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Department of Mental Health and Alcohol Research,
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COMORBIDITY, OUTCOME AND TREATMENT OF DSM-IV MAJOR DEPRESSIVE DISORDER IN PSYCHIATRIC CARE

Tarja Melartin

Academic Dissertation

To be publicly discussed, with the permission of the Medical Faculty of the University of Helsinki, in the auditorium of the Department of Psychiatry in Helsinki, Lapinlahdenkatu 1, on January 21, 2005, at 12 noon.

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"...sillä minä olen itse metsä, kulku metsän läpi, askel joka miettii, miettii eikä saavu koskaan perille, puiden järkytys ja villiaasin laukka läpi lehtojen,
minä olen itse pako ja kohtaaminen, pako ja kohtaaminen, hitaat vaunut ja särkynyt pyörä, melu pyörän sektorissa, toisessa sektorissa hiljaisuus,
olen äänetön ajuri ja outo vieras, joka astuu peilin sisältä ja hämmästyy,
en tiedä kuka olen, sillä kun käsitän itseni olen jo toinen, olen moni, olen yksin ja matkalla kaukaiseen vihertävään tähteen jonka kirjon olen vanginnut tähän,...
...olemme matkalla, yhä vain matkalla puheen vaunuissa; puhe tulee menneisyydestä ja leviää peruuttamattomien sanojen alati sykkiväksi kehäksi,
äänessäsi on pilviä, sade virtaa puiden latvoista, kuljen läpi lehtien, sateiden, tulee yö, toiset avaruudet kajastavat,
minä yhä kuljen, pitkän talvisen matkan."

Yö tulee varhain.
Kohta on talvi
kuin kaivo, syvä ja kylmä.

Eeva-Liisa Manner

Hevonen minun veljeni, Hevosrunot 1956-1976;
katkelmat runoista Hukattu motiivi ja
Syksyn tulon kuvaus

To Lauri, Siiri, and Heta

CONTENTS

TIIVISTELMÄ

Tämä tutkimus on osa Kansanterveyslaitoksen ja Helsingin ja Uudenmaan sairaanhoitopiirin Peijaksen sairaalan psykiatrian tulosyksikön vakavan masennustilan etenevää seurantatutkimusta (Vantaa Depression Study), jossa seurataan 269 ajankohtaisesta (DSM-IV) vakavasta masennustilasta kärsivää psykiatrisen erikoissairaanhoidon avohoito- ja sairaalapotilasta.

Kaiken kaikkiaan Peijaksen psykiatrisessa erikoissairaanhoidossa depressiivisten oireiden osalta seulottiin 806, ja haastateltiin puolistrukturoidulla haastattelumenetelmällä (WHO Schedule for Clinical Assessment in Neuropsychiatry [SCAN], Version 2.0) 542 aikuispotilasta (20-59v.). Tutkimukseen valikoituneet (N=269) täyttivät ajankohtaisen vakavan masennustilan oirekriteerit, ja heidät haastateltiin puolistrukturoiduin haastattelumenetelmin myös kaikkien muiden psykiatristen häiriöiden diagnosoimiseksi. Poissulkukriteerit olivat DSM-IV bipolaarihäiriö I ja II, skitsoaffektiivinen häiriö, skitsofrenia ja muut psykoosit, sekä orgaaninen tai kemiallisen aineen aiheuttama mielialahäiriö.

Sisäänottovaiheen jälkeen 6 ja 18 kk:n seurannoissa vakavan masennuksen ja muiden samanaikaisten häiriöiden oireet kartoitettiin haastattelemalla potilaat uudelleen puolistrukturoiduin diagnosointihaastattelumenetelmin. Tämän lisäksi ajankohtaisen sekä toistuvien/uusiutuvien depressioepisodien ajallinen kesto koottiin yksityiskohtaiseksi graafiseksi kuvaajaksi (lifechart), jossa seuranta-aika on jaettu DSM-IV kriteereiden mukaan kolmea eri toipumistasoa kuvaavaan jaksoon: 1) täydellinen toipuminen (0/9 oiretta), 2) osittainen toipuminen (1-4/9 oiretta) ja 3) ei toipunut (5+/9 oiretta). Hoitokäynti- ja oirestatustietojen lisäksi kartoitettiin seuranta-ajan elämäntapahtumat, joiden avulla pyrittiin myös lisäämään ajoituksen tarkkuutta.

Tutkimuksessa todettiin tyypillisen psykiatrisen erikoissairaanhoidon masennuspotilaan kärsivän monista samanaikaisista ajankohtaisista häiriöistä. Yli puolella diagnosoitiin samanaikainen ahdistuneisuushäiriö (57%), vajaalla puolella persoonallisuushäiriö (44%), ja neljänneksellä alkoholiriippuvuus tai alkoholin väärinkäyttö (25%). Ainoastaan viidenneksellä (21%) potilaista oli yksinomaan vakava masennustila.

Vakavasta masennustilasta täydelliseen toipumisen todettiin vievän keskimäärin kahdeksan kuukautta, joten huolimatta uusista hoitomenetelmistä ennuste ei tässä suhteessa ole parantunut. Potilaat tosin reagoivat hoitoon suhteellisen nopeasti, noin 4-8 viikossa, mutta ongelmaksi muodostui pitkäkestoinen osittaisen toipumisen tila, jossa toimintakyky usein oli edelleen alentunut ja depressiivinen oireilu jatkui, vaikkakin lievempänä. Lisäksi noin 40% potilaista masentui vakavasti uudelleen puolentoista vuoden seurannan aikana. Uusiutuvien

episodien kesto oli kuitenkin lyhyempi, ja ne olivat lievempiä kuin ensimmäinen, hoitoon tuonut sairausjakso. Toipumisaikaa ennustivat useat tekijät, merkittävimmin masennuksen syvyys ja ajankohtainen monihäiriöisyys. Oiresyvyys oli myös voimakas uusiutumista ennustava tekijä. Monihäiriöisyys tai masennuksen ennustetekijät eivät eronneet merkittävästi vakavan masennustilan melankolisessa ja ei melankolisessa alatyypissä. Melankoliset piirteet eivät myöskään seurantaepisodeissa olleet kovin pysyviä.

Psykiatrisessa erikoissairaanhoidossa akuutin vaiheen alussa lääkehoitoa sai 88% ja psykososiaalista tukea 98% masennuspotilaista, ja useimmat suhtautuivat hoitoon myönteisesti. Tästä huolimatta antidepressiivinen lääkehoito keskeytyi liian aikaisin noin puolella potilaista, usein potilaan omasta päätöksestä. Kokonaan ilman hoitokontaktia seurannan lopussa oli noin kolmannes niistä potilaista, jotka eivät saavuttaneet täydellistä toipumista. Negatiivinen hoitoasenne kohdistui useammin lääkitykseen kuin psykososiaaliseen tukeen, ja vaikutti ennustavan hoidon liian aikaista keskeytymistä. Voidaankin tiivistäen todeta, että suurin haaste nykyisessä psykiatrisessa erikoissairaanhoidossa on hoidon asianmukaisen jatkuvuuden turvaaminen. Ilman jatkuvuutta masennuksen Käypä hoito-suositusten mukainen hoito ei voi toteutua. Tässä tehtävässä perusterveydenhuollon ja erikoissairaanhoidon yhteinen vastuunkantaminen ja yhteistyö on välttämätöntä, ja toimivien alueellisten hoitoketjujen luominen yhteisine tavoitteineen vääjäämätön haaste.

ABBREVIATIONS

APA	American Psychiatric Association
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CRF	Corticotrophin releasing factor
DIS	Diagnostic Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
ECA	Epidemiological Catchment Area Study
ECT	Electroconvulsive therapy
EPI	Eysenck Personality Inventory
GHS-MHS	Mental Health Supplement of German National Health Interview and Examination Survey
HAM-D	Hamilton Rating Scale for Depression
HPA	Hypothalamic-pituitary-adrenal
HS	Beck Hopelessness Scale
HUCS	Helsinki University Central Hospital
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases, 10th edition
IMSR	Interview Measure of Social Relationships
IRLE	Interview for Recent Life Events
LIFE	Longitudinal Interval Follow-up Evaluation
LR	Logistic regression
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
MDE	Major depressive episode
NaSSA	Noradrenergic and specific serotonergic antidepressant
NCS	National Comorbidity Survey
NCS-R	National Comorbidity Survey Replication
NIMH	National Institute of Mental Health
NOS	Not otherwise specified
NS	Non significant
CDS	Collaborative Depression Study
OR	Odds Ratio
PD	Personality disorder

PMCD	Peijas Medical Care District
PSSS-R	Perceived Social Support Scale - Revised
RDC	Research Diagnostic Criteria
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	Serotonin-selective reuptake inhibitor
SUD	Substance use disorder
TCA	Tricyclic antidepressant
VDS	Vantaa Depression Study
WHO	World Health Organization

1. ABSTRACT

This study forms part of a collaborative depression research project, the Vantaa Depression Study (VDS), run by the Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki, and the Department of Psychiatry of the Peijas Medical Care District (PMCD), Vantaa. The VDS is a prospective, naturalistic cohort study of 269 secondary-level care psychiatric out- and inpatients with a new episode of DSM-IV major depressive disorder (MDD).

Overall, the VDS involved screening 806 adult patients (aged 20-59 years) in the PMCD for a possible new episode of DSM-IV MDD, and interviewing the 542 consenting patients with a semistructured interview (the WHO Schedules for Clinical Assessment in Neuropsychiatry [SCAN], version 2.0). Thereby, 269 patients with current DSM-IV MDD were included in the study, and further interviewed with semistructured interviews to assess all other psychiatric diagnoses as well. Exclusion criteria were DSM-IV bipolar I and II, schizoaffective disorder, schizophrenia or another psychosis, organic and substance-induced mood disorders.

The outcomes of major depressive episode (MDE) and the comorbid disorders were investigated at six and 18 months after baseline using repeated semistructured interviews. The exact duration of the index episode and the timing of possible relapses/recurrences were prospectively examined using a graphic life chart based on DSM-IV criteria and definitions. Time after baseline was divided into three periods: (1) state of full remission (none of the 9 MDE criteria symptoms), (2) state of partial remission (1-4 of the 9 symptoms), or (3) state of MDE (5+ of the 9 symptoms). Besides symptom ratings and visits to attending personnel, life-events during the follow-up were also asked about in order to improve the accuracy of timing.

When presenting for psychiatric care, a typical psychiatric patient with MDD suffered from many comorbid disorders; over half had current comorbid anxiety disorders (57%), nearly half personality disorders (44%), and a quarter alcohol use disorders (25%). Only one fifth (21%) had pure depression without any comorbid disorder.

Achieving full remission took about eight months, so despite the use of the new antidepressants the outcome of MDD appears not to have improved in psychiatric care. Although patients typically responded early to the treatment (most in 4 to 8 weeks), the major problem was the long period with only partial remission, during which functional impairment and depressive symptoms persisted, albeit at a milder level. In addition, about 40% of the patients had a recurrence of MDD during the 18 months, although these new episodes were milder and shorter than the index episode. Numerous factors predicted the duration of MDE to some extent, but severity of depression and current comorbidity were

the two most robust predictors. Severity of depression was also a significant predictor of recurrence. There appeared to be no major differences in current comorbidity or course of depression between melancholic and non-melancholic patients. Moreover, the consistency of DSM-IV melancholic features across episodes appeared weak.

