity for work, was omitted in order to avoid circularity. Three different logistic regression models were employed to investigate 1) baseline factors predicting pension, 2) effect of duration of depression, and 3) independent prediction by sick-leave at baseline of received a disability pension. We first adjusted for gender, age, marital status, severity and number of previous episodes of depression, alcoholism, personality disorders, BAI, PSSS-R, HS, SSI, SAS-SR, and SOFAS scores at baseline, and duration of depression, and then omitted non-significant factors.

The analysis program used was SPSS, versions 9.01 and 13.0 (SPSS Inc. 1989-2004).

7. RESULTS

7.1 Treatment received for depression in psychiatric care (Study I)

7.1.1 Clinical and sociodemographic characteristics of the cohort

The vast majority of those receiving a clinical diagnosis of MDE were females, 513 of 803 (63.9%). One-fifth (20%) of both genders made inpatient visits, with a mean of 1.8 inpatient treatment periods (median=1, range 1-20) during the overall treatment period investigated. The median length of a hospital stay was 14 days. During the whole treatment period, the depressed patients averaged only a few visits to psychiatrists (median=2; range, 1-52), but more to other health professionals including psychiatric nurses, social workers, and psychologists (median=7; range, 1-148). Half the subjects (52%) were married or cohabiting. One-third (32%) were employed at the beginning of the treatment period; and more (34%) at the end of the treatment or follow-up (at the end of 1997). Detailed data on clinical and sociodemographic characteristics are presented in Table 2. Genders differed significantly only for alcohol misuse, men showing this twice as often as women.

Table 2. Sociodemographic characteristics of the 803 psychiatric patients in the Peijas Medical Care District of Vantaa, Finland.

	Males (n=290)	Females (n=513)	Total (n=803)
Mean age ±SD(y)	43 ± 9.3	43 ± 10.2	43 ± 9.9
Marital status (%)			
Married	42	41	41
Cohabiting	12	11	11
Divorced	29	31	31
Widowed	1	4	3
Unmarried	16	13	14
Occupational status (%)			
Entrepreneur	10	3	5
White-collar worker	26	36	33
Blue-collar worker	57	50	52
Pensioner	3	4	4
Student	4	4	4
Other	0	3	2
Work status at the beginning of the treatment (%)			
Unemployed	27	20	22
On sick-leave	20	20	20
Pensioned, psychiatric reason	14	14	14
Pensioned, somatic reason	6	3	4
Employed	30	33	32
Studying	3	4	4
Other	0	4	3
Unknown	0	1	1
Work status at end of treatment or follow-up (%)			
Unemployed	22	13	16
On sick-leave	10	8	8
Pensioned, psychiatric reason	30	28	29
Pensioned, somatic reason	7	3	5
Employed	27	37	34
Studying	2	5	4
Other	0	3	2
Unknown	0	2	1
Deceased	2	0	1
Severity of depression (%)			
Mild	7	10	9
Moderate	35	37	36
Severe	29	29	29
Severe with psychotic features	11	9	10
Undefined	18	15	16
Use of alcohol (%)[a]			
No alcohol misuse	61	80	73
Alcohol misuse	39	20	27
Previous psychiatric care (%)			
No	52	49	50
Yes	48	51	50
Quartiles of duration of current treatment period (week)			
25	16	23	21
50	60	65	63
75	119	121	120

a = Males vs. females $Chi^2 = 33.4$, df = 1, $p<0.0001$

7.1.2 Antidepressant treatment

Of the 803 patients, 675 (84.1%) underwent at least one antidepressant trial. Antidepressant treatment received by degree of depression severity was the following: mild, 49 of 72 (68.1%); moderate, 251 of 292 (86.0%); severe, 211 of 232 (90.9%); psychotic, 70 of 80 (87.5%); not specified, 94 of 127 (74.0%). A minority (11.3%) of these took clearly subtherapeutically low doses. Selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants were used in adequate doses in nearly all (527) cases: 514 (97.5%), whereas of 148 those receiving tricyclic antidepressants (TCAs) took adequate doses only 70 (47.3%) (Chi^2=245.7, p<0.0001).

The antidepressants used are shown in Table 3. The newest, mirtazapine and venlafaxine, had been in use for only a short period. In a logistic regression model with stepwise backward elimination, including gender, living alone or together, occupation, alcohol misuse, use of anxiolytics and hypnotics, and degree of severity of depression as covariates, use of TCAs was significantly associated with older age (odds ratio per year of age=1.06, Wald Chi^2=19.92, df=1, p<0.0001, 95% confidence interval [CI]=1.03 to 1.08), previous psychiatric care (odds ratio=1.58, Wald Chi2=4.52, df=1, p=0.03, 95% CI=1.04 to 2.42), and use of neuroleptics (odds ratio=2.57, Wald Chi2=17.70, df=1, p<0.0001, 95% CI=1.65 to 3.98).

Table 3. Characteristics of antidepressant treatment periods by type of antidepressant.

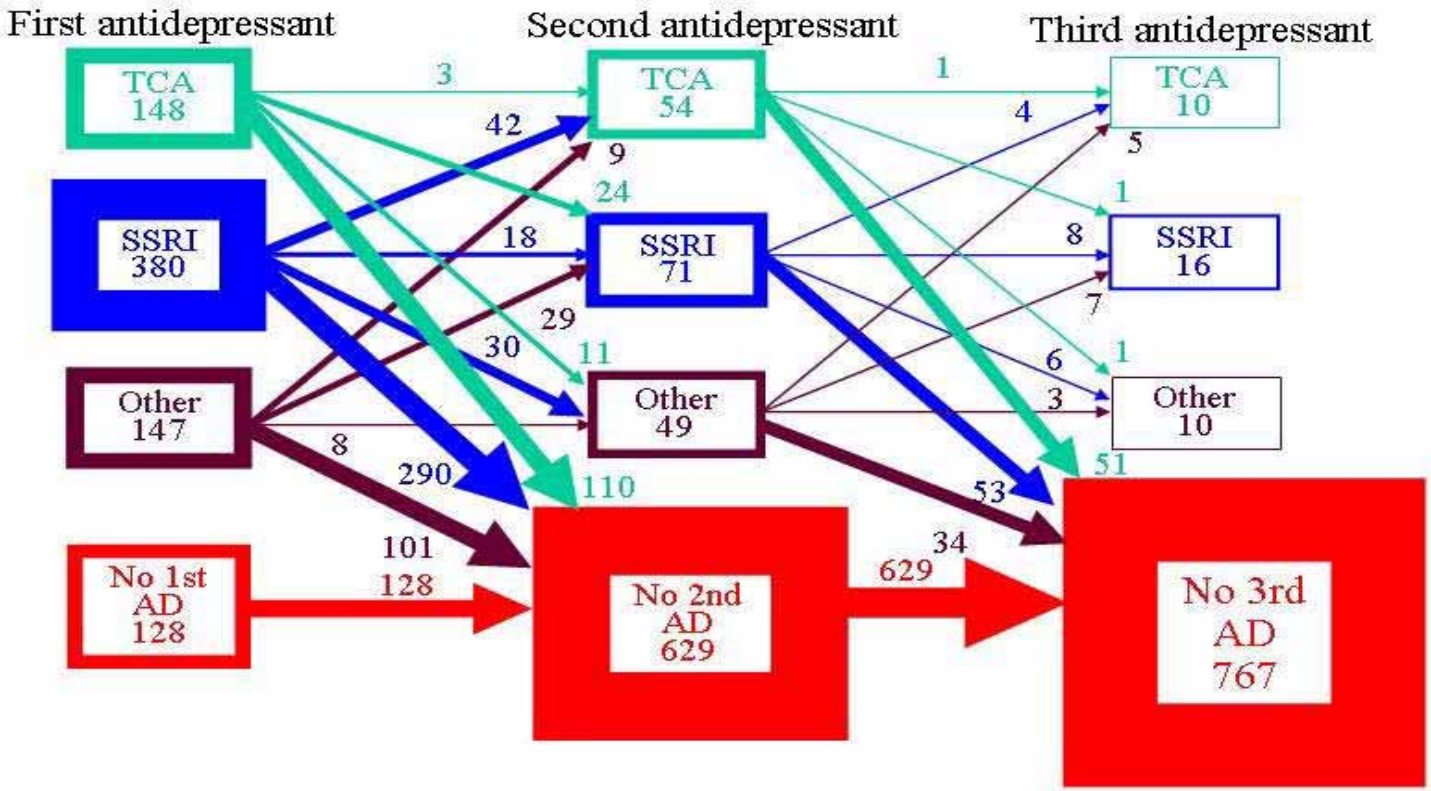
		N	(%)	Mean dose[a] (mg)	Dose range (mg)	Median duration[b,c] (wk)
Tricyclics						
	amitriptyline	70	(10.4)	93	(25 – 250)	96
	clomipramine	33	(4.9)	120	(10 – 250)	51
	doxepin	30	(4.4)	85	(25 – 250)	67
	imipramine	2	(0.3)	138	(125 – 150)	5
	nortriptyline	1	(0.1)	100	(100)	163
	trimipramine	12	(1.8)	92	(50 – 150)	70
SSRIs						
	citalopram	138	(20.4)	28	(10 – 60)	63
	fluoxetine	184	(27.3)	26	(8 – 60)	34
	fluvoxamine	26	(3.9)	102	(50 – 300)	35
	paroxetine	16	(2.4)	23	(20 – 40)	28
	sertraline	16	(2.4)	84	(50 – 200)	44
Tetracyclics						
	maprotilin	6	(0.9)	81	(38 – 150)	89
	mianserin	54	(8.0)	54	(10 – 90)	29
	trazodone	12	(1.8)	208	(100 – 300)	74
NaSSA						
	mirtazapine	6	(0.9)	30	(15 – 45)	21
SNRI						
	venlafaxine	1	(0.1)	75	(75)	-
RIMA						
	moclobemide	68	(10.1)	417	(150 – 600)	32
Total		675	(100.0)			44

[a] = Means of highest daily doses used during treatment, [b] = Exact duration of treatment unknown in 59 cases, [c] = Duration of use of tricyclics vs. SSRIs, vs. tetracyclics and vs. others significantly longer (in Kruskal-Wallis test $Chi^2=11.68$, df=3, p=0.009)

7.1.2.1 Antidepressant switching strategies

Switching strategies of antidepressants were quite conservative: Among the 675 patients, the first antidepressant had been switched to another compound for only one-fourth of those receiving any antidepressant, 174 (25.8%), and to a third compound for only 36 (5.3%) patients (Figure 4). Only two patients had undergone up to five antidepressant trials. During the whole treatment period, only TCAs were prescribed for 113 (14.1%), SSRIs only by 307 (38.2%), and other antidepressants only by 106 (13.2%). At least two different types of antidepressants were prescribed for 149 (18.6%). The median duration of the first antidepressant trial was about 10 months (median 44 weeks, range 0.4-524 weeks). Of the 675 patients 47 (7%) were on antidepressant combinations. No significant differences appeared between genders in terms of receiving only one or two antidepressants. No other augmentation medications were prescribed.

Figure 4. The three first antidepressants used, and changed. TCAs are in light green, SSRIs in blue, others in brown and no antidepressant at all in red. Width of borders of the boxes and of the arrows represent the number of patients using antidepressants or having their antidepressants changed. Numbers besides the arrows of the same colour represent number of antidepressant changed.