Most depressive patients in psychiatric care were found to be receiving adequate antidepressant (88%) and psychotherapeutic treatments (98%) in the early acute phase, and to have favourable attitudes towards them. Nevertheless, antidepressants were terminated too early in about half of the patients, often following their autonomous decision. About a third of the patients not achieving full remission were without any psychosocial treatment at 18 months. Negative treatment attitudes were more common towards antidepressants than psychosocial treatments, and tended to predict premature termination. Summing up, the main challenge in psychiatric care appears to be continuity of treatments. Without adequate continuity it is impossible to provide treatment that meets standards in practice guidelines. In this task, however, collaborative work and shared responsibilities between primary and secondary care are essential, and developing regional cooperation is an inevitable challenge.

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 Melartin T, Rytsälä H, Leskelä U, Lestelä-Mielonen P, Sokero P, Isometsä E. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. Journal of Clinical Psychiatry 2002;63:126-134.

II Melartin T, Rytsälä H, Leskelä U, Lestelä-Mielonen P, Sokero P, Isometsä E. Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. Journal of Clinical Psychiatry 2004;65:810-819.

III Melartin T, Leskelä U, Rytsälä H, Sokero P, Lestelä-Mielonen P, Isometsä E. Comorbidity and stability of melancholic features in DSM-IV major depressive disorder. Psychological Medicine 2004;34:1443-1452.

IV Melartin T, Rytsälä H, Leskelä U, Lestelä-Mielonen P, Sokero P, Isometsä E. Continuity - the main challenge in treatment of major depressive disorder in psychiatric care. Journal of Clinical Psychiatry, in press.

3. INTRODUCTION

Depressive feelings as a response to loss or painful events are part of human life. This normal affect of depression is self-limited and does not significantly interfere with a person's functional capacity. As an illness, however, major depressive disorder (MDD) imposes a substantial burden by inflicting continuous pain and suffering on individuals and their families. It is a highly prevalent, aetiologically multifactorial, clinically heterogeneous and severe illness characterized by sad mood and inability to experience pleasure, usually including serious abnormalities in cognition and physiological function. MDD is also one of the most important mental disorders in terms of public health impact. About a fifth of the population (Kessler et al., 1994; 2003), women more often than men, will experience a clinically significant episode of MDD at some point in their lives. MDD involves a marked risk of functional disability (Hays et al., 1995; Murray & Lopez, 1997; Rytsälä et al., in press), self-destructive behaviour and premature death (Harris & Barraclough, 1997; Sokero et al., 2003), and adversely affects interpersonal relationships (Wade & Cairney, 2000). The risk of completed suicide among patients with MDD is about 20-fold (Harris & Barraclough, 1997; Hoeyer et al., 2000; Ösby et al., 2001), and depression is associated with limitations in daily functioning and well-being comparable to those in chronic medical conditions (Hays et al., 1995). By 2020, depression has been predicted to become, after ischaemic heart disease, the major cause of disability worldwide (Murray & Lopez, 1996).

The high disease burden is also understandable from consideration of the nature and course of depression. Previously viewed as an acute and self-limiting illness, it is now clear that depression is not only highly prevalent but also a chronic, recurrent and comorbid illness. Following this paradigm shift in the concept of depression, studies of the natural history of MDE have come to be seen as essential for further understanding the nature of the disorder and developing more effective treatment strategies (Judd, 1997). Although the comorbid form of MDD is highly prevalent (Kessler et al., 1996b; 2003), there is only one study reporting concurrent prevalences of major categories of axis I disorders (Sanderson et al., 1990), and none reporting overall current comorbidity with all axis I and II disorders. Nor has the effect of overall comorbidity on the length of MDE or risk of recurrence been systematically investigated. Furthermore, much of what we now accept regarding the course of depression and its comorbidity is derived from studies based on selected samples, e.g. inpatients, patients of tertiary level university clinics, and samples predating the era of the current new antidepressants and the now widespread use of maintenance therapies.

As well as causing enormous individual suffering, depression also imposes a substantial burden in terms of the costs to society caused by disability and loss of productivity. Despite this, it is known from epidemiological studies that most depressive persons in the general population receive inadequate treatment, or none at all (Kessler et al., 2003; Hämäläinen et al., 2004). Studies in primary care indicate that depression commonly goes unrecognized (Pignone et al., 2002), and treatment for it often fails to meet evidence-based treatment guidelines (APA, 2000; Suomen Psykiatriyhdistys, 2004) for either drug therapy or psychotherapy (Gilbody et al., 2003; Kessler et al., 2003). Moreover, even in psychiatric care it is still largely unknown how the treatment provided meets the standards of these guidelines (Young et al., 2001), and which are the factors that predict treatment inadequacy, premature termination and non-adherence among depressive patients.

The Vantaa Depression Study (VDS) is a prospective, naturalistic cohort study of 269 secondary-level care psychiatric out- and inpatients with a new episode of DSM-IV MDD. In the VDS the predictors of chronicity, recurrences, suicide attempts as well as functional and work disability are investigated, and the adequacy of treatments evaluated. The present thesis focuses on current comorbidity, outcome and treatments received among depressive patients followed up for 18 months.

4. REVIEW OF THE LITERATURE

4.1 Diagnosis of major depressive disorder (MDD)

The current psychiatric classifications are categorical systems that divide mental disorders into types based on sets of criteria with defining features. The naming of categories has been the fundamental approach used in all systems of medical diagnosis (Kaplan & Sadock, 1998). Categorical diagnoses possess many strengths: they are a quick short-hand for clinicians, and they often lead to well-defined treatments, and statements about prognosis (Goldberg, 1996; Kendell & Jablensky, 2003). However, it is also likely that disorders as currently diagnosed represent a heterogeneous set of disorders with multiple causes (Kaplan & Sadock, 1998; Charney & Manji, 2004). Diagnostic classification should not be applied mechanically and without using clinical judgment. The classifications currently in use are the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 1987; 1994; 2000) and the International Statistical Classification of Diseases and Related Health Problems (ICD) (WHO, 1992; 1993; Tautiluokitus, 1996). In DSM-IV, unipolar forms of primary mood disorders are divided into three groups: MDD, dysthymic disorder, and depression not otherwise specified. Mood disorders are generally defined as an illness characterized by different combinations of several co-occurring symptoms for a defined period of time contributing to significant psychosocial impairment or marked distress (APA, 1994; 2000; WHO, 1992; 1993). MDD is characterized by one or more major depressive episodes lasting at least two weeks. Persistent depressive mood or significant loss of interest or pleasure is the required core symptom, which must be accompanied by at least four associated symptoms (total of 5 symptoms), such as significant weight change, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or extreme guilt, decreased ability to think or concentrate, and suicidal ideation or thoughts of death, in order to warrant a diagnosis of MDD (APA, 1987; 1994; 2000). DSM-IV also lists three levels of severity of MDD. Based on the number of criteria symptoms, the severity of the symptoms and the degree of functional disability and distress, MDD can be mild, moderate or severe (with or without psychotic features). Symptoms that are due to a general medical condition, mood-incongruent delusions or hallucinations, or bereavement must be ruled out. The terms and codes in DSM-IV are mostly compatible with ICD-10, and diagnosis of MDD is basically similar in both classifications. However, compared with DSM-IV, ICD-10 splits one criterion (feelings of worthlessness and unreasonable guilt), requires one symptom less

for diagnosis, and also includes fatigue or loss of energy among the core symptoms. Research programmes usually apply the DSM classification rather than ICD as it provides more detailed guidelines for case definition. In this thesis, unless otherwise specified, depression refers to unipolar DSM-IV MDD.

4.1.1 Melancholic features of MDD

Diagnosing the melancholic features of depression is seen to be important for identifying a group of patients whom some studies indicate are more responsive to somatic therapies (e.g. tricyclic antidepressants [TCAs] and/or eletroconvulsive therapy [ECT]). The term melancholia was first operationally defined in the DSM-III criteria (APA, 1980), although the Research Diagnostic Criteria (RDC; Spitzer et al., 1978) classification of endogenous depression served as the model for these criteria. After DSM-III and DSM-III-R (APA, 1987) appeared, several studies questioned the validity of the melancholia and melancholic type criteria (Zimmerman & Spitzer, 1989; Zimmerman et al., 1989). The shorter DSM-III feature listing, but with broadened and better defined criteria, was restored in the DSM-IV (APA, 1994; 2000). The DSM-IV melancholic features specifier includes either of the following: A) loss of pleasure in all, or almost all, activities and lack of reactivity to pleasurable stimuli, or B) three (or more) of the following: distinct quality of depressed mood, depression regularly worse in the morning, early morning awakening, marked psychomotor retardation or agitation, significant anorexia or weight loss, or excessive or inappropriate guilt (APA, 2000). The validity of the DSM-IV criteria in differentiating melancholic and non-melancholic depression has been criticized with the suggestion that observable psychomotor disturbances are the only necessary and sufficient feature of the definition of melancholia, whereas the other features are prevalent in both melancholic and non-melancholic subjects and are thus nonspecific (Parker & Hadzi-Pavlovic, 1996; Parker et al., 2000a; Parker, 2000; 2003).

The debate over whether melancholic or non-melancholic subtypes of depression represent two aetiologically distinct syndromes or one syndrome differing only in severity represents one of the important controversies in the classification of mental disorders (Carney et al., 1965; Kendell, 1976; Zimmerman & Spitzer, 1989; Rush & Weissenburger, 1994; Kendler, 1997; Parker, 2000), and concerns the descriptive as well as the construct validity of these models. The currently dominant classificatory model of depression is unitarian, defining it as a single entity varying only in severity, rather than distinguishing between melancholic and non-melancholic, or more illness types (Parker, 2000).

4.1.2 Atypical features of MDD

The term atypical was first used to describe a type of depression that responded well to monoamine oxidase inhibitors (MAOIs), and less well to TCAs and ECT (West & Dally, 1959; Sargant, 1961). The validity criteria of the atypical features subtype has been questioned, and the decision to include this subtype in the DSM-IV was controversial (Spitzer & Williams, 1982; Posternak & Zimmerman, 2002). Nevertheless, according to DSM-IV (APA, 1994) the current atypical subtype of MDD comprises five features: mood reactivity plus at least two of the following four symptoms: hypersomnia, either increased appetite or weight gain, severe lethargy ("leaden paralysis"), and a pathological rejection sensitivity.

4.2 Prevalence of MDD in general populations

The prevalence of depressive disorders in general population has been estimated in numerous epidemiological studies, and recently in a survey covering almost the whole word (WHO World Mental Health Survey Consortium, 2004). Experience, however, suggests that depression prevalence comparisons should be treated with caution. The variations in time frames, age ranges, diagnostic criteria and interview schedules (DIS, CIDI) complicate the synthesis of findings. In addition, the portability of major depression diagnostic criteria across countries requires further confirmation (Patten, 2003). However, studies on epidemiological samples generally indicate that depression is highly prevalent in the general population (Kessler et al., 1994; 2003; Ayuso-Mateos et al., 2001; Jacobi et al., 2004). It has been estimated that about a fifth of the population (Kessler et al., 1994; 2003), women more often than men, will experience a clinically significant MDE at some point in their lives, and up to 75-85% of these subjects go on to have a recurrence during their lifetime (Angst, 1986; 1995a; Mueller et al., 1999; Keller & Boland, 1998).