7.1.2.2 Antidepressants received by pensioned patients

During the treatment period, of the 655 not before pensioned, 125 (19%) were granted a disability pension due to the psychiatric reasons. Two-thirds (67%) of the pensioned patients had received only a single antidepressant trial or none at all, but 82% of the other patients. The first antidepressant trial was equally long for both groups (44 vs. 45 weeks, NS). Those patients granted a disability pension for major depression received TCAs more often than did others (31% vs. 11%). Being granted a disability pension was significantly associated with use of TCAs (Chi^2=29,5, df=1, p<0.0001). This finding remained significant after adjusting for possible confounding factors (age, gender, living with a partner, occupation, work status at the beginning of treatment, severity of depression, alcohol misuse, and use of anxiolytics, hypnotics, and neuroleptics) in the logistic regression model with stepwise backward elimination (odds ratio=2.17, Wald Chi^2=7.39, df=1, p=0.007, 95% CI=2.17 [1.24, 3.78]).

7.1.3 Patient drop-outs and refusal of treatment

One-fifth of the cohort (22%) were drop-outs from outpatient visits. In the logistic regression model, dropping out was significantly predicted by younger age (odds ratio per year of age=1.03, Wald Chi^2=7.72, df=1, p=0.006, 95% CI=1.03 [1.01, 1.05]), being employed at the beginning of treatment (odds ratio=1.60, Wald Chi^2=4.81, df=1, p=0.03, 95% CI=1.60 [1.05, 2.44]), and milder severity of depression (odds ratio=2.35, Wald Chi^2=17.83, df=1, p<0.0001, 95% CI=2.35 [1.58, 3.49]). The most common explanation for not receiving antidepressants was refusal. Subjective reasons for this were impossible to ascertain. Markedly more common refusals occurred among those with mild rather than more severe degrees of depression (8.0 % vs. 3.5 %, Chi^2=5.182, df=1, p=0.03), and were also associated with younger age and being employed after treatment.

7.1.4 Changes in work status and treatment of pensioned patients

Only a minimal change occurred in the proportion of employed patients at the end of the treatment period compared with at the beginning (Table 2). Pensioned patients (125) were significantly older than those not receiving a pension (mean ages 48.5 vs. 39.7 years, one-way ANOVA p>0.0001). Patients granted a work disability pension suffered more often from severe or psychotic depression than did others (58% vs. 42%, p=0.0001). Their psychosocial and medication treatment also was more intensive than the others': more visits to professionals than the others (mean 15.1 vs. 9.4, median 11 vs. 7, one-way ANOVA p=0.0003), and significantly more concomitant medications; including anxiolytics 53% vs. 36% (p=0.001), hypnotics 43% vs. 33% (p=0.03) and neuroleptics 42% vs. 29% (p=0.007).

7.2 Functional and work disability in depression (Study II)

7.2.1 Level of social and occupational functioning

Patients at the baseline of VDS suffered from functional disability currently ranging from mild to severe (SOFAS mean ± SD=51.8 ± 10.85, median=55.0, range 20 - 80). The most significant predictor of low SOFAS score was high severity of depression. Differences between in- or outpatients, or those at work or on sick-leave, were also very significant. Older age and any personality disorder, especially cluster A or C, were associated with lower SOFAS scores (Table 4). In a multivariate linear regression model adjustment for gender and age and with SOFAS as the dependent variable, severity of depression (Ham-D score) was the most significant factor associated with disability ($p<0.001$), and number of previous episodes of depression also predicted disability ($p=0.013$).

7.2.2 Social adjustment

Patients showed considerable variation in their social adjustment across different areas of social life. Both the mean and median overall SAS-SR scores were 2.47, range 1.33 to 3.69. In contrast to the findings related to SOFAS, Axis I and II comorbidity had a significant independent impact on patients' social adjustment. In the linear regression models, after adjusting for gender and age, we found that severity (Ham-D) ($p<0.001$ in overall score) and total duration of depression ($p=0.003$ for overall score), and phobic disorders ($p=0.001$ in overall score) were the most significant factors predicting poor social adjustment. Personality disorders had the most significant effect for the social and leisure subscale ($p<0.001$). Alcoholism was the dominant factor for the economic subscale ($p=0.002$), and phobic disorders were significant in the family-related subscales ($p=0.005$ in the extended family and $p=0.008$ in the family unit subscale).

Table 4. Differences between SOFAS and SAS-SR overall scores of the Vantaa Depression Study cohort according to sociodemographic and clinical characteristics.

SOFAS						**SAS-SR**				
	N	Mean	SD	M-Wz[a]	p	N	Mean	SD	M-Wz[a]	p
Gender										
Male	71	52.9	11.2			71	2.53	0.46		
Female	196	51.4	10.7			197	2.45	0.45		
Age group										
20 – 39	132	53.5	10.9			131	2.48	0.44		
40 – 59	135	50.2	10.6	-2.57	0.01	137	2.46	0.47		
In- or outpatient										
Inpatients	46	41.7	13.1			46	2.53	0.50		
Outpatients	221	53.9	9.0	-6.22	<0.0001	222	2.46	0.45		
Work status										
On sick-leave	67	46.5	10.7			68	2.50	0.46		
Working	89	57.9	7.4	-6.89	<0.0001	89	2.44	0.44		
Anxiety Disorder										
None	116	52.7	11.4			116	2.39	0.46		
Any	151	51.1	10.4			152	2.54	0.45	-2.49	0.013
Phobic Disorder										
None	158	52.5	10.8			158	2.39	0.45		
Any	109	50.8	10.9			110	2.60	0.44	-3.70	0.0002
Personality Disorder										
None	149	53.5	10.7			150	2.39	0.44		
Any	118	49.8	10.8	-2.73	0.006	118	2.58	0.45	-3.34	0.001
Cluster A										
No	216	52.5	10.9			217	2.46	0.47		
Yes	51	49.0	10.1	-2.33	0.02	51	2.54	0.39		
Cluster B										
No	228	52.1	11.0			229	2.44	0.46		
Yes	39	50.1	9.6			39	2.64	0.41	-2.62	0.009
Cluster C										
No	182	53.0	10.5			183	2.41	0.44		
Yes	85	49.4	11.3	-2.36	0.018	85	2.59	0.46	-2.67	0.008
Alcohol abuse or dependence										
No	201	52.4	10.1			203	2.42	0.46		
Yes	66	50.0	12.8			65	2.62	0.41	-2.95	0.003
	N	Mean	SD	K-W Chi[2b]	p	N	Mean	SD	K-W Chi[2b]	p
Severity of depression										
Mild	16	59.4	7.3			17	2.18	0.41		
Moderate	134	57.7	7.3			134	2.41	0.42		
Severe or psychotic	117	44.0	9.6	122.31	<0.0001	117	2.59	0.47	14.06	0.001

[a] M-W z = Mann-Whitney test, z, [b] K-W Chi^2 = Kruskal-Wallis test, Chi^2

7.2.3 Effect on sick-leave

The work status of the cohort at baseline is shown in Table 5.

Table 5. Work status of the Vantaa Depression Study cohort at baseline.

Work status	Male		Female		Total	
	N	%	N	%	N	%
Employed	33	45.8	56	28.4	89	33.1
Sick-leave	11	15.3	57	28.9	68	25.3
Unemployed	20	27.8	37	18.8	57	21.2
Student	3	4.2	21	10.7	24	8.9
Pensioned for psychiatric reason	3	4.2	7	3.6	10	3.7
Pensioned for somatic reason	0	0.0	3	1.5	3	1.1
Other	1	1.4	12	6.1	13	4.8
Unknown	1	1.4	5	2.0	6	2.2
Total	72	100.0	197	100.0	269	100.0

Two-fifths of 157, 68 (43%) of the employed patients were on sick-leave, with a significant gender difference: of 44 males, 11 (25.0%), vs. 57 (50.4%) of 113 females (Chi2=7.35, df=1, p=0.007). Furthermore, a strong non-linear relationship emerged between age and work status. Significantly more of the employed 20 to 49-year-old patients were at work compared to those 50 to 59 years old: of 125, 80 (64.0%), vs. 9 (28.1%) of 32, respectively, (Chi2=11.93, df=1, p=0.001).

Employed patients suffering from mild to moderate depression were more often at work than were those with severe to psychotic depression: of 92, 67 (72.8%) vs. 22 (33.8%) of 65(Chi2=22.01, df=1, p<0.0001). Patients at work had significantly lower Ham-D scores than did those on sick-leave in the paired t-test (17.0 vs.18.9, paired t=2.26, df=155, p=0.025). Patients on sick-leave had significantly more prior episodes of depression than did those at work (mean 2.00, range 0-20, vs. 1.06, range 0-5, Mann-Whitney p=0.027). In the older age group (40-59 years), patients with a somatic disease receiving medical treatment were more often on sick-leave than were those without: of 46, 24 (52.2%) vs. 13 (29.5%) of 44, (Chi2=3.87, df=1, p=0.049). Neither substance abuse of the 35 on sick-leave, affecting 12, Chi2=1.06, df=1, p=0.303) nor personality disorders of the 72 on sick-leave, 34 (Chi2=0.56, df=1, p=0.454) had a significant impact on likelihood of sick-leave. Independent predictors of sick-leave in the final

logistic regression model were female gender, age, severity of depression, and number of episodes of depression (Table 6).

Table 6. Results of the multivariate logistic regression model of the Vantaa Depression Study patients at work or on sick-leave.

Variable	Logistic coefficient	S.E	P-value	Odds ratio	95% confidence interval
Female gender	1.3738	0.4456	0.0020	3.9502	1.65 - 9.46
Age	0.0520	0.0192	0.0068	1.0534	1.01 - 1.09
Ham-D	0.0765	0.0346	0.0269	1.0796	1.01 -1.16
Number of episodes of depression [a]	0.4587	0.2195	0.0366	1.5821	1.03 - 2.43

[a] = Classified as none, one, or two or more previous episodes, Ham-D = Hamilton Rating Scale for Depression

7.3 Functional disability and social adjustment in MDD (Study III)

7.3.1 Sociodemographic and clinical characteristics of the cohort

During the follow-up from baseline through 6 to 18 months, patients' symptoms of depression dissolved, global disability was alleviated, and social adjustment was strengthened. Both social and occupational functioning (lower worst) and social adjustment values (higher worst) correlated well at 6 and 18 months (Pearson Correlation -0.605 and -0.547, respectively, both significant at the 0.01 level).

Patients included in the follow-up were significantly (nearly 5 years) older than those not in the follow-up cohort (age 36.1 years, ANOVA F=11.24, p=0.001). Groups did not differ from each other in terms of the other characteristics in Table 7. During follow-up, symptoms of depression, anxiety, and hopelessness diminished, and patients perceived their social support as a little better. Their disability, assessed by all tools used, was alleviated. Patients' clinical data at baseline and at 6 and 18 months are shown in Table 8.

Table 7. Sociodemographic and clinical characteristics of MDD patients at baseline in the follow-up study.

Variable	Baseline N=193	
Sociodemographic characteristics		
Age, years (S.D.)	41.0	(11.1)
Females (%)	139	(72.0)
Married or cohabiting (%)	104	(53.9)
Secondary school level of education (%)	68	(35.2)
Below secondary school level (%)	125	(64.8)
Clinical characteristics		
Outpatients (%)	163	(84.5)
No previous episodes of depression (%)	65	(33.7)
One or more episodes of depression (%)	128	(66.3)
Achieved full remission during follow-up time (%)	117	(60.6)
Did not achieve full remission during follow-up (%)	76	(39.4)

Table 8. Baseline, 6-, and 18-month clinical data for MDD patients (N=193) in the follow-up study.