The National Comorbidity Survey Replication (NCS-R), conducted in 2001-2002, found a lifetime prevalence of MDD of 16.2% and a 12-month prevalence of 6.6% among US adults (Kessler et al., 2003). The Mental Health Supplement of the German National Health Interview and Examination Survey (GHS-MHS) reports the lifetime prevalence of any unipolar depression to be 17.1%, and the 12-month prevalence 10.7%, in the German population (Jacobi et al., 2004). In Finland, the Health 2000 project reports the 12-month prevalence of MDD to be 4.9% (Pirkola et al., in press), while the prevalence was found to be 9.3% in the Finnish Health Care Survey (Lindeman et al., 2000). The use of a diagnostic interview with stringent exclusion criteria probably explains the lower prevalence in the more recent Health 2000 project (Pirkola et al., in press). The Mini Finland Health Survey reported that only one third of those diagnosed with depression were actually receiving treatment, although they were assessed to be in need of it (Lehtinen et al., 1990; Lehtinen & Joukamaa, 1994). However, only about a half of those suffering from depression in Finland perceive a need for mental health services (Isometsä et al., 1997). The Finnish

Health Care Survey (Hämäläinen et al., 2004) also found that a considerable proportion (41%) of patients with even the most severe depression were not receiving any treatment. Among US adults in the NCS-R, health care treatment for depression was adequate in only a fifth of the cases with 12-month MDD (Kessler et al., 2003).

4.3 Aetiology of MDD

4.3.1 Multifactorial model

MDD is a multifactorial, clinically heterogeneous disorder with a wide range of possible aetiological factors (Kendler, 1993, 2002). The concept of depression has shifted from one where genetic, biological, developmental and environmental risk factors were thought to be unrelated and to define a particular clinical syndrome, to one where these risk factors are seen to be related and interacting (Goodyer et al., 2000; O'Keane, 2000; Kendler et al., 2002; 2004; Caspi et al., 2003; Charney & Manji, 2004). Based on this concept an individual's probability of suffering from a MDD is affected by many factors, including predisposing genetic influences (Sullivan et al., 2000; Caspi et al., 2003; Korszun et al., 2004; Lesch, 2004), exposure to early adverse experience such as maternal stress during pregnancy (Oates, 2002; O'Connor et al., 2002), parental depression (Lyons-Ruth et al., 1986; 2002; Lieb et al., 2002), childhood physical or sexual abuse (Heim et al., 2000; Gladstone et al., 2004), loss of a parent (Tennant, 1988), predisposing personality traits (Boyce et al., 1991; Caspi et al., 1996; Kendler et al., 2004), anxiety (Kessler et al., 1996b; Young et al., 2004), low social support (Cooper & Paykel, 1994), recent stressful life events (Paykel et al., 1969; Brown & Harris, 1978, Kendler et al., 2004), and many hormonal and neurobiological influences (Arborelius et al., 1999; Sapolsky, 2000; Young et al., 2000; Manji et al., 2001). However, aetiological risk factors for MDD are not necessarily similar to factors affecting the outcome and course of the disorder.

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

4.3.2 Heritability and genetic risk factors

Heritability for depression is usually reported to be in the 20-45% range (Sullivan et al., 2000; Wallace et al., 2002), but even 70% has been reported (Lesch, 2004). In a recent meta-analysis (Sullivan et al., 2000) first-degree relatives of depressed subjects had a nearly three-fold increase in their risk for MDD compared with the general population. Linkage studies in unipolar depression have also been published recently, and these suggest a number of candidate regions on different chromosomes (Abkevich et al., 2003; Zubenko et al., 2003; Holmans et al., 2004). Although MDD undoubtedly has a genetic basis, there is now compelling evidence that even early life stress constitutes a major risk factor for the subsequent development of depression. The emerging evidence suggests that a combination of genetics, early life stress and ongoing stress may ultimately determine individual responsiveness to stress and vulnerability to depression (Caspi et al., 2003). Findings by Caspi et al. (2003) suggest that childhood maltreatment interacts with allelic variation of 5-HTT expression and function (polymorphism in the 5'-flanking transcriptional control region of the 5-HTT gene [5HTTLPR]) increasing the vulnerability to developing mood disorders, and that emotionality and stress reactivity can be influenced by experiences early in life. Moreover, this allelic variation of 5-HTT expression and function is also associated with personality traits of negative emotionality, including anxiety, neuroticism and agreeableness (Lesch et al., 1996; Greenberg et al., 2000). Interestingly, some recent functional imaging studies of the brain report that serotonin transporter polymorphism also associates with reduced hippocampal volume (Frodl et al., 2004), or with greater amygdala neuronal activity (Hariri et al., 2002; Hariri & Weinberger, 2003). These findings confirm that genetically driven variation of serotonergic function might contribute to the response of brain regions underlying emotional behaviour.

4.3.3 Structural, functional and neurochemical findings

Recent studies have investigated potential structural brain changes in depression, and there is now evidence demonstrating reductions in the prefrontal cortex (Botteron et al., 2002; Bremner et al., 2002; Hastings et al., 2004), amygdala (Hastings et al., 2004), and hippocampus (Mervaala et al., 2000; Campbell et al., 2004; Videbech & Ravnkilde, 2004), as well as regional reductions in the numbers and/or sizes of glia and neurons. Activation of the hypothalamic-pituitary-adrenal (HPA) axis seems to have a role in mediating stress-induced neuronal changes (Sapolsky, 2000), and it has been suggested that aberrations in the corticotrophin releasing factor (CRF) carry most of the responsibility for HPA-axis hyperactivity (Arborelius et al., 1999), and thus hypersecretion of cortisol. In addition to directly causing neuronal atrophy, life stress and glucocorticoids also reduce cellular resilience (Manji et al., 2001). It is also likely that genetic factors contribute not only to neurochemical alterations, but also to the impairments of cellular plasticity and resilience observed in MDD (Manji et al., 2000; 2001; 2003). Actually, modifications in the expression of genes related to neurotransmission, survival of

neuronal and glial cells, and signal transduction have been recently identified (Knable et al., 2002; 2004). Neurotrophic signalling cascades involved in regulating neural plasticity, resilience and neurodegeneration may have a particularly important role in explaining the aetiology of depression (Manji et al., 2000; 2003; Charney & Manji, 2004), as well as the response to antidepressants (Manji et al., 2000; 2003; Popoli et al., 2002; Harvey et al., 2003; Charney & Manji, 2004).

4.4 Comorbidity of MDD

4.4.1 Definition of the concept

Comorbidity refers to the occurrence of two or more distinct disorders in a person in a defined period of time (Klerman, 1990). The concept of comorbidity has its origin in general medicine (Feinstein, 1970), but has also been increasingly applied in psychiatry (Klerman, 1990; Wittchen, 1996; Keller et al., 1996a), largely as a consequence of the introduction of the explicit descriptive, operational criteria for mental disorders (Feighner, 1972; Spitzer et al., 1978; APA, 1980). In particular, DSM-III (APA, 1980) supported the use of multiple diagnoses within a multiaxial classification system, and comorbidity has even been criticized for being an artefact produced by the categorical diagnostic classification systems (Klerman, 1990; Tyrer, 1995). Non-comprehensive definitions of comorbidity, variations in diagnostic assessments, timing of diagnosing, time-frame (e.g. lifetime or current), and different health care settings have led to substantial discrepancies in reported prevalences of comorbid disorders, producing a rather complex picture of their significance (Weiss et al., 1992; Zimmerman, 1994; Tyrer, 1995; Wittchen, 1996; Griez & Overbeek, 1997; Bogenschutz & Nurnberg, 2000; Vella et al., 2000).

The diagnostic categorical approach makes the strict assumption that a comorbid disorder is present or absent according to the presence or absence of specified criteria (Wittchen, 1996). The categories of disorder are very useful to practicing clinicians; for example, they provide information about the likelihood of recovery, and guide decisions about treatment (Goldberg, 1996; Kendell & Jablensky, 2003). However, many have argued for dimensional models, especially for personality disorders (Shea, 1995). There is actually growing evidence that the dimensional approach may be useful, and a dimensional rather than categorical approach to defining the depressive phenotype has recently been used for identifying susceptibility genes (Hasler et al., 2004; Korszun et al., 2004) and risk factors predicting suicidality (Verona et al., 2004). Moreover, the greater stability of comorbid anxiety and depression than either disorder alone, and the substantial persistence of subthreshold levels of these disorders has also been reported in an epidemiological sample (Merikangas et al., 2003). Interestingly, in their vision of the future Hasler and colleagues (2004) propose to dissect the behavioural phenotypes into key components, and integrate specific environmental risk factors and neurobiological

endophenotypes into the new classification system. Thus, in order to find possible connections between various accumulating symptoms, personality traits and features (Cloninger, 1987; 1993; Eysenck, 1987), and to establish better, genetically relevant depressive phenotypes (Hasler et al., 2004), our thinking should go beyond the categorical approach. Therefore, when assessing comorbidity, categorical and dimensional approaches should be allowed to coexist, and symptom patterns and subthreshold conditions may also be useful and informative. In this study (I-IV), however, comorbidity refers to current categorical (DSM-IV) diagnostic comorbidity.

4.4.2 Comorbidity of MDD in general populations

Numerous epidemiological studies and surveys have reported high comorbidity of depression (Regier et al., 1990; 1998; Grant & Harford, 1995; Angst, 1996; Kessler et al., 1996a; 1996b; 2003), and the impact of this on both outcome and health services utilization (Kessler et al., 1996a; Wu et al., 1999). Comorbid depression is more of a rule than exception: nearly half of the subjects with MDD have a current anxiety disorder (Regier et al., 1990; 1998; Kessler et al., 1996b), and about a fifth have a current substance use disorder (SUD) (Regier et al., 1990; Grant & Harford, 1995; Kessler et al., 1996a). Only about a fifth of cases with 12-month MDD had no axis I comorbid DSM-IV disorders in the recent NCS-R study (Kessler et al., 2003).

The prevalence of personality disorders in a representative sample of the general population has been reported to be between 6% and 13% (Samuels et al., 1994; Torgersen et al., 2001). However, only one study has reported the prevalence of axis II disorders in a community sample with depressive disorders, the overall prevalence being 22% (Casey et al., 2004). In addition, calculating from the figures of the Baltimore site of the Epidemiological Catchment Area (ECA) study (Samuels et al., 1994), a prevalence of 8% for comorbid axis II disorders was obtained. The prevalence of axis II disorders among subjects with lifetime MDD has varied between 23% and 47% in non-patient samples predominantly comprising first-degree relatives of psychiatric patients (Zimmerman & Coryell, 1989; Maier et al., 1992).

4.4.3 Comorbidity of MDD in clinical samples

While the construct validity of the concept of comorbidity of psychiatric disorders remains controversial, there is nevertheless accumulating evidence of the clinical significance of comorbidity in terms of treatment responses and overall clinical outcome. Clinical studies have reported that comorbidity is one of the major factors associating with poor outcome of MDD, by increasing the risk of relapse or recurrence (Alnaes & Torgersen, 1997), chronicity (Keller et al., 1984; Mueller et al., 1994), residual symptoms (Paykel et al., 1995), suicide (Fawcett et al., 1990; Cheng, 1995; Cheng et al., 1997; Fawcett, 1997; Foster et al., 1999; Hansen et al., 2003) and psychosocial impairment (Van Valkenburg et al., 1984; Rytsälä et al., in press). The current comorbidity pattern may

also influence the choice of treatment modality, as suggested in the APA Revised Practice Guideline for the Treatment of Patients with MDD (APA, 2000). In psychiatric settings, the reported prevalences of current comorbid disorders among patients with MDD have varied widely (Tables 1 and 2). Overall, about half of patients with MDD in psychiatric care also have a current anxiety and personality disorder, and about one fifth a current substance use disorder (Tables 1 and 2).

Many of the early studies focused on a single type of comorbid disorder, a design which may well inflate the prevalence of comorbidity found. For example, the estimates for prevalence of current panic disorder are two-fold higher (weighted mean 22%) in studies focused solely on comorbid panic disorder (Van Valkenburg et al., 1984; Coryell et al., 1988; Grunhaus et al., 1994) compared to studies (Sanderson et al., 1990; Fava et al., 1996a; Schatzberg et al., 1998; Zimmerman et al., 2000) focusing on several comorbid anxiety disorders concurrently (weighted mean 11%). The extent to which single type studies overestimate prevalences may vary by the type of disorder. The possible explanations for this phenomenon include less than perfect rule-outs in structured interviews, biased patient samples, and publication bias favouring high prevalences.

Only one study on comorbidity of MDD has reported prevalences of major categories on axis I disorders (Sanderson et al., 1990), and none has reported overall current comorbidity with all axis I and II disorders. Moreover, variations in patterns of comorbidity in terms of sociodemographic factors such as age, gender, marital status, education, income and type of residential area, as well as clinical characteristics such as number of lifetime depressive episodes, axis I by axis II, age at onset, and severity of depression, have been relatively little investigated in clinical populations (Pfohl et al., 1984; Flick et al., 1993; Golomb et al., 1995a; 1995b; Fava et al., 1996a; 1996b; Sato et al., 1996; Comtois et al., 1999; McGlashan et al., 2000). Furthermore, most previous studies have been conducted on inpatient populations in tertiary-level treatment centres, which might affect the generalizeability of their findings to secondary-level psychiatric settings because of the possibility of selection bias. In addition, almost all studies on comorbidity of depression have been based on DSM-III-R criteria; very few have been DSM-IV studies (Zimmerman et al., 2000).

4.5 Course and outcome of MDE

4.5.1 Methodological aspects in defining outcome

The lack of a standard and valid set of outcome definitions hinders study of the naturalistic course of depressive disorders (Frank et al., 1991; Prien et al., 1991; Keller, 2003; 2004). As descriptors for the clinical course of depressive illness, terms such as remission, relapse and recurrence have been incoherently applied as measures of outcome. The inconsistency of outcome definitions across studies leads to difficulties

when comparing and interpreting results, and their relationship to clinical practice. The first effort to achieve a terminology consensus was made by Frank et al. (1991), who suggested conceptual definitions for MDD outcome. Unfortunately, and partly because of incompatible and changing lengths of duration used for remission and recovery in these criteria, they somewhat failed to achieve consistency (Keller, 2003).

Clinical experience indicates that remission is the optimal outcome of treatment (Keller, 2003; 2004), and very recently it has been proposed that remission as optimal should be a completely asymptomatic state, with absence of both symptoms and functional impairment (Keller, 2003). This standard for remission seems essential because the presence of residual symptoms is considered a strong predictor of relapse or recurrence (Paykel et al., 1995; Judd et al., 1998; 1999), a more chronic course of depression (Judd, 2000), shorter time between episodes (Judd et al., 1998), decreased likelihood of recovery (Keller et al., 1992), and impaired social functioning (Kennedy & Paykel, 2004). Thus, the presence of even minimal residual symptoms may warrant continuation of treatment. By some standards, however, patients may be considered in remission despite still having one or two minor symptoms (Keller et al., 1982; 1983; 1992). In conclusion, as Keller has recently stated, "currently there is not a universally accepted definition of remission" (Keller, 2003).

4.5.2 Duration of MDE in general populations

Data on the duration of major depressive episodes in general populations are sparse. However, a few studies (Sargeant et al., 1990; Lehtinen et al., 1993; Angst & Merikangas, 1997; Eaton et al., 1997; Spijker et al., 2002) suggest that the prognosis of depression in a general population is somewhat better than in psychiatric care. In the ECA study, a median duration of MDE of 8-12 weeks was found (Eaton et al., 1997), and recently Spijker et al. (2002) reported a median duration of three months (95% CI 2.2-3.8). In the most recent epidemiological report from the NCS-R (Kessler et al., 2003) the mean duration of MDE was 16 weeks (95% CI 15.1-17.3). These MDEs fall into a lower range of duration than found in clinical studies (Keller et al., 1982; 1992; Coryell et al., 1994; Angst & Preisig, 1995; Solomon et al., 1997; Furukawa et al., 2000; Kennedy et al., 2003). However, a rate of 20% for chronicity in a general population (Spijker et al., 2002) was similar to findings in clinical populations (Keller et al., 1982; 1992; Coryell et al., 1994; Angst & Preisig, 1995; Solomon et al., 1997; Furukawa et al., 2000; Kennedy et al., 2003).

4.5.3 Outcome of MDD

On the basis of available studies of its outcome, MDD appears to be a chronic illness with a high risk of recurrence over the lifetime. Prospective long-term (Angst 1986; Keller et al., 1992; Angst & Priesig, 1995a; 1995b; Mueller et al., 1996; 1999; Keller & Boland, 1998; Solomon et al., 1997; 2000; Kennedy et al., 2003) and shorter-term outcome studies

(Maj et al., 1992; Wells et al., 1992; Ramana et al., 1995; Parker et al., 2000b; Sherrington et al., 2001; Myers et al., 2002), as well as retrospective long-term outcome studies (Kiloh et al., 1988; Lee & Murray, 1988; Andrews et al., 1990; Thornicroft & Sartorius, 1993; Surtees & Barkley, 1994; Brodaty et al., 2001) document high recurrence and chronicity of major depressive episode. It seems that approximately eight out of ten people experiencing MDE will have at least one more episode during their lifetime (Angst, 1986; Mueller et al., 1999), and about one fifth will have a chronic course of MDE lasting ≥2 years (Keller et al., 1992). Moreover, previous long-term studies have shown that symptoms at sub-syndromal level are common and persist for many years after an episode of MDD (Angst & Merikangas, 1997; Judd et al., 1998), even with antidepressant treatment (Kennedy et al., 2004).

The tendency for patients in tertiary-level treatment centres to have undergone many prior treatments may produce bias towards more chronic, severe and recurrent illnesses compared with more unselected cohorts of MDD patients (Furukawa et al., 2000; Roy-Byrne et al., 2000; Spijker et al., 2002; Kanai et al., 2003). Thus, the length of depressive episode and rate of recurrence can be expected to vary by the level of treatment setting and inpatient or outpatient status. In fact, several short-term (Kessler et al., 1985; Sargeant et al., 1990; Ormel et al., 1993; Lin et al., 1998; Simon, 2000; Spijker et al., 2002) and a few long-term (Coryell et al., 1991; Angst & Merikangas, 1997; Eaton et al., 1997; van Weel-Baumgarten et al., 1998) outcome studies suggest that the prognosis of depression is better in community and primary health care settings than in psychiatric care. Moreover, the most influential outcome studies (Piccinelli & Wilkison, 1994; Judd, 1997) were undertaken during the past era of tricyclic antidepressants and before the recommendation of continuation and maintenance treatments, which again somewhat undermines the ability to generalize such findings to current psychiatric settings.

4.5.3.1 Clinical factors as predictors of outcome

Preventing chronicity and recurrence of depressive episodes is the central aim of treatment, and information on risk factors for chronicity and recurrences is important for identifying patients at particularly high risk. Severity of the MDE, comorbid dysthymia (double depression), and longer duration of index episode before entry have been consistently associated with non-recovery or longer time to remission (Keller et al., 1982; 1984; 1992; Ramana et al., 1995; Mueller et al., 1999; Parker et al., 2000b; Solomon et al., 2000; Myers et al., 2002). Some studies have shown that severity of depression predicts relapse (Ramana et al., 1995), while other have found that it does not (Keller et al., 1983; Sherrington et al., 2001), and severity is a risk factor for partial remission (Paykel et al., 1995). The presence of residual symptoms is further considered a strong predictor of relapse or recurrence (Paykel et al., 1995; Judd et al., 1998; 1999), a more chronic course of depression (Judd, 2000), shorter time between episodes (Judd et al., 1998), a decreased likelihood of recovery (Keller et al., 1992), and impaired social functioning (Kennedy & Paykel, 2004). The number of prior MDEs and longer duration of the

MDE prior to entry have also predicted relapse/recurrence (Keller et al., 1982; 1983; Coryell et al., 1991; Maj et al., 1992; Surtees & Barkley, 1994; Lin et al., 1998; Mueller et al., 1999). Information on age and gender as risk factors for both chronicity and recurrence is inconsistent (Keller et al., 1982; 1986; 1992; Sargeant et al., 1990; Coryell et al., 1991; Keitner et al., 1992; Huges et al., 1993; Surtees & Barkley, 1994; Zlotnick et al., 1996; Simpson et al., 1997; Solomon et al., 1997; Mueller et al., 1999; Hoencamp et al., 2001; Myers et al., 2002; Kennedy et al., 2004). Sociodemographic factors appear to have no significant effects on the outcome of MDD when depression severity and level of functional status are controlled for (Wells et al., 1992; Mueller et al., 1996).

4.5.3.2 Comorbidity as a predictor of outcome in clinical studies

Rates of non-recovery, recurrence and relapse among patients with MDD and comorbid disorders are likely to be greater than among patients with depression alone. Depressed patients with panic disorder or with higher symptom ratings of anxiety have shown a longer time to recovery (Keller et al., 1986; Coryell et al., 1988; 1992; Clayton et al., 1991; Keitner et al., 1992; Parker et al., 2000b). The US National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS) is the only study to have investigated the effects of current comorbid alcoholism among patients with MDD, finding those with current alcoholism to be only half as likely to recover from their MDE (Mueller et al., 1994). However, there is surprisingly little information on current axis I comorbidity and risk of relapse/recurrence in clinical cohorts of depressive patients. The CDS found some anxiety syndromes, but not current alcoholism, to be associated with higher risk of relapse (Coryell et al., 1992; Mueller et al., 1994).

In a few naturalistic outcome studies in which semistructured interviews for both MDD and axis II disorders were used, personality disorders predicted longer time to remission (Sato et al., 1993; Greenberg et al., 1995; Ilardi et al., 1997; Viinamäki et al., 2002; 2003), and risk of relapse (Alnaes & Torgersen, 1997; Ilardi et al., 1997). Convergently, high neuroticism (Surtees & Wainwright, 1996; Gormley et al., 1999) and low self-esteem (Andrew et al., 1993; Surtees & Wainwright, 1996; Sherrington et al., 2001) have also been related to longer duration of MDE.

Overall, the available evidence on the effects of current comorbidity on outcome of MDD in clinical cohorts is somewhat difficult to interpret because of several methodological limitations. These include not using semi/structured interviews for both MDD and comorbid disorders, or not controlling for the effects of additional comorbid disorders, or not using life-chart methodology (and thus reporting only cross-sectional findings). A recent review of personality pathology and outcome in MDD, while pointing out many methodological problems in measurements, suggests that comorbid personality pathology should not be seen as an impediment to good treatment response (Mulder, 2002).