Variable	Baseline		6 months		18 months	
	Mean	SD	Mean	SD	Mean	SD
Ham-D [a]	17.1	5.3	8.2	6.7	7.1	6.4
BDI [b]	25.8	7.9	11.9	9.0	10.4	9.5
BAI	21.5	10.6	13.2	9.8	11.6	10.3
PSSS-R	39.1	12.9	41.9	12.9	42.6	13.5
HS	10.1	4.7	7.5	5.2	6.4	4.8
SOFAS [c]	52.4	10.4	67.2	14.4	72.5	14.4
SAS-SR overall [d]	2.4	0.4	2.1	0.5	2.0	0.4
Number of days spent ill in bed from baseline			12.8	28.0	21.8	53.2

[a] =Without item 7, ability to work, [b] =Without item 15, ability to work, [c] = One value missing at baseline and at 18 months, [d] = One value missing at 18 months, Ham-D, Hamilton Rating Scale for Depression, BDI, Beck Depression Inventory, BAI, Beck Anxiety Inventory, PSSS-R, Perceived Social Support Scale – Revised, HS, Beck Hopelessness Scale, SOFAS, Social and Occupational Functioning Assessment Scale for DSM-IV, SAS-SR, Social Adjustment Scale-Self Report, overall score

7.3.2 SOFAS and SAS-SR univariate analyses

The most important factors predicting social and occupational disability and poor social adjustment at the18-month follow-up in ANOVA analyses were recurrent depression at baseline (two or more lifetime episodes) (in SOFAS p=0.004 and SAS-SR p=0.005) and not achieving full remission during follow-up (in SOFAS p<0.001 and SAS-SR p<0.001). Having either any, or specifically, a cluster C (obsessive-compulsive, dependent, avoidant, and passive-aggressive) personality disorder was an important factor predicting social and occupational disability (any or none p=0.006 and cluster C p=0.006) and poor social adjustment any or none p=0.002 and cluster C p=0.017). During the course of depression, the social adjustment of women (p=0.015) improved significantly more than did men's. Similar better improvement was also as a trend in social and occupational functioning for women (p=0.056). The older age group was slightly more disabled than was the younger.

7.3.3 Predictors of disability from baseline to 6 months

SOFAS values and overall scores of SAS-SR at 6 months were analysed by a linear regression model, with these independent factors at baseline: gender, age, marital status, Ham-D, and phobic disorders including agoraphobia, specific and social phobia, alcoholism, any personality disorder, any somatic disease for which patients were receiving medical treatment, and BAI and PSSS-R. The strongest predictive factors for SOFAS were BAI (p=0.001), PSSS-R (p=0.002), and number of previous episodes of depression (p=0.008), and for SAS-SR, overall scores were BAI (p<0.001) and PSSS-R values (p=0.001) and number of previous episodes of depression (p=0.001): classified as none or as one or more previous episodes.

7.3.4 Predictors of disability from 6 to 18 months

SOFAS values and overall scores of SAS-SR at 18 months were analysed by a linear regression model, with the independent factors at 6 months mentioned above. The most significant factors predicting SOFAS at 18 months were degree of depression (Ham-D; p<0.001), perceived social support (p=0.002), and having any previous episode of depression (p=0.040). Poor social adjustment was mostly associated with lack of perceived social support (p<0.001) and higher scores of neuroticism (p<0.001). Degree of depression at 6 months was significant to a lesser degree (p=0.036).

7.3.5 Predictors of disability at 18 months

Factors predicting disability and problems in social adjustment at 18 months were analysed by linear regression models with other factors as described in statistical methods. Current degree of depression (Ham-D; p<0.001), higher BAI score (p=0.039), worse perceived social support (p=0.005), shorter time in full remission during 18 months (p=0.004), and relapse or recurrence during 18 months (p=0.010) were very

significant factors predicting poor social and occupational functioning. Poor social adjustment was significantly associated with the degree of depression (p=0.025), higher BAI score (p<0.001), worse perceived social support (p<0.001), relapse or recurrence during 18 months (p=0.001), and higher neuroticism score (p<0.001).

7.3.6 Predictors of days spent ill in bed

Nearly half (90 of 193, 46.6%) of the patients spent at least one day ill in bed because of depression during the whole 18-month follow-up time (range from 2 to 500, mean values in Table 8). Excluding those with no bed days, mean ± SD for number of days spent ill in bed was 46.7 ± 70.2 and median 20.0 days during the whole follow-up time. In the logistic regression model, we found that the most significant factors predicting days spent ill in bed (dichotomized to no or any days spent ill in bed) were severity of depression (Ham-D) at baseline (p=0.001), time spent in MDE during 18 months (p=0.018), and having any phobic disorder (p=0.046).

7.4 Long-term work disability in MDD (Study IV)

7.4.1 Sociodemographic and clinical differences

In the 18-month follow-up 186 patients participating were not pensioned at baseline. Of these 21 (11.3%) were granted a disability pension during the 18-month follow-up. The patients who had received a pension were significantly older, less often had vocational education and were more often on sick leave than those not pensioned, but did not differ with regard to any other sociodemographic or clinical factors (Table 9.). However, at the 6-month follow-up, these groups had differed in nearly all variables, with these differences diminishing over the following year (Table 10). Two-thirds (14 of 21, 67%) of pensioned patients vs. one-fourth (42 of 161, 25%) of those not pensioned (df=1, Chi2=13.6, P<0.001) were on sick leave at baseline. The mean time spent in major depressive episodes (MDEs) was 10.6 months for pensioned patients and 4.1 months in non-pensioned patients (ANOVA F=34.4, P<0.001, medians 13.7 and 2.5 months, respectively). One-third (7 of 21) of pensioned patients vs. only 3% of the others (5 of 165, df=1, Chi2=23.5, P<0.001) did not reach even partial remission during follow-up. Social phobia was the only Axis I or II comorbid disorder to be more common among pensioned patients (8 of 21, 38% vs. 25 of 165, 15%, df=1, Chi2=5.2, P=0.022).

In a logistic regression analysis adjusted for gender, age, and severity of depression, greater age, hopelessness, disability, and no vocational education predicted disability pension (Table 11). The time spent in MDE during the 18 months was very significant when included in the model, with hopelessness remaining only a trend (Table 12). Finally, we analysed the same model, including the variable “being on sick leave” at baseline, and omitting SOFAS to avoid circularity. In this model, male gender became significant and hopelessness disappeared. After all adjustments, the risk for being

granted a disability pension during the next 18 months was markedly elevated (OR 6.1) among patients on sick leave at baseline (Table 13).

Table 9. Sociodemographic and clinical data at baseline for patients pensioned or not pensioned at the 18-month follow-up.

	Not pensioned (n=165)		Pensioned (n=21)		Total (n=186)	
Female, n (%)	120	72.7	14	66.7	134	72.0
Age at 18-month, mean (SD) [a]	40.8	10.5	52.4	7.6	42.1	10.8
Married or cohabiting, n (%)	87	52.7	13	61.9	100	53.8
No vocational education, n (%) [b]	61	37.0	13	61.9	112	60.2
Inpatients, n (%)	22	13.3	4	19.0	160	86.0
On sick leave, n (%) [c]	40	24.2	14	66.7	54	29.0
Severity of depression						
Mild, n (%)	9	5.5	2	9.5	11	5.9
Moderate, n (%)	92	55.8	7	33.3	99	53.2
Severe without psychotic sympt. n (%)	61	37.0	12	57.1	73	39.2
Severe with psychotic sympt. n (%)	3	1.8	0	0.0	3	1.6
Recurrence of depression						
First episode, n (%)	61	37.0	4	19.0	65	34.9
Recurrent depression, n (%)	104	63.0	17	81.0	121	65.1
MDD without comorbidity, n (%)	39	23.6	3	14.3	42	22.6
Axis I comorbidity						
Dysthymia, n (%)	15	9.1	4	19.0	19	10.2
Any anxiety disorder, n (%)	88	53.3	13	61.9	101	54.3
Any alcohol use disorder, n (%)	35	21.2	3	14.3	38	20.4
Axis II comorbidity						
Any personality disorder, n (%)	68	41.2	12	57.1	80	43.0
Cluster A, n (%)	31	18.8	5	23.8	36	19.4
Cluster B, n (%)	23	13.9	4	19.0	27	14.5
Cluster C, n (%)	49	29.7	9	42.9	58	31.2

[a] = ANOVA $F=24.1$, $p<0.001$, [b] = $Chi^2=3.9$, $p=0.050$, [c] = $Chi^2=14.3$, $p<0.001$

Table 10. Mean and standard deviation (SD) values of univariate analyses of patients pensioned or not pensioned at the 18-month follow-up.

	Not pensioned		Pensioned		F	P
BDI at baseline, mean (SD)	25.5	7.7	27.8	8.1	1.7	0.188
BDI at 6 months, mean (SD) [a]	10.7	8.7	19.4	8.4	18.9	<0.001
BDI at 18 months, mean (SD) [b]	9.9	9.4	15.2	9.8	5.9	0.016
Ham-D at baseline, mean (SD)	16.9	5.3	19.6	4.3	4.9	0.028
Ham-D at 6 months, mean (SD) [a]	7.4	6.5	13.3	6.5	15.3	<0.001
Ham-D at 18 months, mean (SD)	6.7	6.2	10.4	6.9	6.4	0.012
SOFAS at baseline, mean (SD) [b]	53.6	10.2	47.2	6.7	7.7	0.006
SOFAS at 6 months, mean (SD) [a]	69.4	13.8	53.9	8.0	25.1	<0.001
SOFAS at 18 months, mean (SD) [b]	73.9	13.8	65.6	14.8	6.5	0.012
SAS-SR overall at baseline, mean (SD)	2.4	0.4	2.6	0.3	3.5	0.062
SAS-SR overall at 6 months, mean (SD) [c]	2.0	0.5	2.4	0.3	13.7	<0.001
SAS-SR overall at 18 months, mean (SD) [d]	2.0	0.5	2.1	0.4	1.2	0.271
BAI at baseline, mean (SD)	21.1	10.8	27.6	8.2	7.0	0.009
BAI at 6 months, mean (SD) [a]	11.9	9.3	22.0	7.4	22.8	<0.001
BAI at 18 months, mean (SD)	10.9	10.0	15.4	10.5	3.7	0.057
PSSS-R at baseline, mean (SD)	39.6	12.7	34.3	12.6	3.2	0.075
PSSS-R at 6 months, mean (SD) [a]	42.9	12.8	35.5	12.4	6.3	0.013
PSSS-R at 18 months, mean (SD)	43.5	13.0	37.6	16.6	3.6	0.058
HS at baseline, mean (SD)	9.9	4.6	12.8	4.1	7.7	0.006
HS at 6 months, mean (SD) [a]	6.8	5.0	11.7	4.2	18.2	<0.001
HS at 18 months, mean (SD) [d]	6.1	4.8	8.6	5.4	5.1	0.025
SSI at baseline, mean (SD) [b]	5.5	7.4	10.6	9.6	8.2	0.005
SSI at 6 months, mean (SD) [e,f]	1.6	4.1	3.6	7.5	2.6	0.107
SSI at 18 months, mean (SD) [a, f]	1.2	3.8	3.0	6.7	3.0	0.084

[a] = Data on 5 patients missing in not-pensioned group, [b] = Data on one patient missing in not-pensioned group, [c] = Data on 4 patients missing in not-pensioned group, [d] = Data on 2 patients missing in not-pensioned group, [e] = Data on 56 patients missing in not-pensioned group, [f] = Data on 4 patients missing in pensioned group

Table 11. Logistic regression model of significant clinical baseline variables. The dependent variable is either being pensioned or not pensioned at the 18-month follow-up.