Although comorbidity in MDD is prevalent, the effect of overall comorbidity on the length of episode or risk of recurrence has not been systematically investigated. Furthermore, prevalences of comorbid cases have been quite low in some earlier studies (Keller et al., 1983; Mueller et al., 1999) compared with those reported in more recent clinical investigations (Zimmerman et al., 2000).

4.5.3.3 Psychosocial factors as predictors of outcome

Adverse life events, together with genetic vulnerability and temperament factors, are likely to form one of the key domains of liability to MDD (Kendler et al., 1993; 2002; 2004), and interactions between these risk factors seem important. Stressful life events leading to depression, and the declining association between life events and risk for MDD with increasing number of previous MDEs may be moderated by genetic vulnerability (Kendler et al., 2001; Caspi et al., 2003). However, studies investigating possible effects of psychosocial factors on the outcome of MDD in psychiatric samples are relatively sparse. Stressful life events and lack of social support are associated with worse outcome of depression in community and some clinical studies (Coryell, 1988; Paykel, 1994), although in most prospective studies of severe and recurrent depression little effect on time to remission or subsequent relapse has been found (Andrew et al., 1993; Paykel, 1994; Sherrington et al., 2001).

4.5.3.4 Melancholic subtype as predictor of outcome and stability of melancholic features

Most outcome studies (Keller et al., 1984; 1986; Kiloh et al., 1988; Parker et al., 1992; Ramana et al., 1995; Broadity et al., 2001; Kennedy et al., 2003) have found no difference in outcome between endogenous/melancholic and non-melancholic depression, while some have found a correlation between endogeneity and less favourable outcome (Lee & Murray, 1988; Duggan et al., 1991). In the Maudsley Study (Lee & Murray, 1988), the melancholic subjects tended to have more severe episodes but better non-episode functioning.

One crucial aspect of descriptive validity of the DSM definition for melancholic depression, i.e. longitudinal stability across illness episodes, has received little attention. If the two subtypes correspond to two different disorders, then this dichotomy should show stability over time (Coryell et al., 1994). The findings reported in earlier studies (Kendell, 1974; Paykel et al., 1976; Young et al., 1987; Coryell et al., 1994) are somewhat inconsistent. In the US NIMH CDS (Coryell et al., 1994) the RDC endogenous subtype was stable among patients with primary depression, but not among those with secondary depression. Overall, it has been suggested that the non-endogenous subtype may become endogenous during subsequent episodes more frequently than the reverse development (Rush & Weissenburger, 1994). A very recent study found no evidence that either symptoms or subtype of recurrent MDD are stable across episodes (Oquendo et al., 2004).

4.5.3.5 Atypical and psychotic subtypes as predictors of outcome

Little is known about the course of MDD with atypical features. One study has reported that patients with atypical features had longer (Asnis et al., 1995), and another shorter episodes of depression (Kendler et al., 1996). It has also been reported that atypical depressives tend to have a more chronic course compared with non-atypical patients in clinical but not epidemiologically derived samples (Nierenberg et al., 1998). Psychotic features have been associated with a more severe form of depressive illness with greater levels of psychosocial impairment (Coryell et al., 1987; 1996; Lee &Murray, 1988).

4.6 Treatment of MDD

Several sets of evidence-based treatment guidelines have been published to improve detection and treatment of major depressive disorder (Schulberg et al., 1998; Crismon et al., 1999; Anderson et al., 2000; APA, 2000; Bauer et al., 2002; Suomen Psykiatriyhdistys, 2004). Effective treatments include antidepressant medications, psychotherapy, a combination of medication plus psychotherapy, and ECT (Schulberg et al., 1998; Crismon et al., 1999; Anderson et al., 2000; APA, 2000; Bauer et al., 2002; Suomen Psykiatriyhdistys, 2004), and guidelines suggest treatment should be continued until remission of symptoms and normal level of functioning.

4.6.1 Antidepressant treatment

Adequate antidepressant treatment of MDD consists of an acute phase, during which remission is induced, a continuation phase, during which remission is preserved, and a maintenance phase, during which the vulnerable patient is protected against recurrence of subsequent episodes (APA, 2000; Suomen Psykiatriyhdistys, 2004). In the acute phase antidepressants should be provided as an initial primary treatment modality for mild to severe MDD (APA, 2000; Suomen Psykiatriyhdistys, 2004). Because the effectiveness of the various antidepressants is comparable, the selection of an antidepressant will largely be based on its profile of side-effects, the safety or tolerability of these side-effects, interactions with other medications, and patient's preference. If at least moderate improvement is not observed in the following six to eight weeks, there should be reappraisal of the treatment regimen (APA, 2000; Suomen Psykiatriyhdistys, 2004). In the continuation phase, i.e. the four to nine months following remission, patients should be maintained on antidepressants. Following the continuation phase, maintenance phase treatment should be considered to prevent recurrences (Viguera et al., 1998; APA, 2000; Geddes et al., 2003; Nierenberg et al., 2003; Suomen Psykiatriyhdistys, 2004). The factors that should be considered when deciding whether to use maintenance treatment include number of prior episodes, presence of comorbid conditions, residual symptoms, suicidality, psychotic features, certain functional impairments, possible side-effects, and patient preference (APA, 2000).

4.6.2 Psychosocial treatment

In the acute phase, a specific, effective psychotherapy (cognitive, behavioural, interpersonal, psychodynamic) alone as an initial treatment may be provided for patients with mild to moderate MDD (APA, 2000; Suomen Psykiatriyhdistys, 2004). Clinical features that may suggest the use of psychotherapeutic interventions include the presence of psychosocial stressors, intrapsychic conflict/interpersonal difficulties, or comorbid axis II disorder (APA, 2000). There is increasing evidence to support the use of a specific psychotherapy in the continuation and maintenance phases to prevent recurrences (APA, 2000; Nierenberg et al., 2003; Suomen Psykiatriyhdistys, 2004). Frequency of visits usually decreases in the maintenance phase (APA, 2000; Suomen Psykiatriyhdistys, 2004).

4.6.3 Combination treatment

The combination of psychotherapy and medication is recommended for those with psychosocial/interpersonal problems, or comorbid axis II disorder together with moderate to severe MDD. Poor adherence to treatments may also warrant a combination of treatment modalities (APA, 2000). In a recent systemic review Pampallona et al. (2004) concluded that combined antidepressant therapy and psychosocial treatment is associated with a higher improvement rate than pharmacotherapy alone.

4.6.4 Treatment adherence

The degree to which a patient follows a treatment regimen has been defined in a variety of ways, and different terms have been used. Compliance has traditionally been referred to as "the extent to which a person’s behaviour confirms to medical advice, and especially the extent to which the patient takes the medications as described" (Bruer, 1982; Frank et al., 1992), while adherence is defined as "patient acceptance of recommended health behaviours" (Wright, 1993). The literature (Frank et al., 1992; Lingam & Scott, 2002; Nemeroff, 2003) tends to prefer the term adherence as it may also remind clinicians to form a good therapeutic alliance with the patient, and emphasises active rather than passive participation of the patient in this process. Intervention studies have shown that psychoeducation is an effective way to enhance treatment adherence by offering structured and detailed information to patients about their treatments (Demyttenaere & Haddad, 2000; Lin et al., 2003; Vergouwen et al., 2003). However, confusion about terminology in this field remains somewhat unresolved (Lingam & Scott, 2002; Nemeroff, 2003), and the terms "compliance" and "adherence" are still used interchangeably.

Practice guidelines suggest that psychiatrists should recognize patients’ non-adherence, and encourage them to discuss any concerns regarding adherence (APA, 2000). The components of communication to patients that have been shown to improve adherence include reminding them of when and how often to take the medicine, the need for at least 2-4 weeks

before beneficial effects may be noticed, the need to take medication even after feeling better, the need to consult with the doctor before discontinuing medication, and what to do if problems arise (APA, 2000).

4.6.5 Studies on treatment adequacy and adherence

Primary care (Katon et al., 1995; Lin et al., 2000; Demyttenaere et al., 2001) and retrospective database studies (Melfi et al., 1998; Claxton et al., 2000) have reported frequent shortcomings in depression treatment, including inadequate follow-up of dosage and monitoring of antidepressant treatment. However, few recent psychiatric care studies have investigated the extent to which treatment recommendations, especially after the immediate acute phase, are carried out (Ramana et al., 1999; Sirey et al., 1999; Simon et al., 2001; Cuffel et al., 2003; Kennedy et al., 2003). Treatment received, and predictors of treatment inadequacy and premature termination, are rarely reported, even though premature termination of treatments is a great concern for clinicians.

Medication non-adherence is common; estimates of non-adherence for affective disorders range from 10% to 60%, with a median of 40% (Lingam & Scott, 2002). However, according to the recent review, only 1% to 2% of all publications on treatment of affective disorders explore factors associated with medication adherence (Lingam & Scott, 2002). Part of this neglect is explained by the unresolved confusion about terminology, and highly variable methods (i.e. prescription counts, pill counts, appointments kept, drug/metabolite plasma concentrations) used in measuring non-adherence (Demyttenaere et al., 2001; Lingam & Scott, 2002; Pampallona et al., 2002; Demyttenaere, 2003).

Recent studies, although limited in number, show increasing attention being focused on various risk factors for non-adherence, such as stigma, health-beliefs and negative attitudes towards psychiatric treatments (Melfi et al., 1998; Demyttenaere & Haddad, 2000; Demyttenaere et al., 2001; Sirey et al., 2001; Keller et al., 2002; Lingam & Scott, 2002; Demyttenaere, 2003; Lin et al., 2003). However, the extent to which patients' negative treatment attitudes, fear of side-effects, perceived side-effects per se, comorbidity and severity of depression influence premature terminations of treatments, or non-adherence, is still poorly understood (Lingam & Scott, 2002; Pampallona et al., 2002; Demyttenaere, 2003).