Variable	B	S.E.	Wald	P	OR	95% CI for B
Age	0.144	0.041	12.327	0.0004	1.155	1.066; 1.251
HS	0.204	0.073	7.683	0.0056	1.226	1.061; 1.415
SOFAS	-0.075	0.030	6.200	0.0128	0.928	0.875; 0.984
No vocational education	1.241	0.580	4.576	0.0324	3.461	1.110; 10.792

HS = Beck Hopelessness Scale , SOFAS = Social and Occupational Functioning Assessment Scale.

Table 12. Logistic regression model of significant clinical baseline variables and time spent in MDE during the 18-month follow-up. The dependent variable is either being pensioned or not pensioned at follow-up.

Variable	B	S.E.	Wald	P	OR	95% CI for B
Age	0.144	0.045	10.227	0.0014	1.155	1.057; 1.262
HS	0.150	0.079	3.616	0.0572	1.162	0.995; 1.356
SOFAS	-0.069	0.031	4.855	0.0245	0.933	0.877; 0.992
Time in MDE	0.152	0.048	9.948	0.0016	1.164	1.059; 1.279
No vocational education	1.449	0.644	5.056	0.0245	4.258	1.204; 15.051

HS = Beck Hopelessness Scale, SOFAS = Social and Occupational Functioning Assessment Scale, MDE = Major depressive episode

Table 13 Logistic regression model of significant clinical baseline variables, time in MDE during the 18-month follow-up, and being on sick leave at baseline. The dependent variable is either being pensioned or not pensioned at follow-up.

Variable	B	S.E.	Wald	P	OR	95% CI for B
Gender	-1.772	0.813	4.758	0.0292	0.170	0.035; 0.835
Age	0.141	0.047	9.137	0.0025	1.151	1.051; 1.261
Time in MDE	0.184	0.049	14.079	0.0002	1.202	1.092; 1.323
No vocational education	1.242	0.648	3.670	0.0554	3.461	0.972; 12.327
Being on sick-leave at baseline	1.804	0.688	6.867	0.0088	6.074	1.576; 23.412

MDE = Major depressive episode.

7.4.2 Treatment

Pensioned patients had been treated somewhat more intensively than the others. All pensioned patients were on antidepressants at baseline, whereas of 165 non-pensioned patients, 23 (14%) had none (Fisher's exact test, p=0.081). At 6 months, of 21 pensioned patients, 17 (81%) had used antidepressants uninterruptedly from baseline vs. 87 (53%) of 165 their counterparts (df=1, Chi^2=4.930, P=0.026); at 18 months the corresponding figures were 14 (67%) of 21 and 70 (42%) of 165 (df=1, Chi^2=3.496, p=0.062). The median number of visits to doctors during the 18 months was also higher (6.0) among the pensioned patients than among those not pensioned (2.0) (Mann-Whitney test, Z=-4.051, p<0.001). The median number of visits to any personnel was 19.0 vs. 14.0 visits, respectively (NS).

No other significant differences were found in other aspects of treatment, attitudes towards treatment, or adherence to it. All but one (95.2%) of the pensioned and of 142, 116 (81.7%) of the non-pensioned patients received adequate antidepressant treatment in the acute phase of MDE. Antidepressant combinations were received during follow-up by 5 of 21 (23.8%) vs. 25 of 165 (15.2%). Of 21 pensioned patients, 2 (10%) vs. 26 (16%) of 165 non-pensioners received weekly psychotherapy. Patients' attitudes towards medication did not differ significantly either; of 21, 1 (5%) pensioned patient vs. 27 (16%) of 165 of others reported a negative attitude towards antidepressants. Of the pensioned subjects, 19 (95.0%) of 20 reported having taken antidepressants regularly or somewhat irregularly, among the non-pensioned of 106, 96 (90.6%). Of the pensioned patients of 21, 5 (23.8%) had been hospitalized (1 to 4 times) either during baseline or follow-up vs. 33 (20%) of 165 (1 to 14 visits) of those not pensioned. The mean length of hospital stay for pensioned patients was 33.8 days (SD 14.9) vs. 44.9 days (SD 57.3), respectively.

8. DISCUSSION

8.1 Main findings

The most important finding in the record-based study (I) was that the majority of psychiatric patients treated in psychiatric settings were likely to receive antidepressants in doses found effective in clinical trials. However, the quality-of-care problems were quite different from their past quality-of-care problems.

Of the baseline factors, the follow-up (Study II) found severity of depression to be the dominant factor explaining all types of disability among patients with major depressive disorder, as in other studies (Judd et. al., 2000; Sorvaniemi et al. 2003). The preceding history of depressive illness, presence of comorbid mental and physical disorders, gender, and age were each significantly associated with at least some aspects of disability. During follow-up (Study III), concurrently with recovery from depression, patients' overall functioning and social adjustment were markedly alleviated. Although multiple factors predicted disability at various time-points, current level of depression and cumulative history of depression were the two most robust predictors of disability and adjustment. In addition, psychiatric comorbidity, plus social support as perceived by the patient were also consistent predictors. Factors associated with being on sick-leave at baseline were not necessarily identical to those associated with functional and social disability or poor adjustment.

Factors associated with work disability (Study IV) were somewhat different from those of disability and adjustment. Many sociodemographic and clinical factors clearly predicted long-term work disability among psychiatric patients with MDD. Even after adjusting for clinical variables, the sociodemographic factors of older age and lack of vocational education independently predicted disability pension. Of the baseline clinical predictors, hopelessness was the strongest, but level of disability and lack of vocational education also had an effect. Thus those who are most hopeless about their future appear to more often eventually be granted a work disability pension. During follow-up, slow recovery from depression (time spent in MDEs) was one of the strongest factors affecting patients' work ability. A major public health policy issue is the role of sick-leaves. Being on sick leave at baseline strongly predicted (OR 6.1) disability pension, even after adjusting for all other significant predictors.

8.2 Methods

8.2.1 Study cohorts

8.2.1.1 Record-based study cohort

The major strength of this record-based study is that it was based on a large patient population representing psychiatric secondary care in Finland's fourth largest city. We could not include patients who had visited private psychiatrists outside the PMCD, or the very few treated at Helsinki University Central Hospital. Based on another study (Knudsen et al., 1992) and an unpublished epidemiologic survey of the city of Vantaa, we estimated our sample to represent two-thirds of all depressed subjects in the general population of Vantaa seeking psychiatric treatment (Isometsä & Lönnqvist, unpublished data, 1999). Thus, we expect our findings to be generalizable in secondary care settings in Finland (Sorvaniemi et al., 1998) in the latter half of the 1990s and, given their similarities to findings from some other recent studies, (Bingefors et al., 1997; Nurnberg et al., 1999; Sirey et al., 1999; Donoghue, 2000) to psychiatric settings in other Western countries as well.

The data were collected from a computerised database comprising the full psychiatric patient records of the catchment area. We consider the quality of these comprehensive records available to us to be good, which allowed us to investigate the clinical characteristics and the treatments received in more detail than in previous investigations.

8.2.1.2 Prospective study cohort

As in the record-based study, this relatively large cohort also represents well the secondary-level psychiatric in- and outpatients from a well-defined urban catchment area. Drop-outs from the main cohort during the follow-up were quite rare, because 87% of the baseline cohort could be interviewed at least once after baseline. In Study III, patients who had completed the entire follow-up study represented 72% (193 of 269) of all the subjects interviewed at baseline, and in Study IV 69% (186 of 269) of the baseline cohort. The gender distribution of VDS (73% females) is quite similar to many other well-defined MDD cohorts (Stuart et al., 1992, Pepper et al., 1995, Sato et al., 1996). However, the proportion of women was somehow higher in this age group than in some Finnish epidemiological studies (Lehtinen & Joukamaa, 1994 Lindeman et al., 2000). The over-representation of women might be a result of the different health behaviour of men. It is possible that they do not seek help as often as women, and perhaps they solve their problems easily with alcohol.

8.2.2 Validity and reliability of the diagnoses

8.2.2.1 Record-based study

This study was based on clinical diagnoses of depression, the validity of which was randomly estimated as good according to data from psychiatric records. The possibility of false-negative, undiagnosed cases cannot, however, be excluded. Psychiatric records were carefully investigated to exclude false-positive cases likely to have had some other psychiatric disorder.

8.2.2.2 The VDS cohort study

In the follow-up study, unlike in any preceding study, the effect of the whole spectrum of Axis I and II comorbidity of MDD patients on their social and occupational functioning, social adjustment, and work ability were possible to examine. Axis I diagnoses were made by SCAN-interview having an excellent reliability (kappa=0.86) for the diagnosis of MDD. Axis II diagnoses were made by the semi-structured SCID-II interview for DSM-III-R, because the SCID II for DSM-IV was not yet available in February 1997. Differences between DSM-III-R and DSM-IV were taken into account.

8.2.3 The life-chart methodology

During the follow-up we assessed the course of depression by using a life-chart methodology. This Longitudinal Interval Follow-up Evaluation (LIFE) was first used to investigate the outcome of depression in the NIMH-CDS (Keller et al., 1987). We inquired about change points in the psychopathologic state, using probes related to important events. In the VDS the outcome of MDD was investigated by use of a graphic life chart, which is quite similar to the LIFE.

8.2.4 Measuring functioning, adjustment, and work disability

The SOFAS scale was used to measure global level of functioning at the time of evaluation. This scale measures purely the level of social and occupational functioning, without taking symptoms into account.

8.2.5 Limitations of the studies

8.2.5.1 The record-based study (I)

The validity of depression diagnoses in this study were estimated to be good, but making diagnoses only according to psychiatric records involves many difficulties. The possibility of false-negative, undiagnosed cases also cannot be excluded. Since the study population was based on the 12-month prevalence of depression in the PMCD, inclusion of cases was influenced both by the incidence of depression and by the duration of treatment period, which enriches chronic patients in the population.

However, as such, the population accurately represents the caseload of the attending personnel. Work disability and pensions in this study were based on the data in the medical records.

8.2.5.2 Baseline findings of the VDS cohort study (II)

Measuring pure disability without taking into account severity of symptoms is the ideal, but some contamination of the symptom ratings is hard to avoid, even with the SOFAS with a good validity (Hilsenroth et al., 2000; Hay et al., 2003). Furthermore, patients' insight regarding their disability in interview, or in the self-reported SAS-SR, may vary. Moreover, as most of the SAS-SR subscales are relevant only for a subgroup of patients, the overall score comprises a variable composition of subscales relevant for each of the patients, but uniformly scored. Whereas the psychometric properties of the subscales were acceptable in all cases, and in some of them were good, some others were far from ideal. We therefore considered it important to study not only patients' views of their functional status, but also their objective functioning and ability to work.

8.2.5.3 Functional disability and social adjustment (III)

We analysed only those 193 who remained unipolar and had complete data from every interview. Those not included were significantly younger than the study cohort, but in other characteristics the groups did not differ. We used three main measures of disability, objective SOFAS and subjective self-rated SAS-SR and number of days spent ill in bed. Measurement of pure functional disability comprises numerous methodological difficulties. SOFAS and SAS-SR include some problems mentioned earlier. Accuracy of estimating number of days in bed may vary. In order to exclude possible circularity, we tested the correlations between SAS-SR and PSSS-R with and without family-related items, and both of them gave the same results. Similarly, current depressed state complicates diagnosing current comorbid mental disorders, particularly personality disorders, or assessments of personality features. However, this is not different from clinical diagnostic evaluations, which must be based on the information currently available. We decided not to use treatment received as a predictor for functional outcome, as it was largely driven by perceived need (i.e., severity of depression), and we assumed its impact on functional status to be mediated via impact on outcome of depression per se, which was an important predictor. Finally, as the characteristics of our patients and outcome of their depression and functional status are largely in line with other studies (Isometsä et al. 2000; Judd et al. 2000a; Hays et al. 2001; McDermut et al. 2001), we believe that our findings are mostly generalizable to other psychiatric settings.

8.2.5.4 Long-term work disability study (IV)

Our study sample comprised only 69% (186 of 269) of the unipolar MDD patients of our initial cohort since only those patients who were potential labour force contributors

at baseline were included. Moreover, part of the initial cohort dropped out, and some switched to bipolar disorder. The relatively small number of pensioned patients limits the statistical power of results and might also increase the risk for spurious findings. However, our findings were found to be statistically highly significant. The main measure of disability was SOFAS, which may have some contamination between symptoms of depression and those of comorbid disorders. As this measure contains ability to work as one of its major domains, it was clearly circular with being on sick leave, and could not be used as a predictor in all analyses.

8.3 Treatment received for depression in psychiatric care (Study I)

The main finding in this study was that the large majority of depressed patients received adequate antidepressant treatment, although often in low doses. Inadequate treatment was common only among those receiving TCAs, whereas treatment with newer antidepressants almost always occurred with doses found to be effective in clinical trials. In the earlier studies conducted in the 1980s, antidepressant treatment received by psychiatric patients was generally found to be absent or inadequate (Keller, 1988). Some recent smaller studies (Sorvaniemi et al., 1998) have indicated improvement in the quality of care during the last decade. It should be noted that mirtazapine and venlafaxine entered the Finnish market in 1996, so only a few patients in our study received them. The median duration of the treatment period was found to be over one year; thus, acute, continuation, and maintenance treatment phases were probably included in most cases. The modest intensity of the treatment provided, largely due to limited resources in terms of monitoring antidepressant treatment as well as psychosocial treatments, is clearly a problem. Most patients visited psychiatrists only one to three times. However, even considering this, we found the psychiatrists to have been quite conservative in switching antidepressants. This was true even when poor response was obvious, e.g., in those granted a disability pension.

Depression-related functional disability (Broadhead et al., 1990; Wells et al., 1989) and the necessity of disability pensions (Isometsä et al., 2000) due to depression are major losses to both the individual and society. Treatment of depression has been shown to markedly reduce depression-related disability (Mintz et al., 1992). In our sample, one-fifth of those not already receiving a disability pension were granted one during the treatment period investigated. Patients in this subgroup were considerably older and more severely ill, used more concomitant psychotropic medication, and had slightly more visits to professionals than did patients in other subgroups. Nevertheless, about two-thirds of these patients (67%) received a disability pension after only a single trial of an antidepressant.

We have also made a similar finding in another nationally representative study of patients with major depression who were granted a disability pension in Finland (Isometsä et al., 2000). Furthermore, use of TCAs, often in inadequately low doses, was

more common (31% vs. 11%) among patients granted a disability pension during the study period than among the other patients. While it remains unknown whether more intensive pharmacotherapy or psychosocial treatment could have prevented their permanent disability, it is at least obvious that more intensive treatment efforts are warranted. Our concern is that cutting costs in the quality of care may result in much higher permanent costs to society.

8.4 Functional and work disability in depression (Study II)

Severity of depression was the dominant factor explaining all types of disability among patients with major depressive disorder, but not the sole factor. The preceding history of depressive illness, presence of comorbid mental and physical disorders, gender, and age were each significantly associated with at least some aspects of disability. Furthermore, factors associated with functional and social disability or poor adjustment were not necessarily identical to those associated with being on sick-leave.

In the VDS cohort study we used the SOFAS scale to measure global level of functioning at the time of evaluation. Our patients suffered from variable functional impairment, although moderate to serious on average. The level of disability emerged as strongly associated with the severity of depression, which accords with most studies of clinical depression (Wells et al., 1989; Tollefson et al., 1993; Leader & Klein, 1996; von Korff et al., 1992) including the NIMH Collaborative Depression Study (Judd et al., 2000a), exceptions being some studies with relatively homogeneous inpatient populations (Goethe & Fischer, 1995; Lyness et al., 1993).

However, even after adjusting for current severity and other possible confounding factors, the number of previous episodes of depression was significantly associated with current level of functioning. Our results further support findings that poorer functional status is associated with older age (Lyness et al., 1993) and personality disorders (McDermut et al., 2001; Skodol et al., 2002). There were also interesting, albeit slight differences between our findings with the SOFAS and the SAS-SR. Global functional status estimates with the SOFAS appear most strongly influenced by severity and recurrences of depression. In contrast, the SAS-SR is an indicator of broader social adjustment, and more reflects problems related to other aspects of psychopathology, such as substance abuse, personality disorders, and phobic avoidance. Nevertheless, severity of depression was still the major factor explaining problems in social adjustment as measured by the SAS-SR overall scale. Differences between age groups or genders were seen only in the family unit subscale, which reflects functioning in family roles.

Depression leads to major costs to society due to decreased work performance and days lost from work (Mintz et al., 1992; Kessler & Frank, 1997; Hensing et al., 2000, Druss et al., 2000 Druss et al., 2001). In our representative sample, two-fifths of the employed patients with MDD were on sick-leave. This was more common among females, older

patients, and those with somatic diseases, as in earlier reports (Hensing et al., 2000; Lyness et al., 1993). It appears that many patients, particularly males, with moderate to severe depression are working despite obvious impairments. Of particular clinical importance is the finding that not only current severity, but also number of previous episodes were clearly related to being on sick-leave. Other studies have found recurrent depression to be a significant predictor of poor functioning (Basso & Bornstein, 1999; Sheline et al., 1999) or poor work adjustment (Bauwens et al., 1998), but this is the first to show its relation to actual work absence, even adjusting for current severity of depression. This finding emphasizes the important role of maintenance treatment to prevent recurrences and work disability related to MDD Alternative explanations, such as patients' learning to seek sick-leaves after successive episodes, or greater acceptance of sick-leave by doctors in cases with previous episodes, are possible but unlikely, given the consistently lower SOFAS in recurrent cases. Therefore, whether actual work disability (in contrast to sick-leave) really increases after each successive episode of depression should be investigated in prospective studies.

8.5 Functional disability and social adjustment in MDD (Study III)

Concurrently with recovery from depression, patients' overall functioning and social adjustment were markedly alleviated. Although multiple factors predicted disability at various time-points, current level of depression and cumulative history of depression were the two most robust predictors of disability and adjustment. In addition, psychiatric comorbidity, plus social support as perceived by the patient were also consistent predictors.

In this study was hypothesised that not only would current severity of depression affect functioning, but also that the preceding course of illness would have an independent effect on level of functioning. Findings from earlier studies have not been fully consistent. For example, in a meta-analysis, Mintz et al. (1992) found alleviation of depression and improvements in functional capacity to work to follow a somewhat different trajectory. In contrast, Judd et al (2000a) in the NIMH Collaborative Depression Study found functional disability to be largely state-dependent, patients were disabled while depressed, but when asymptomatic, level of functioning improved markedly. In our study, both current severity and preceding course of depression were powerful predictors of functional status, as hypothesised. It may well be true that depressive episodes have enduring adverse consequences for life structure (Coryell et al. 1993). Alternatively, it is possible that their effect is a reflection of more fundamental illness processes such as long-term deficiencies in neuropsychological functioning caused by repeated illness episodes (Basso and Bornstein, 1999). Previous follow-up studies have found that severity (Melartin et al. 2004) and recurrence of depression (Ormel et al. 2004) are the most important independent predictors of symptomatic outcome. The present findings highlight the importance of the cumulative course of the illness specifically for disability in depression.

Another hypothesis was that the presence of psychiatric comorbidity (Isometsä et al. 2000; McDermut et al. 2001), perceived social support (Hays et al. 2001), and certain personality traits (Lyness et al. 1998) would each determine disability independently. Overall, this prediction appears to have been mostly correct. We examined all comorbid Axis I and II disorders and found comorbid anxiety symptoms to be a determinant of functional disability and social adjustment over the whole follow-up period. Anxiety disorders are often temporally primary and long-lasting, and may both predispose to and worsen outcome of depression (Wittchen et al., 2000; Melartin et al., 2004). In contrast, it appeared that comorbid personality disorders per se had only a limited independent effect on disability. However, similar to findings concerning elderly depressed patients (Lyness et al. 1998), we found neuroticism as a personality trait affecting social adjustment. Even after adjusting for possible confounders and level of depression, patient-perceived social support seemed to play an important role in our cohort, more in ours than in other studies (Hays et al. 2001). Overall, it seems that disability among patients with depression cannot be explained merely in terms of current or preceding depression, but is also significantly related to symptoms of comorbid disorders, personality traits, and the social network as the patient perceives it.

8.6 Long-term work disability in MDD (Study IV)

Many sociodemographic and clinical factors clearly predict long-term work disability among psychiatric patients with MDD. Even after adjusting for clinical variables, the sociodemographic factors of older age and lack of vocational education independently predicted disability pension. Of the baseline clinical predictors, hopelessness was the strongest, but level of disability and lack of vocational education also had an effect. Thus those who are most hopeless about their future appear to more often eventually be granted a work disability pension. During follow-up, slow recovery from depression (time spent in MDEs) was one of the strongest factors affecting patients' work ability. A major public health policy issue is the role of sick leaves. Being on sick-leave at baseline strongly predicted (OR 6.1) disability pension, even after adjusting for all other significant predictors.

Older age was a major factor predicting work disability and disability pension, even after adjusting for other predictors. After adjusting for other possibly significant factors, lack of vocational education clearly predicted long-term work disability. This finding was convergent with a US study by Elinson et al. (2004), although we found no differences related to marital status. Being granted a disability pension for depression is obviously dependent on other factors in addition to clinical ones.

Several clinical factors were found to significantly predict long-term work disability. Of the baseline variables, hopelessness was more pronounced and functional disability worse among the pensioned than among the other patients. In our view, subjects who see their future in negative terms may be more inclined to cope with their depression by

seeking a long-term disability pension. Furthermore, poor level of functioning in the acute phase is, hardly unexpectedly, a strong predictor of disability also during follow-up. Contrary to the findings of Spijker et al. (2004) in the Dutch general population, duration of MDE was in pensioned patients significantly longer, and one-third did not reach even partial remission. At six months, the differences between groups were greatest in nearly all measures, which also reflects the slow recovery from depression. Severity and number of previous episodes of depression and comorbidity were not effective predictors of long-term work disability; their role was overshadowed by the impact of time spent in MDEs during follow-up.