Table 1. Current Axis I comorbidity of major depressive disorder in psychiatric settings

Study reference	N	Outpatients %	Sex/ Females %	Method	%
Any anxiety disorder					
Sanderson et al., 1990	197	100	56	SCID (DSM III-R)	42
Pini et al., 1997	38	100	75	SCID-P (DSM-III-R)	92
Schatzberg et al., 1998	85	38	49	SCID-P (DSM-III-R)	29
Fava et al., 2000	255	100	NR	SCID-P (DSM-III-R)	45
Zimmerman et al., 2000	373	100	67	SCID (DSM-IV)	57
Panic disorder					
Van Valkenburg et al., 1984	114	NR (in/outpatients)	44	semi-structured interview (Feighner, DSM-III)	27
Coryell et al., 1988	523/387*	NR (mostly inpatients)	60	SADS (RDC)	19
Sanderson et al., 1990	197	100	56	SCID (DSM-III-R)	10
Grunhaus et al., 1994	176/136*	NR (in/outpatients)	71	SADS (RDC)	34
Fava et al., 1996a	396	100	66	SCID-P (DSM-III-R)	8
Schatzberg et al., 1998	85	38	49	SCID-P (DSM-III-R)	7
Fava et al., 2000	255	100	NR	SCID-P (DSM-III-R)	8
Zimmerman et al., 2000	373	100	67	SCID (DSM-IV)	17
Generalized anxiety disorder					
Sanderson et al., 1990	197	100	56	SCID (DSM-III-R)	20
Fava et al., 1996a	396	100	66	SCID-P (DSM-III-R)	9
Fava et al., 2000	255	100	NR	SCID-P (DSM-III-R)	10
Zimmerman et al., 2000	373	100	67	SCID (DSM-IV)	15
Social phobia					
Sanderson et al., 1990	197	100	56	SCID (DSM-III-R)	15
Fava et al., 1996a	396	100	66	SCID-P (DSM-III-R)	26
Alpert et al., 1997	243	100	55	SCID-P (DSM-III-R)	27
Schatzberg et al., 1998	85	38	49	SCID-P (DSM-III-R)	13
Fava et al., 2000	255	100	NR	SCID-P (DSM-III-R)	26
Zimmerman et al., 2000	373	100	67	SCID (DSM-IV)	33
Simple phobia					
Sanderson et al., 1990	197	100	56	SCID (DSM-III-R)	2
Fava et al., 1996a	396	100	66	SCID-P (DSM-III-R)	14
Schatzberg et al., 1998	85	38	49	SCID-P (DSM-III-R)	5
Fava et al., 2000	255	100	NR	SCID-P (DSM-III-R)	15
Zimmerman et al., 2000	373	100	67	SCID (DSM-IV)	14

Study reference	N	Outpatients %	Sex/ Females %	Method	%
OCD					
Sanderson et al., 1990	197	100	56	SCID (DSM-III-R)	4
Fava et al., 1996a	396	100	66	SCID-P (DSM-III-R)	4
Schatzberg et al., 1998	85	38	49	SCID-P (DSM-III-R)	9
Fava et al., 2000	255	100	NR	SCID-P (DSM-III-R)	5
Zimmerman et al., 2000	373	100	67	SCID (DSM-IV)	10
PTSD					
Sanderson et al., 1990	197	100	56	SCID (DSM-III-R)	0
Schatzberg et al., 1998	85	38	49	SCID-P (DSM-III-R)	4
Zimmerman et al., 2000	373	100	67	SCID (DSM-IV)	13
Alcohol use disorders					
Sanderson et al., 1990	197	100	56	SCID (DSM-III-R)	8
McDermut et al., 2001	373	100	67	SCID (DSM-IV)	9

Only studies with 1) semistructured or standardized diagnostic interviews for both MDD and comorbid disorders, 2) sample size of at least 25 patients, 3) unipolar MDD as their main sampling inclusion criterion, 4) adult age, and 5) only studies conducted in psychiatric settings are included.

*= unipolar MDD
NR= not reported

Table 2. Overall Axis II comorbidity of major depressive disorder in psychiatric settings

Study reference	N	Outpatients %	Sex/ Females %	Method	%
Any personality disorder					
Kocsis et al., 1986	26 (39*)	100	69 (69)	semi-structured interview (DSM-III)	40 (47)
Alnaes & Torgersen, 1988	289/97**	100	71	SCID (DSM-III) SCID (DSM-III)	86
Sanderson et al., 1992	197 (32***)	100	56 (56)	SCID-P (DSM-III-R) SCID-II (DSM-III-R)	50 (69)
Stuart et al., 1992	59	100	75	SADS (RDC) PDE (DSM-III-R)	24
Flick et al., 1993	352/165**	100	60	SCID (DSM-III-R) SCID-II (DSM-III-R)	61
Golomb et al., 1995b	316/117****	100	66	SCID-P(DSM-III-R) SCID-II (DSM-III-R)	56
Pepper et al., 1995	45 (97*)	100	67 (75)	SCID (DSM-III-R) PDE-R (DSM-III-R)	18 (60)
Sato et al., 1996	96	100	57	SCID-P (DSM-III-R) SCID-II (DSM-III-R)	55
Fava et al., 2002	384	100	55	SCID-II (DSM-IV?)	64

Only studies with 1) semistructured or standardized diagnostic interviews for both MDD and comorbid disorders, 2) sample size of at least 25 patients, 3) unipolar MDD as their main sampling inclusion criterion, 4) adult age, and 5) only studies conducted in psychiatric settings are included.

*= including dysthymia and double depression
**= patients with MDD
***= double depression
****= SCID II for 117 subjects; only the results of SCID II reported here; the older group was also included (mean age 49.2±5.8 years)

5. AIMS OF THE STUDY

This study investigated current comorbidity, outcome and treatments received in a sample of 269 MDD patients in secondary level psychiatric care.

The specific aims of the study were:

I To comprehensively investigate current axis I and II comorbidity, and variations by clinical and sociodemographic factors, in a representative psychiatric sample.

II To determine the outcome of MDE in a modern secondary-level psychiatric setting, and the influence of psychiatric and somatopsychiatric comorbidity plus psychosocial factors on the outcome.

III To investigate and compare the stability, outcome and comorbidity of the melancholic versus non-melancholic subtype of MDD.

IV To describe the quality and continuity of psychotherapeutic and antidepressant treatments received in acute, continuation and maintenance phases of MDD, patients' self-reported level of adherence and treatment attitudes, and factors explaining these.

6. METHODS

6.1 General study design

The VDS is a collaborative depression research project between 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 catchment area 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 centers - each covering a specified catchment area - and two day hospitals.

6.2 Screening

The first phase of patient sampling for the VDS involved screening all patients in the PMCD with a possible new episode of DSM-IV MDD between 1st February 1997 and 31st May 1998. During that period, every patient (N=806) aged 20-59 years 1) seeking treatment at, 2) being referred to, or 3) already receiving care and now showing signs of deteriorating clinical state in the Department of Psychiatry but without a clinical diagnosis of ICD-10 schizophrenia or bipolar I disorder, was screened for the presence of depressive symptoms. The screening instrument included the five screening questions for depression from the WHO Schedule for Clinical Assessment in Neuropsychiatry (SCAN), Version 2.0 (Wing et al., 1990). The Scale for Suicidal Ideation (SSI) (Beck et al., 1979) was also completed 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 in the SSI, irrespective of the presence of depressive symptoms, the patient was fully informed about the study project, and written informed consent requested. Of the 703 eligible patients, 161 (22.9%) refused to participate in the study, but 542 (77.1%) agreed and gave written informed consent (Table 3). The patients who refused did not differ significantly (P>.05) in age or gender from those who consented. The Ethics Committee of Peijas Hospital approved the study on 2nd December 1996.

Figure 1. Flow-chart of the sampling procedure in the VDS

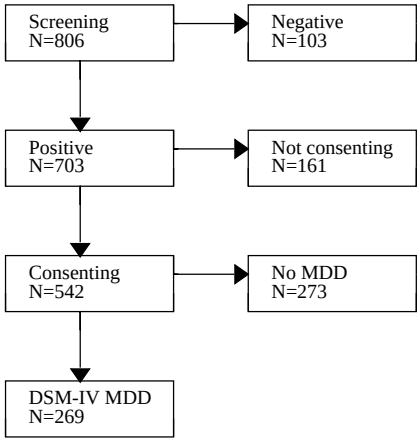


Table 3. Methods in the Vantaa Depression Study

Timing of screening	Between February 1, 1997, and May 31, 1998
Catchment area	City of Vantaa (population 169 000 in 1997)
Setting	Department of Psychiatry of the Peijas Medical Care District, Vantaa, Finland
Target group	All psychiatric patients aged 20-59 years 1) seeking treatment 2) referred to treatment, or 3) already in treatment with an acute deteriorating clinical state
Excluded from screening	ICD-10 schizophrenia, bipolar I disorder
Screening procedure	a) The five screening questions for depression from SCAN, one positive, or b) The Scale for Suicide Ideation (SSI), a score of six or more
Screened total	806
Screened positive	703
Refusals	161 (23% of the screened positive)
Diagnostic interview	After informed consent DSM-IV (axis I, SCAN), and DSM-III-R (SCID-II modified to DSM-IV)
Inclusion criteria	DSM-IV unipolar MDD with a new depressive episode
Excluded from study	DSM-IV bipolar I and II disorder, shizoaffective disorder, organic or substance-induced mood disorder
Diagnostic reliability	20 videotaped diagnostic interviews, kappa coefficient 0.86 (0.58-1.00); for comorbidity and melancholic MDD not tested

6.3 Baseline evaluation

6.3.1 Diagnostic measures

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

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

6.3.2 Exclusion criteria

Patients with a diagnosis of DSM-IV bipolar I or II disorder, shizoaffective disorder, schizophrenia or another psychosis, organic or substance-induced mood disorder were excluded from the study, even if they fulfilled the symptom criteria of current MDE (Table 3). So were the cases with a history of MDD if the current episode did not fulfill the criteria of the disorder.

6.3.3 Observer and self-report scales

The 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) and the 21-item Beck Depression Inventory (BDI; Beck et al., 1961) were used to assess severity of depression, the SSI suicidal behaviour; the Social and Occupational Functioning Assessment Scale for DSM-IV (SOFAS; Goldman et al., 1992) functional level; the Interview for Recent Life Events (IRLE; Paykel, 1983) life-events, and the Interview Measure of Social Relationships (IMSR; Brugha et al., 1987) and the Perceived Social Support Scale - Revised (PSSS-R; Blumenthal et al., 1987) social support. Self-report scales, in addition

to the BDI, included the Beck Anxiety Inventory (BAI; Beck et al., 1988), the Beck Hopelessness Scale (HS; Beck et al., 1974), the Social Adjustment Scale-Self Report (SAS-SR; Weissman et al., 1976), and the Eysenck Personality Inventory (EPI; Eysenck & Eysenck, 1964).

6.3.4 Melancholic subtype and neurotisicm

The distinction between melancholic and non-melancholic depression was based on the SCAN and DSM-IV criteria. The psychomotor symptoms (marked retardation or agitation) were observed and rated as part of DSM-IV diagnostic assessments at baseline and follow-up interviews. Neurotisicm was rated with the EPI. When analyzing stability of melancholic features subtypes, only those patients who met the criteria for MDE at the time of the follow-up interviews could be evaluated. Patients who remained with the full MDE criteria for the whole follow-up period were excluded from these analyses.

6.3.5 Patients' attitudes towards treatments

Attitudes towards antidepressant and psychotherapeutic treatments at baseline were assessed separately by interview and rated on a Likert scale with the following items: patient 1) actively wants treatment, 2) passively accepts treatment, 3) has reservations about treatment, 4) has definitely negative attitudes towards treatment, or 5) could not answer. At the follow-ups, patients were interviewed with scales comprised of the following items: attitudes are 1) very positive, 2) positive, 3) neutral, 4) negative, 5) very negative towards treatment, or 6) could not answer.

Patients with reservations about, or definitely negative attitudes towards treatments were also asked their subjective reasons for these attitudes, with the following alternatives: 1) generally negative attitudes toward treatment, 2) fear of side-effects (antidepressants) / not wanting to confide in a stranger (psychotherapeutic treatments), 3) fear of dependence, 4) not knowing enough about treatment, 5) patient's / other's negative earlier experiences of treatment, 6) negative information from media, 8) no belief that treatment will help, 9) treatment too expensive, or 10) could not answer.