Surprising was the strong role of being on sick leave at baseline as a predictor of disability pension later, even after adjusting for the other predictors for disability pension. Thus, of patients with apparently similar clinical characteristics, those who are currently on sick leave seem to have a markedly higher probability of pension in the future. This finding is unlikely to be tautological, i.e., merely due to preceding long sick-leaves being a precondition for a pension to be granted. The study design was prospective, and the majority of patients on sick-leave at baseline returned to work or unemployment during follow-up. However, a major limitation in our study was that we were not able to measure motivational factors related to work that may also influence seeking a pension. To our knowledge, this research area has not been investigated in other studies concerning depression and disability, but it is obviously a major health policy issue. Studies of somatic diseases (Rabkin et al., 2004) have found that returning to work is difficult after time out of work-life. The extent to which sick leaves have adverse, disability-reinforcing or negative motivational consequences among patients with depression warrants further investigation.

A previous study focusing on the early 1990s (Isometsä et al, 2000) found pharmacotherapy among subjects granted a disability pension for depression to have been largely suboptimal. In the present study, all of the pensioned patients received antidepressants at baseline, and in nearly all cases, the treatment was classified as adequate. Thus, disability is unlikely to have been caused by inferior treatment. However, given the high costs related to disability, the intensity of treatment provided was far from optimal.

9. CONCLUSIONS AND FUTURE IMPLICATIONS

9.1 Conclusions

Major depressive disorder is a common illness causing severe human suffering and short- and long-term disability, and thus leading to enormous economic costs to both the individual and society. Although this record-based study found an emerging perception of improved quality of pharmacotherapy in psychiatric settings — with the exception of treatment with tricyclics — problems in the quality of care for depression in psychiatric settings are more likely to be related to suboptimal intensity and monitoring of treatment than to mere lack of treatment. Too few visits to psychiatrists and other professionals to allow systematic follow-up and psychosocial treatments, exclusive reliance on the low end of the dose range of antidepressants, limited number of antidepressant trials or augmentations, and acceptance of permanent disability without first pursuing vigorous treatment are all likely to be major problems in current psychiatric settings. However, it must be noted that this study represents the treatment situation nearly ten years ago. Therefore currently the treatment situation may be different.

The prospective part of this thesis investigated factors predicting problems in social adjustment, and functional and work disability. To better find and understand those we studied comprehensively MDE patients' Axis I, II, and III comorbidity and a large variety of sociodemographic and clinical factors.

During the current depression period, the most important single factor explaining disability appears to be severity of depression. Lack of perceived social support was one of the most important factors associated with disability. However, factors such as recurrent depression, older age, anxiety disorders, particularly phobic disorders, alcoholism, or personality disorders also probably contribute. Somatic diseases may be important among older patients. Furthermore, the importance of any of these factors as predictors of disability appears to vary somewhat depending on the area of life investigated. Finally, factors associated with functional, social or work disability, or absence from work, are unlikely to be identical.

During the course of treatment and recovery from depression, the factors predicting a patient's disability are somehow different from those in the beginning of the episode. This prospective study indicates that the current level of functioning and social adjustment of a patient with depression is predicted not only by current state, but also by the preceding history of depression. Furthermore, the presence of comorbid psychiatric disorders, personality trait neuroticism, and perceived social support also significantly influence level of functioning and social adjustment. Predictors of long-lasting work disability are multiple sociodemographic and clinical factors, not only

clinical factors. Baseline level of functioning and duration of depressive episodes are key clinical predictors of future disability.

9.2 Clinical implications

Recognition of depression and specifically the risk factors associated with functional and work disability such as older age, lack of perceived social support, comorbidity, earlier history of depression, and current functioning are key factors in avoiding the necessity to pension individuals. Being on sick-leave has its specific effect on the later outcome of depression and restoration of functional and work ability.

Early beginning of treatment and sufficiency of treatment resources are necessary despite the current lack of psychiatrists. Reducing time spent depressed in the acute phase by optimal treatment is one of the most important aims for reducing long-term disability. Otherwise lengthened sick-leaves or even work disability pensions are possible results.

Management of depression-related disability is challenging. Pharmacological treatment seems to be minimally adequate (patients often receive too small antidepressant doses though formally adequate ones). Treatment of refractory depression is the most challenging indicating integrated treatment approaches. However, problems in the intensity and monitoring of treatment stand in the way of patients' rapid recovery and thus restoration of their functional and work ability.

9.3 Future implications for research

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 worrisome.

Research is needed on treatment to better identify those special treatment methods helping high risk patients to recover sooner and maintain their functional abilities.

The independent and significant role of sick-leaves predicting pensioning was unexpected. The positive and negative consequences of sick-leave also require elucidation.

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11. REFERENCES

Alonso J et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004a;109:21-27.

Alonso J et al. Use of mental health services in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004b;109:47-54.

Alonso J et al. 12-Month comorbidity patterns and associated factors in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004c:28-37

American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition revised (DSM-III-R). Washington, DC. American Psychiatric Association, 1987.

American Psychiatric Association (APA). Practice guideline for major depressive disorder in adults. American Psychiatric Association. Am J Psychiatry 1993; 150(4 Suppl):1-26

American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington DC, USA. American Psychiatric Association, 1994.

American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder (Revision). Am J Psychiatry 2000;157:(4,suppl):1-45.

Andrews G, Henderson S, Hall W. Prevalence, comorbidity, disability and service utilisation. Overview of the Australian National Mental Health Survey. Br J Psychiatry 2001;178:145-153.

Angst J. The course of affective disorders. Psychopathology 1986;19: 47-52.

Appelberg BG, Syvälahti EK, Koskinen TE, Mehtonen OP, Muhonen TT, Naukkarinen HH. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. J Clin Psychiatry 2001;62:448-452.

Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol 1999;160:1-12.

Ban TA. Pharmacotherapy of depression: a historical analysis. J Neural Transm 2001;108:707-716.

Basso MR, Bornstein RA. Relative memory deficits in recurrent versus first-episode major depression on a word-list learning task. Neuropsychology 1999;13:557-563.

Bauer M, Whybrow PC, Angst J, Versiani M, Moller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Acute and continuation treatment of major depressive disorder. World J Biol Psychiatry 2002;3:5-43.

Bauwens F, Pardoen D, Staner L, Dramaix M, Mendlewicz J. Social adjustment and the course of affective illness: a one-year controlled longitudinal study involving bipolar and unipolar outpatients. Depress Anxiety 1998;8:50-57.

Beck AT, Ward CH, Mendelson M, Moch JE, Erbaugh JK. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-571.

Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the scale for suicide ideation. J Consult Clin Psychol 1979;47:343-352.

Beck AT, Weissman A, Lester D, Trexler L. The measure of pessimism: the hopelessness scale. J Consult Clin Psychol 1974;42:861-865.

Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J. Consult Clin Psychol 1988;56:893-897.

Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998;33:587-595.

Bingefors K, Isacson D, von Knorring L. Antidepressant dose patterns in Swedish clinical practice. Int Clin Psychopharmacol 1997;12:283-290.

Birzniece V, Backstrom T, Johansson IM, Lindblad C, Lundgren P, Lofgren M, Olsson T, Ragagnin G, Taube M, Turkmen S, Wahlstrom G, Wang MD, Wihlback AC, Zhu D. Neuroactive steroid effects on cognitive functions with a focus on the serotonin and GABA systems. Brain Res Rev 2006:51;212-239.

Blumenthal JA, Burg MM, Barefoot J, Williams RB, Haney T, Zimet G. Social Support, Type A Behavior, and Coronary Artery Disease. Psychosom Med 1987;49:331-340.

Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA 1990;264:2524–2528.

Brodaty H, Luscombe G, Peisah C, Anstey K, Andrews G. A 25-year longitudinal, comparison study of the outcome of depression. Psychol Med 2001;31:1347-1359.

Brown GW, Harris TO. Social Origins of Depression: A Study of Psychiatric Disorder in Women. Tavistock: London, 1978.

Brugha TS, Bebbington PE. The undertreatment of depression. Eur Arch Psychiatry Clin Neurosci 1992; 242:103-108.

Buzsaki G: Large-scale recording of neuronal ensembles. Nat Neurosci 2004;7:446-451.

Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry 2004;161:598-607.

Caspi A, Moffit TE, Newman DL, Silva PA. Behavioral observations at age 3 years predict adult psychiatric disorders: longitudinal evidence from a birth cohort. Arch Gen Psychiatry 1996;53:1033-1039.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-389.

Castrén E: Is mood chemistry? Nat Rev Neurosci 2005;6:241-246.

Cooper Z, Paykel ES. Social Factors in the Onset and Maintenance of Depression. In Bhugra D, Leff J (Eds.), Principles of Social Psychiatry. Oxford: Blackwell Scientific Publications 1994:99-121.

Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL. The enduring psychosocial consequences of mania and depression. Am J Psychiatry 1993;150:720-727.

Demyttenaere K et al. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. JAMA 2004;291:2581-2590.

Depressio (online). Käypä hoito-suositus. Duodecimin ja Suomen Psykiatriyhdistys ry:n asettama työryhmä. Helsinki: Suomalainen Lääkäriseura Duodecim 2004. Saatavilla Internetissä:www.kaypahoito.fi

Dinan TG, Barry S. A comparison of electroconvulsive therapy with a combined lithium and tricyclic combination among depressed tricyclic nonresponders. Acta Psychiatr Scand 1989;80:97-100.

Donoghue J. Antidepressant use patterns in clinical practices. comparisons among tricyclic antidepressants and selective serotonin reuptake inhibitors. Acta Psychiatr Scand 2000;101:57-61.

Druss BG. Rosenheck RA. Sledge WH. Health and disability costs of depressive illness in a major U.S. corporation. Am J Psychiatry 2000; 157:1274-1278.

Druss BG, Schlesinger M, Allen HM Jr. Depressive symptoms, satisfaction with health care, and 2-year work outcomes in an employed population. Am J Psychiatry 2001;158:731–734.

Eaton WW, Anthony JC, Gallo J, Cai G, Tien A, Romanoski A, Lyketsos C, Chen L-S. Natural history of Diagnostic Interview Schedule/ DSM-IV major depression. The Baltimore epidemiologic catchment area follow-up. Arch Gen Psychiatry 1997;54:993-999.

Elinson L, Houck P, Marcus SC, Pincus HA. Depression and the ability to work. Psychiatr Serv 2004;55:29-34.

Essex MJ, Klein MH, Cho E, Kalin NH. Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. Biol Psychiatry 2002;52:776-784.

Eysenck HJ, Eysenck SBG. 1964. Manual of the Eysenck Personality Inventory. University of London Press Ltd: London, England.

Ezquiaga E, Garcia A, Pallares T, Bravo MF. Psychosocial predictors of outcome in major depression: a prospective 12-month study. J Affect Disord. 1999;52:209-216.

Fingelkurts AA, Fingelkurts AA, Rytsälä HJ, Suominen K, Isometsä E, Kähkönen S. Impaired functional connectivity at EEG alpha and theta frequency bands in major depression. Human Brain Mapping (Published Online: 15 Jun 2006).

Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003;361:653-661.

Goethe JW, Fischer EH. Functional impairment in depressed inpatients. J Affect Disord 1995;33:23-29.

Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, Mayberg H. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry 2004;61:34-41.

Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992;149:1148-1156.

Hahn MK, Blakely RD. Monoamine transporter gene structure and polymorphisms in relation to psychiatric and other complex disorders. Pharmacogenomics J 2002;2:217-235.

Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiat 1960;23:56-62.

Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry 2005;62:1097-1106.

Hay P, Katsikitis M, Begg J, Da Costa J, Blumenfeld N. A two-year follow-up study and prospective evaluation of the DSM-IV axis V. Psychiatr Serv 2003;54:1028-1030

Hays JC, Steffens DC, Flint EP, Bosworth HB, George LK. Does social support buffer functional decline in elderly patients with unipolar depression? Am J Psychiatry. 2001;158:1850-1855.

Heim C, Newport J, Heit S, Graham Y, Wilcox M, Bonsall R, Miller A, Nemeroff C. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 2000;284:592-597.

Hensing G. Brage S. Nygard JF. Sandanger I. Tellnes G. Sickness absence with psychiatric disorders - an increased risk for marginalisation among men? Soc Psychiatry Psychiatr Epidemiol. 2000;35:335-340.

Hilsenroth MJ, Ackerman SJ, Blagys MD, Baumann BD, Baity MR, Smith SR, Price JL, Smith CL, Heindselman TL, Mount MK, Holdwick DJ, Jr. Reliability and validity of DSM-IV axis V. Am J Psychiatry 2000;157:1858-1863

Hirschfeld RM, Dunner DL, Keitner G, Klein DN, Koran LM, Kornstein SG, Markowitz JC, Miller I, Nemeroff CB, Ninan PT, Rush AJ, Schatzberg AF, Thase ME, Trivedi MH, Borian FE, Crits-Christoph P, Keller MB. Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. Biol Psychiatry 2002;51:123-133.

Hirschfeld RM: Efficacy of SSRIs and newer antidepressants in severe depression: comparison with TCAs. J Clin Psychiatry 1999;60:326-335.

Hua JY, Smith SJ. Neural activity and the dynamics of central nervous system development. Nat Neurosci 2004;7:327-332.

Hämäläinen J, Isometsä E, Laukkala T, Kaprio J, Poikolainen K, Heikkinen M, Lindeman S, Aro H. Use of health services for major depressive episode in Finland. J Affect Disord 2004;79:105-112.

Isometsä E, Aro S, Aro H. Depression in Finland: a computer assisted telephone interview study. Acta Psychiatr Scand 1997;96:122-128.

Isometsä ET, Katila H, Aro T: Disability pension for major depression in Finland. Am J Psychiatry 2000;157:1869-1872.

Isometsä E, Lindfors O, Pirkola S, Seppälä I, Salminen JK, Luutonen S, Marttunen M, Mattila M, Jäättelä A. The national Finnish current care guidelines for the treatment of depression - an overview. Psychiatria Fennica 2003;34:181-196.

Johnson J, Weissman MM, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. JAMA 1992;267:1478-1483.

Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Paulus MP, Kunovac JL, Leon AC, Mueller TI, Rice JA, Keller MB. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry 1998;55:694-700.

Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, Endicott J, Coryell W, Kunovac JL, Mueller TI, Rice JP, Keller MB. Psychosocial disability during the long-term course of unipolar major depressive disorder. Arch Gen Psychiatry 2000a;57:375-380.

Judd LL, Paulus MJ, Schettler PJ, Akiskal HS, Endicott J, Leon AC, Maser JD, Mueller T, Solomon DA, Keller MB: Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? Am J Psychiatry 2000b;157:1501-1504

Karpansalo M, Kauhanen J, Lakka TA, Manninen P, Kaplan GA, Salonen JT. Depression and early retirement: prospective population based study in middle aged men. J Epidemiol Community Health 2005;59:70-74.

Katon W, Sullivan MD. Depression and chronic medical illness. J Clin Psychiatry 1990;51 Suppl:3-11; discussion 12-14.

Katz LC, Shatz CJ. Synaptic activity and the construction of cortical circuits. Science 1996;274:1133-1138.

Keitner GI, Miller IW. Family functioning and major depression: an overview. Am J Psychiatry. 1990;147:1128-1137.

Keller J, Flores B, Gomez RG, Solvason HB, Kenna H, Williams GH, Schatzberg AF. Cortisol Circadian Rhythm Alterations in Psychotic Major Depression. Biol Psychiatry 2006;60:271-281.

Keller MB, Klerman GL, Lavori PW, Fawcett JA, Coryell W, Endicott J. Treatment received by depressed patients. JAMA 1982;248:1848-1855.

Keller MB, Lavori PW, Klerman GL, Andreasen NC, Endicott J, Coryell W, Fawcett J, Rice JP, Hirschfeld RM. Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. Arch Gen Psychiatry 1986;43:458-466.

Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen NC. The Longitudinal Interval Follow-up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987;44:540-548.

Keller MB. Undertreatment of major depression. Psychopharmacol Bull 1988;24:75-80.

Keller MB, Boland RJ. Implications of failing to achieve successful long-term maintenance treatment of recurrent unipolar major depression. Biol Psychiatry 1998;44:348-360.

Kendler KS, Heath AC, Neale MC, Kessler RC, Eaves LJ. A population-based twin study of alcoholism in women. JAMA 1992; 268:1877-1882.

Kendler KS, Kessler RC, Neale MC, Heath AC, Eaves LJ. The prediction of major depression in women: toward an integrated etiologic model. Am J Psychiatry 1993;150:1139-1148.

Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. Am J Psychiatry 2001;158:582-586

Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in women. Am J Psychiatry 2002;159:1133-1145.

Kendler KS, Hettema JM, Butera F, Gardner CO, Prescott CA. Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalised anxiety. Arch Gen Psychiatry 2003;60:789-796.

Kendler KS, Kuhn J, Prescott CA. The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. Am J Psychiatry 2004;161:631-636.

Kendler KS, Myers J, Prescott CA. Sex differences in the relationship between social support and risk for major depression: a longitudinal study of opposite-sex twin pairs. Am J Psychiatry 2005; 162:250-256.

Kendler KS, Gatz M, Gardner CO, Pedersen NL. A Swedish national twin study of lifetime major depression. Am J Psychiatry 2006a;16:109-114.

Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in men. Am J Psychiatry 2006b;163:115-124.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19.

Kessler RC, Frank RG. The impact of psychiatric disorders on work loss days. Psychol Med 1997;27:861-873.

Kessler RC, Berlund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder. Results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095-3105.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617-627.

Knudsen HC, Krasnik A, Jessen-Petersen B, Nordentoft M, Saelan H. Patients in the care of private psychiatric practitioners. Comparison with public hospital patients and the background districts' population. Soc Psychiatry Psychiatr Epidemiol 1992;27:156-160.

Kocsis JH, Frances AJ, Voss C, Mann JJ, Mason BJ, Sweeney J. Imipramine treatment for chronic depression. Arch Gen Psychiatry 1988;45:253-257.

Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. Bull World Health Organ 2004;82:858-866.

Laukkala T, Isometsä E, Hämäläinen J, Heikkinen M, Lindeman S, Aro H. Antidepressant treatment of depression in the Finnish general population. Am J Psychiatry 2001;158:2077-2079.

Leader JB, Klein DN. Social adjustment in dysthymia, double depression and episodic major depression. J Affect Disord 1996;37:91-101.

Lehtinen V, Joukamaa M, Lahtela K, Raitasalo R, Jyrkinen E, Maatela J, Aromaa A. Prevalence of mental disorders among adults in Finland: basic results from the Mini-Finland Health Survey. Acta Psychiatr Scand 1990a;81:418-425.

Lehtinen V, Joukamaa M, Jyrkinen E, Lahtela K, Raitasalo R, Maatela J, Aromaa A. Need for mental health services of the adult population in Finland: results from the Mini-Finland Health Survey. Acta Psychiatr Scand 1990b;81:426-431.

Lehtinen V, Joukamaa M. Epidemiology of depression: prevalence, risk factors and treatment situation. Acta Psychiatr Scand Suppl 1994;377:7-10

Lehtinen V, Veijola J, Lindholm T, Moring J, Puukka P, Väisänen E. Incidence of mental disorders in the Finnish UKKI Study. Br J Psychiatry 1996;168:672-678.

Lehtinen V. Sohlman B. Nummelin T. Salomaa M. Ayuso-Mateos JL. Dowrick C. The estimated incidence of depressive disorder and its determinants in the Finnish ODIN sample. Soc Psychiatry Psychiatr Epidemiol 2005;40: 778-784.

Lesch KP. Gene-environment interaction and the genetics of depression. J Psychiatry Neurosci 2004;29:174-184.

Lieb R, Isensee B, Hofler M, Pfister H, Wittchen HU. Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. Arch Gen Psychiatry 2002;59:365-374.

Lifschytz T, Gur E, Lerer B, Newman ME. Effects of triiodothyronine and fluoxetine on 5-HT1A and 5-HT1B autoreceptor activity in rat brain: regional differences. J Neurosci Methods 2004;140:133-139.

Lindeman S, Hämäläinen J, Isometsä E, Kaprio J, Poikolainen K, Heikkinen M, Aro H. The 12-month prevalence and risk factors for major depressive episode in Finland: representative sample of 5993 adults. Acta Psychiatr Scand 2000;102:178-184.

Linkenkaer-Hansen K, Monto S, Rytsälä H, Suominen K, Isometsä E, Kahkonen S: Breakdown of long-range temporal correlations in theta oscillations in patients with major depressive disorder. J Neurosci 2005;25:10131-10137.

Lloyd AJ, Ferrier IN, Barber R, Gholkar A, Young AH, O'Brien JT. Hippocampal volume change in depression: late- and early-onset illness compared. Br J Psychiatry 2004; 184:488-495.

Lyness JM, Caine ED, Conwell Y, King DA, Cox C. Depressive symptoms, medical illness, and functional status in depressed psychiatric inpatients. Am J Psychiatry 1993;150:910-915.

Lyness JM, Duberstein PR, King DA, Cox C, Caine ED. Medical illness burden, trait neuroticism, and depression in older primary care patients. Am J Psychiatry 1998;155:969-971.

Maes M. Evidence for an immune response in major depression: a review and hypothesis. Prog Neuropsychopharmacol Biol Psychiatry 1995;19:11-38.

Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000;20:9104-9110.

Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nat Med 2001;7:541-547.

Markowitz JC, Skodol AE, Petkova E, Xie H, Cheng J, Hellerstein DJ, Gunderson JG, Sanislow CA, Grilo CM, McGlashan TH: Longitudinal comparison of depressive personality disorder and dysthymic disorder. Compr Psychiatry 2005;46:239-245.

McDermut W, Mattia J, Zimmerman M. Comorbidity burden and its impact on psychosocial morbidity in depressed outpatients. J Affect Disord 2001;65:289-295.

Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET: Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. J Clin Psychiatry 2002;63:126-134.

Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET Severity and Comorbidity Predict Episode Duration and Recurrence of DSM-IV Major Depressive Disorder. J Clin Psychiatry 2004;65: 810-819.

Merikangas KR, Zhang H, Avenevoli S, Acharyya S, Neuenschwander M, Angst J. Longitudinal trajectories of depression and anxiety in a prospective community study: the Zurich Cohort Study. Arch Gen Psychiatry 2003;60:993-1000.

Milak MS, Parsey RV, Keilp J, Oquendo MA, Malone KM, Mann JJ. Neuroanatomic correlates of psychopathologic components of major depressive disorder. Arch Gen Psychiatry 2005;62:397-408.

Miller IW, Kabacoff RI, Keitner GI, Epstein NB, Bishop DS. Family Functioning in the Families of Psychiatric Patients. Comp Psychiatry 1986;27:302-312.

Mintz J, Mintz LI, Arruda MJ, Hwang SS. Treatments of depression and the functional capacity to work. Arch. Gen. Psychiatry 1992;49:761-768.

MMWR, 2000. Prevalence of disabilities and associated health conditions among adults - United States, 1999;MMWR. 50;120-125.

Moldin SO, Scheftner WA, Rice JP, Nelson E, Knesevich MA, Akiskal H. Association between major depressive disorder and physical illness. Psychol Med 1993;23:755-761.

Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry 1999;156:1000-1006.

Mulder RT. Personality pathology and treatment outcome in major depression: a review. Am J Psychiatry 2002;159:359-371.

Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997a;349:1436-1442.

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997b;349:1498-1504.

Nagi SZ: An epidemiology of disability among adults in the United States. Milbank Mem Fund Q Health Soc 1976;54:439-467.

National Collaborating Centre for Mental Health Commissioned by the National Institute for Clinical Excellence (NICE). Depression: Management of depression in primary and secondary care. National Clinical Practice Guideline Number 23. 2004.

Nelson JC, Mazure CM, Bowers MB, Jr., Jatlow PI. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry 1991;48:303-307.

Neumeister A, Wood S, Bonne O, Nugent AC, Luckenbaugh DA, Young T, Bain EE, Charney DS, Drevets WC. Reduced hippocampal volume in unmedicated, remitted patients with major depression versus control subjects. Biol Psychiatry 2005; 57:935-937

Nurnberg HG, Thompson PM, Hensley PL. Antidepressant medication change in a clinical treatment setting: a comparison of the effectiveness of selective serotonin reuptake inhibitors. J Clin Psychiatry 1999;60:574-579

Nutt DJ: Tolerability and safety aspects of mirtazapine. Hum Psychopharmacol 2002; 17 Suppl 1:S37-41.

Oates MR. Adverse effects of maternal antenatal anxiety on children: causal effect or developmental continuum? Editorial. Br J Psychiatry 2002;180:478-479.

O'Connor TG, Heron J, Golding J, Beveridge M, Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. Br J Psychiatry 2002;180:502-508.

Ormel J, Oldehinkel AJ, Nolen WA, Vollebergh W. Psychosocial disability before, during, and after a major depressive episode: a 3-wave population-based study of state, scar, and trait effects. Arch Gen Psychiatry. 2004;61:387-392.

Oslin DW, Datto CJ, Kallan MJ, Katz IR, Edell WS, TenHave T. Association between medical comorbidity and treatment outcomes in late-life depression. J Am Geriatr Soc 2002;50:823-828.

Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munizza C. Combined pharmacotherapy and psychological treatment for depression: a systematic review. Arch Gen Psychiatry 2004;61:714-719.

Papakostas GI, Petersen T, Denninger JW, Tossani E, Pava JA, Alpert JE, Nierenberg AA, Fava M. Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. J Clin Psychopharmacol 2004;24:507-511.

Paykel ES, Myers JK, Dienelt MN, Klerman GL, Lindenthal JJ, Pepper MP. Life events and depression. A controlled study. Arch Gen Psychiatry 1969;21:753-760.

Pepper CM, Klein DN, Anderson RL, Riso LP, Ouimette PC, Lizardi H. DSM-III-R axis II comorbidity in dysthymia and major depression. Am J Psychiatry 1995;152:239-247.

Pintor L, Torres X, Navarro V, Matrai S, Gasto C. Is the type of remission after a major depressive episode an important risk factor to relapses in a 4-year follow up? J Affect Disord 2004;82:291-296.

Pirkola SP, Isometsä E, Suvisaari J, Aro H, Joukamaa M, Poikolainen K, Koskinen S, Aromaa A, Lönnqvist JK. DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population-results from the Health 2000 Study. Soc Psychiatry Psychiatr Epidemiol 2005;40:1-10.

Placidi GP, Oquendo MA, Malone KM, Brodsky B, Ellis SP, Mann JJ: Anxiety in major depression: relationship to suicide attempts. Am J Psychiatry 2000;157:1614-1618.

Rabkin JG, McElhiney M, Ferrando SJ, Van Gorp W, Lin SH. Predictors of employment of men with HIV/AIDS: a longitudinal study. Psychosom Med 2004;66:72-78.

Salminen JK, Saarijärvi S, Raitasalo R. Depression and disability pension in Finland. Acta Psychiatr Scand 1997;95:242-243.

Salminen JK, Saarijärvi S, Tikka J, Raitasalo R, Rissanen S, Toikka T, Puukka P. Vakavan masennuksen hoidossa puutteita Suomen Lääkärilehti 1999;54:1059-1063.

Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925-935.

Sato T, Sakado K, Nishioka K, Uehara T, Sato S, Kasahara Y. The relationship of DSM-III-R personality disorder to clinical variables in patients with major depression: possible difference between personality disorder clusters. Psychiatry Clin Neurosci 1996;50:95-100.

Schiepers OJ, Wichers MC, Maes M: Cytokines and major depression. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:201-217.

Schulberg HC, Katon W, Simon GE, Rush AJ: Treating major depression in primary care practice: an update of the Agency for Health Care Policy and Research Practice Guidelines. Arch Gen Psychiatry 1998;55:1121-1127.

Sheline YI, Sanghavi M, Mintun MA, Gado MH: Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 1999;19:5034-5043.

Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry 2003;160:1516-1518.

Shen YC, Zhang MY, Huang YQ, He YL, Liu ZR, Cheng H, Tsang A, Lee S, Kessler RC. Twelve-month prevalence, severity, and unmet need for treatment of mental disorders in metropolitan China. Psychol Med 2006;36:257-267.

Simon GE, Revicki D, Heiligenstein J, Grothaus L, VonKorff M, Katon WJ, Hylan TR. Recovery from depression, work productivity, and health care costs among primary care patients. Gen Hosp Psychiatry 2000;22:153-162.

Simon GE. Social and economic burden of mood disorders. Biol Psychiatry 2003;54:208-215.

Sirey JA, Meyers BS, Bruce ML, Alexopoulos GS, Perlick DA, Raue P. Predictors of antidepressant prescription and early use among depressed outpatients. Am J Psychiatry 1999;156:690-696.

Skodol AE, Gunderson JG, McGlashan TH, Dyck IR, Stout RL, Bender DS, Grilo CM, Shea MT, Zanarini MC, Morey LC, Sanislow CA, Oldham JM. Functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder. Am J Psychiatry 2002;159:276-283.

Solomon DA, Keller MB, Leon AC, Mueller TI, Shea MT, Warshaw M, Maser JD, Coryell W, Endicott J. Recovery from major depression. A 10-year prospective follow-up across multiple episodes. Arch Gen Psychiatry 1997;54:1001-1006.

Sorvaniemi M, Helenius H, Salokangas RKR. Improved pharmacotherapy of major depression in psychiatric outpatient care. Nordic J Psychiatry 1998;52:155-161.

Sorvaniemi M, Helenius H, Salokangas RK. Factors associated with being granted a pension among psychiatric outpatients with major depression. J Affect Disord 2003; 75:43-48.

Spijker J, de Graaf R, Bilj RV, Beekman ATF, Ormel J, Nolen WA. Duration of major depressive episodes in the general population: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry 2002;181:208-213.

Spijker J, Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Functional disability and depression in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Acta Psychiatr Scand 2004;110:208-214.

Spitzer RL, Williams JBW, Gibbon M, First MB. Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II 9/1/89). New York, NY: Biometric Research, New York State Psychiatric Institute;1987

Sullivan PF, Neale JM, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157:1552-1562.

Starkes JM, Poulin CC, Kisely SR: Unmet need for the treatment of depression in Atlantic Canada. Can J Psychiatry 2005; 50:580-590.

Statistical Package for the Social Sciences for Windows. Releases 9.01 and 13.0, Chicago, Ill, Copyright SPSS Inc. (1989-2004).

Stuart S, Simons AD, Thase ME, Pilkonis P. Are personality assessments valid in acute major depression? J Affect Disord 1992;24:281-289.

Tennant C. Parental loss in childhood: its effect in adult life. Arch Gen Psychiatry 1988;45:1045-1050.

The UK ECT review group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 2003;361:799-808.

Tollefson GD, Souetre E, Thomander L, Potvin JH: Comorbid anxious signs and symptoms in major depression: impact on functional work capacity and comparative treatment outcomes. Int Clin Psychopharmacol 1993;8:281-293.

Torgersen, S. Genetic factors in moderately severe and mild affective disorders. Archives of General Psychiatry 1986;43:222–226.

True WR, Heath AC, Bucholz K, Slutske W, Romeis JC, Scherrer JF, Lin N, Eisen SA, Goldberg J, Lyons MJ, Tsuang MT. Models of treatment seeking for alcoholism: the role of genes and environment. Alcohol Clin Exp Res 1996; 20:1577-1581.

Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry 2004;161:1957-1966.

von Korff M, Ormel J, Katon W, Lin EH. Disability and depression among high utilizers of health care. A longitudinal analysis. Arch Gen Psychiatry 1992;49:91-100.

Vuorilehto M, Melartin T, Isometsä E. Depressive disorders in primary care: recurrent, chronic, and co-morbid. Psychol Med 2005;35:673-682.

Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. Arch Gen Psychiatry 1976;33:1111-1115.

Weissman MM, Wickramaratne P, Nomura Y, Warner V, Verdeli H, Pilowsky DJ, Grillon C, Bruder G. Families at high and low risk for depression: a 3-generation study. Arch Gen Psychiatry 2005;62:29-36.

Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, Berry S, Greenfield S, Ware J. The functioning and well being of depressed patients. Results from the Medical Outcomes Study. JAMA 1989;262:914-919.

Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorious N. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry 1990;47;589-593.

Wittchen HU, Carter RM, Pfister H, Montgomery SA, Kessler, RC. Disabilities and quality of life in pure and comorbid generalized anxiety disorder and major depression in a national survey. Int. Clin. Psychopharmacol 2000;15:319-328.

Wittchen HU, Jacobi F: Size and burden of mental disorders in Europe—a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol 2005;15357-15376.

World Health Organization. The ICD-10 classification of mental and behavioral disorders : clinical descriptions and diagnostic guidelines. Geneva: WHO, 1992.

World Health Organization. The ICD-10 classification of mental and behavioral disorders: diagnostic criteria for research. Geneva: WHO, 1993.

World Health Organization. Schedule for Clinical Assessment in Neuropsychiatry: Version 2.0. Geneva: WHO, 1994.

Young EA, Midgley AR, Carlson NE, Brown MB. Alteration in the hypothalamic-pituitary-ovarian axis in depressed women. Arch Gen Psychiatry 2000;57:1157-1162.

Young EA, Abelson JL, Cameron OG. Effect of comorbid anxiety disorders on the hypothalamic-pituitary-adrenal axis response to a social stressor in major depression. Biol Psychiatry 2004;56:113-120.

Young EA, Veldhuis JD. Disordered Adrenocorticotropin Secretion in Women with Major Depression. J Clin Endocrinol Metab 2006;91:1924-1928.

Yuuki N, Ida I, Oshima A, Kumano H, Takahashi K, Fukuda M, Oriuchi N, Endo K, Matsuda H, Mikuni M: HPA axis normalization, estimated by DEX/CRH test, but less alteration on cerebral glucose metabolism in depressed patients receiving ECT after medication treatment failures. Acta Psychiatr Scand 2005;112:257-265.