6.4 Follow-up procedure

Of the total of 269 subjects with current MDD initially included in the study, 40 subjects were missing (N=229) at six months. Some of these were traced again for the 18-month follow-up (N=207), so only 13% (35/269) dropped out from both follow-up interviews. The patients whose diagnosis switched to bipolar disorder during the 18-month follow-up (5%, 13/269) were censored from the analyses, and eight patients died during follow-up. The median times to follow-up interviews were 6.5 and 18.8 months for six- and 18-month interviews, respectively.

6.4.1 Study drop-outs

The drop-outs were significantly younger (median 31.2 vs. 42.3, Z=-3.32, P=.001), more often living alone (19%, 24/125 vs. 8%, 11/131, χ^2=6.33, df=1, P=.017), scored higher on the EPI-neuroticism scale (median 20.0 vs. 18.0, Z=-2.17, P=.030), and were more likely to have comorbid dysthymia (26%, 8/31 vs. 12%, 27/225, Fisher's exact test, P=.049) than those attending both follow-ups. Patients who dropped out did not differ significantly (P>.05) in DSM-IV melancholic features from those who completed the follow-up.

In some analyses only those attending the 18-month follow-up were included; in this case the drop-outs (bipolar cases excluded) were significantly younger (mean±SD, 35.7±10.2 vs. 41.0±11.1 years, t=3.24, df=254, P=.001), more often unemployed (53%, 31/58 vs. 35%, 68/193, χ^2=6.20, df=1, P=.013), and had current comorbid psychiatric DSM-IV disorders (mean±SD, 3.5±2.0 vs. 3.0±1.7, t=-2.08, df=254, P=.038), panic disorder (26%, 15/58 vs. 13%, 26/198, χ^2=5.41, df=1, P=.020), and social phobia more often (29%, 17/58 vs. 17%, 34/198, χ^2=4.14, df=1, P=.042) than those attending the 18-month follow-up. When baseline treatments were compared, the only significant finding was that drop-outs were without antidepressants more often (22%, 13/58 vs. 12%, 24/198, χ^2=3.84, df=1, P=.050).

6.4.2 Outcome measures

After the baseline assessments, the patients were asked to complete the BDI each month for six months. The outcome of MDD and the comorbid disorders was investigated at six and 18 months by SCAN 2.0 and SCID-II interviews. In addition, all observer- and self-report scales were included at both follow-up assessments. All medical and psychiatric records were also available.

6.4.2.1 Life-chart methodology

The exact duration of the index episode and the timing of possible relapses/recurrences were examined by gathering all available data, which were then integrated into the form of a graphic life chart. This was created at the six- and 18-month interviews after reviewing with the patient all the information from the follow-up period. Besides symptom ratings and visits to attending personnel, change points in the psychopathologic states using probes related to important life-events were also asked in order to improve the accuracy of assessment.

The life-chart was based on DSM-IV criteria and definitions. Time after the first baseline interview was divided into three periods: (1) state of full remission (none of the 9 MDE criteria symptoms), (2) state of partial remission (1-4 of the 9 symptoms), or (3) state of MDE (5+ of the 9 symptoms). As a categorical variable, remission (further specified as full or partial) was defined according to the DSM-IV, as at least two consecutive months

in which criteria for a MDE were not met. Patients were considered to have achieved full remission if they had spent at least two consecutive months in the state of full remission, and partial remission if they had spent at least two months in the state of partial remission. Relapse was defined as return of symptoms fulfilling the DSM-IV criteria for MDE after a period of less than two months (but more than 2 weeks) with symptoms below the MDE threshold. Recurrence was defined as in the DSM-IV definition for 296.3x MDD, as a return of symptoms sufficiently severe to satisfy criteria for an MDE after at least two consecutive months of partial or full remission.

6.4.3 Definitions of duration of the index episode

Two alternative definitions for duration of the index episode after the first baseline interview were used: (1) the uninterrupted duration of the episode in the state of MDE (Time with full MDE criteria), and (2) time to the first onset of state of full remission lasting at least two consecutive months (Time to full remission).

6.5 Treatments provided and their continuity

Psychotherapeutic support comprised regular appointments with a mental health professional aimed at helping the patient by discussing her/his problems (weekly psychotherapy excluded). Weekly psychotherapy was defined as weekly therapy sessions for ≥ four weeks with a qualified, certified therapist (usually with psychodynamic, sometimes cognitive-behavioural training). The adequacy of antidepressant dosage was defined as the usual adult doses in the APA Practice Guidelines (APA, 2000). Continuity of psychotherapeutic and antidepressant treatment was assessed by interviewing patients and investigating all clinical information on treatment, including medical and psychiatric records. Treatment was defined as ongoing as long as it was provided/prescribed according to psychiatric records, while termination was the date when treatment was first documented as not ongoing (or reportedly terminated by the patient if no later contact with a professional). Here, sequential antidepressant trials and their intermediate short wash-out periods were classified as one continuous treatment period.

6.5.1 Self-reported reasons for discontinuing

Patients were asked their subjective reasons for discontinuing antidepressants, with the following alternatives: 1) poor/no response, 2) side-effects, 3) too expensive medication, 4) no need for treatment because of recovery, 5) patient’s autonomous decision, and 6) could not answer.

6.5.2 Self-reported treatment adherence

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

6.6 Data analyses

The Pearson chi-square statistic with Yates' continuity correction test, and Fisher's exact test were used to evaluate categorical and non-parametric data, the Mann-Whitney or Kruskal-Wallis test to compare continuous variables not normally distributed, and the two-sample t-test for continuous variables normally distributed. Logistic regression models were used to adjust for confounding factors. The Kaplan-Meier survival curves were used to estimate the probability of remaining ill, and on an antidepressant during the 18-month follow-up. Cox proportional hazards models (Cox, 1972) were used in the analyses for predicting time to symptom state below MDE criteria or to full remission. In these analyses, censored data included the subjects who (1) had not achieved a symptom state below the MDE criteria or (2) had not met the criteria of full remission by the end of the follow-up period or by the time they left the study, or their diagnosis had switched to bipolar disorder. Treatment received was reported separately for patients with full, partial and no remission from the index episode because of the tendency of sicker patients to receive more treatment in a naturalistic study (Sturm, 1999). Only those who completed the whole 18-month follow-up could be included in analyses of the risk of recurrences, stability of MDD subtypes, and treatments provided during the follow-up. In hypothesis testing a p-value $<.05$ was considered significant, and p-values between 0.05 and 0.10 were reported as trends. Odds rations with 95% confidence interval not including 1 were considered significant. SPSS software, versions 9.0 or 11.0, was used (SPSS, 1999; 2001).

7. RESULTS

7.1 Current comorbidity of psychiatric disorders in MDD (Study I)

7.1.1 Clinical and demographic characteristic of the sample

The majority of the patients in the MDD cohort were females (73%), and outpatients (83%), half (50%) were married or cohabited, and 60% currently employed. Of the cohort patients, 36% met the criteria for DSM-IV melancholic features, while 64% had the non-melancholic subtype (Table 4). The melancholic depressive patients were significantly more often inpatients, had more severe depression, and lower level of functional capacity. There were no statistically significant differences in age, gender, psychotic features, current employment or marital status between patients with melancholic and non-melancholic features (III: Table 1).

7.1.2 Current overall comorbidity

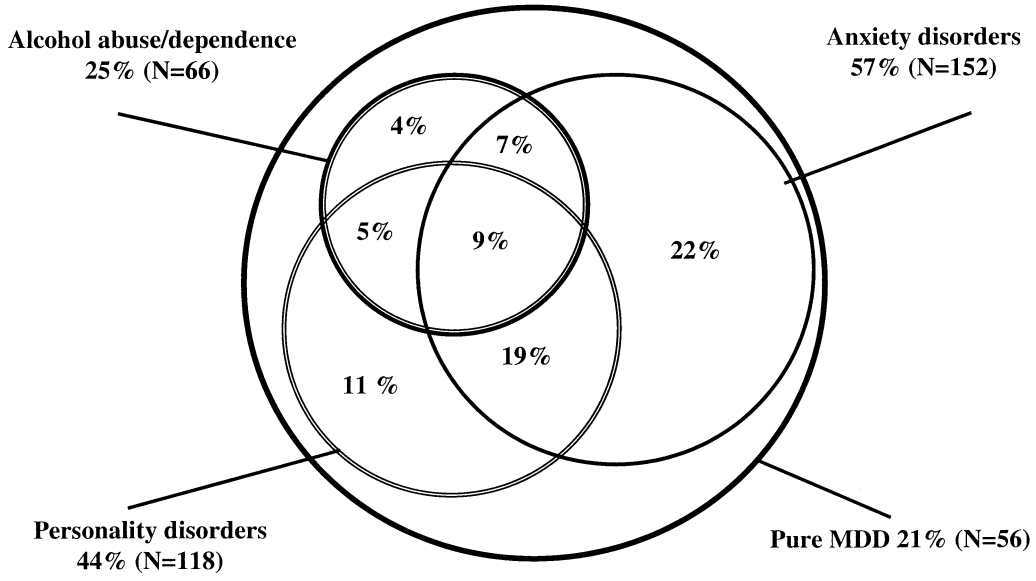
Most (79%) of the patients suffered from at least one current comorbid disorder, and the majority (54%) from two or more. Over half (57%) had an anxiety disorder, a quarter (25%) alcohol abuse or dependence, and nearly half (44%) at least one personality disorder (PD) diagnosis (Figure 2).

7.1.3 Variations of comorbidity by sociodemographic and clinical factors

7.1.3.1 Axis I and axis II

The anxiety disorders (OR 2.36, 95% CI 1.05-5.30), especially panic disorder (OR 2.37, 95% CI 1.03-5.45), as well as alcohol dependence (OR 3.08, 95% CI 1.30-7.50) associated significantly with cluster B PDs, whereas social (OR 3.05, 95% CI 1.58-5.88) and specific phobia (OR 1.84, 95% CI 1.00-3.39) and agoraphobia without panic disorder (OR 2.85, 95% CI 1.27-6.37) associated with cluster C PDs when age, gender and other clusters were controlled for in logistic regression (I: Table 4).

Figure 2. Current comorbidity among patients with DSM-IV MDD in Vantaa Depression Study



7.1.3.2 Gender, age, marital status and residential area

There were some statistically significant variations in comorbidity by gender and residential area, and trends by age and marital status. Significantly more males (39%) than females (19%) suffered from alcohol use disorders (Table 4), and the patients from the somewhat socioeconomically disadvantaged East Vantaa were living outside the family (44% vs. 29%, χ^2=5.38, df=1, P=.020), and had more severe MDD (mean HAM-D score ±SD; 20.30±5.3 vs.18.04±6.4, t=3.101, df=266, P=.002) more often than those in western Vantaa. Also, slightly more patients (19%, 30/155 vs. 11%, 10/95, χ^2=2.79, df=1, P=.095) in eastern Vantaa were drinking heavily (defined as ≥ 16 and ≥ 24 standard [12 g of alcohol] drinks / week for women and men, respectively).

Table 4. Sociodemographic and Clinical Characteristics in Vantaa Depression Study [a]

Characteristics	Females (N=197)		Males (N=72)		Total (N=269)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	39.5	11.4	39.9	10.0	39.6	11.1
Age at onset of first MDE (years) [a]	31.6	12.6	31.5	12.4	31.6	12.5
The 17-item HAM-D	19.7	5.6	19.0	6.8	19.5	5.9
The 21-item BDI	28.2	8.4	26.3	8.9	27.7	8.6
	N	**%**	**N**	**%**	**N**	**%**
Outpatients	165	84	58	81	223	83
Inpatients	32	16	14	19	46	17
Marital status						
Unmarried	43	22	17	24	60	22
Married or cohabiting	99	50	36	50	135	50
Divorced	49	25	17	24	66	25
Widowed	6	3	2	3	8	3
Residential area [b]						
East	125	63	43	61	168	63
West	72	37	28	39	100	37
Currently employed [c]	113	59	44	62	157	60
Family income [d]						
Low	91	51	25	39	116	48
High	87	49	39	61	126	52
Total no of lifetime MDEs[e]						
1(intake)	72	37	21	30	93	35
2	58	30	25	35	83	31
3 or more	66	34	25	35	91	34
Axis I diagnosis						
Dysthymia	21	11	11	15	32	12
Any anxiety disorder	118	60	34	47	152	57[f]
Panic disorder	36	18	9	13	45	17
Agoraphobia w/o panic	26	13	5	7	31	12
Social phobia	39	20	14	19	53	20
Simple phobia	52	26	16	22	68	25
OCD	15	8	3	4	18	7
GAD	24	12	13	18	37	14
PTSD	2	1	0	0	2	1
Bulimia nervosa	2	1	0	0	2	1
Any alcohol use disorder	38	19	28	39	66	25[g]
Dependence	23	12	15	21	38	14
Abuse	15	8	13	18	28	10[h]

Characteristics	Females (N=197)		Males (N=72)		Total (N=269)	
	N	%	N	%	N	%
Axis II diagnosis						
Cluster A	34	17	17	24	51	19
Paranoid	31	16	16	22	47	17
Schizoid	4	2	1	1	5	2
Schizotypal	0	0	0	0	0	0
Cluster B	31	16	8	11	39	14
Antisocial	2	1	2	3	4	2
Histrionic	5	3	0	0	5	2
Borderline	25	13	7	10	32	12
Narcissistic	2	1	2	3	4	2
Cluster C	63	32	22	31	85	32
Obsessive compulsive	13	7	4	6	17	6
Dependent	13	7	5	7	18	7
Avoidant	49	25	15	21	64	24
Passive aggressive	7	4	6	8	13	5
Any personality disorder	87	44	31	43	118	44
Pure MDD	37	19	19	26	56	21
Melancholic features	72	37	25	35	97	36
Psychotic features	18	9	4	6	22	8

[a] All data shown as N and % unless otherwise noted ,[b] missing 0.4%; N=268; [c] missing 2.2%; N=263, [d] missing 10%; N=242, [e] missing 0.7%, N=267, [f] χ^2=2.95, df=1, P=.086, [g] χ^2=9.91, df=1, P=.002, [h] χ^2=5.10, df=1, P=.024

Females tended to have more anxiety disorders (Table 4) than males, and younger patients (aged < 40 years) more borderline personality disorders (16%, 21/132 vs. 8%, 11/137, χ^2=3.27, df=1, P=.071) than older ones. Furthermore, patients living alone had a personality disorder slightly more often (50%, 67/134 vs. 38%, 51/135, χ^2=3.60, df=1, P=.058) than married or cohabiting patients. All significant differences remained after controlling possible confounding factors by logistic regression.

7.1.3.3 Inpatient and outpatient status

Inpatients were more severely depressed (mean HAM-D score ±SD 24.9±5.0 vs. 18.4±5.4, t=7.493; df=267, P<.001), had more often alcohol use disorders (39% vs. 22%, χ^2=5.47, df=1, P=.019), cluster B PDs (26% vs. 12%, χ^2=4.94, df=1, P=.026), panic disorders with agoraphobia (17% vs. 5%, χ^2=6.34, df=1, P=.012), and melancholic (54% vs. 32%, χ^2=7.12, df=1, P=.008) and psychotic features (26% vs. 4%, Fisher's exact test, df=1, P<.001) than outpatients. These results remained significant after controlling for gender and age by logistic regression.

7.1.3.4 Lifetime depressive episodes

In logistic regression (LR) analyses controlled for age and gender, subjects with ≥ three lifetime depressive episodes had a greater likelihood of personality disorders (OR 1.87, 95% CI 1.03-3.38, P=.026), and had pure MDD significantly less frequently than those with a single episode (OR 0.36, 95% CI 0.16-0.80, P=.022) (I: Table 5).

7.1.3.5 Melancholic features (Study III)

There were no significant differences in rates of any axis I and II comorbid disorders, or in EPI neuroticism scores between melancholic and non-melancholic depression (III: Table 2). In order to control for the possible effect of severity the multivariate models were used in the secondary analyses. In the LR models with melancholic features as the dependent variable, the only significant finding was severity of depression (OR 1.10, 95% CI 1.05-1.15, P<.001) when age, gender, severity of MDD, or either personality clusters or neuroticism were simultaneously entered into the models as independent variables (III: Table 3).

7.2 Outcome of MDD (Study II)

7.2.1 Duration of the index episode

The median *time with full MDE criteria* after entry was only 1.5 (95% CI 1.3-1.7) months. Altogether, 78% of the cohort achieved a symptom state below MDE criteria within three months, 86% within six months, and 95% within 18 months (Fig. 3). The median *time to full remission* (lasting at least 2 consecutive months) was 8.1 (95% CI 5.2-11.0) months; 22% of patients reached full remission within three months, 42% within six months, and altogether only 63% within the 18-month follow-up (Fig. 4). The median duration of MDE before the baseline interview was 3.5 (95% CI 2.9-4.1) months; including the prodromal phase, the duration was 6.6 (95% CI 6.1-7.1) months.

7.2.2 Predictors of duration of the index episode

Significant predictors of *time with full MDE criteria* and of *time to full remission* were very similar in the univariate analyses (Table 5).

Predictors for the final models were chosen on the basis of the primary hypothesis, but their clinical and statistical validity and relevance (e.g. state vs. trait) were considered before inclusion. Therefore, some self-reported scales scores (e.g. PSSS-R, HS, and SSI) were not entered into the final multivariate analyses seeking independent predictors (even though they might have been significant in univariate analyses). The final Cox proportional hazards model was performed with age, gender, duration of MDE before entry, number of prior MDEs and somatic disorders, melancholic and psychotic subtypes of depression, personality and alcohol use disorders, mean BAI [anxiety symptoms] and HAM-D scores [severity of depression], and size of social network simultaneously as independent variables. After all non-significant findings were removed, severity of MDD (OR 1.04, 95% CI 1.01-1.07, P=.004), longer duration of MDE prior to entry (OR 1.36, 95% CI 1.02-1.81, P=.04) and personality disorder (OR 1.36, 95% CI 1.02-1.81, P=.04) predicted time with full MDE criteria most significantly, while time to full remission was most effectively predicted by severity of MDD (OR 1.03, 95% CI 1.00-1.07, P=.04) and anxiety symptoms (OR 1.01, 95% CI 1.00-1.04, P=.01) (II: Table 3).

Figure 3. Survival curve for the time with full MDE criteria in the VDS

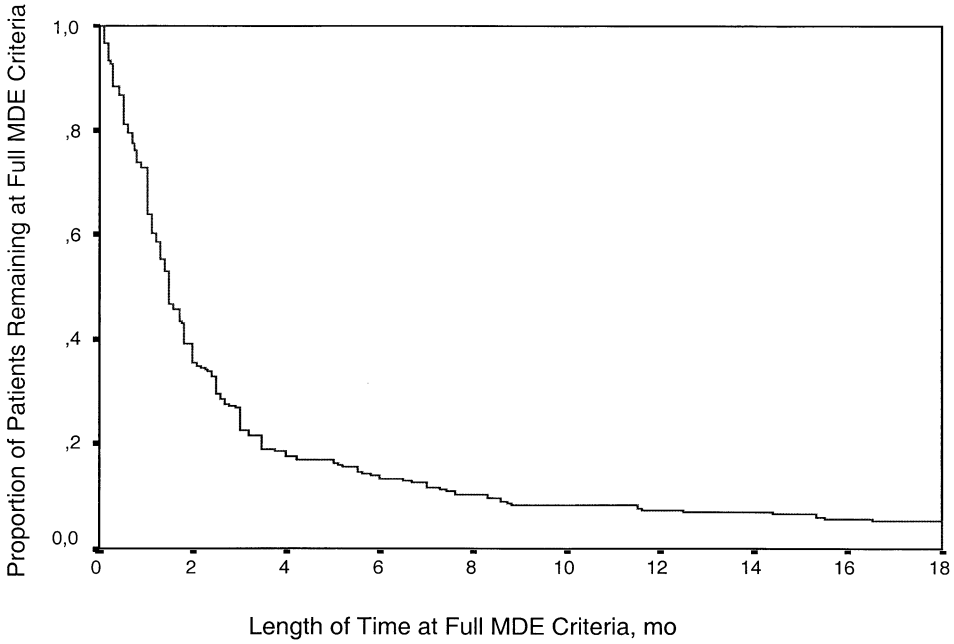
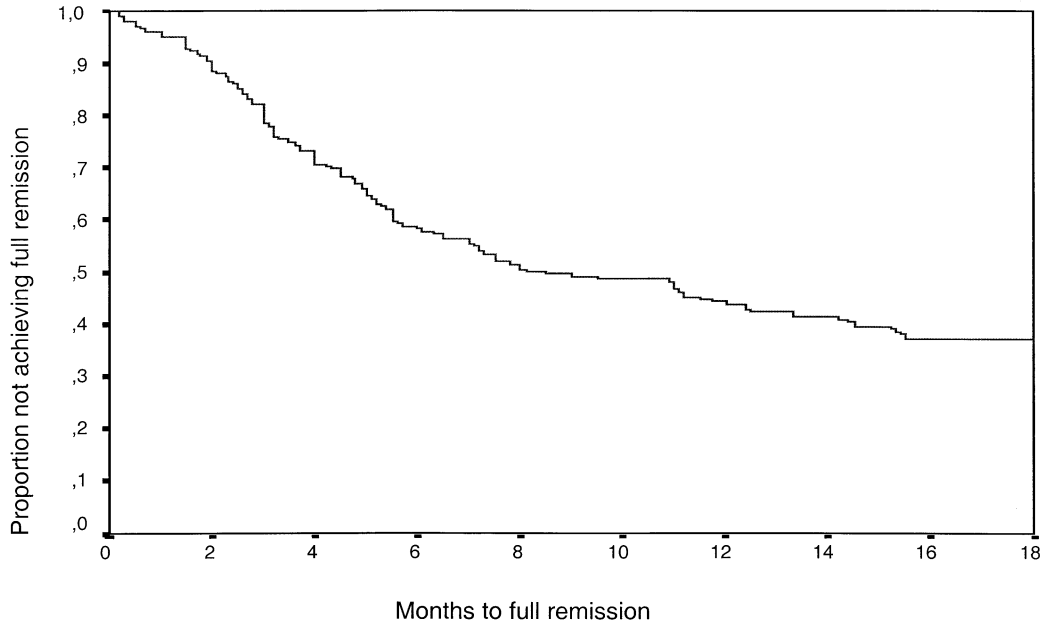


Figure 4. Survival curve to full remission of a MDE or to 18-months in the VDS



7.2.3 Relapses and recurrences

Only 20 (10%) of the 198 patients who completed the 18-month interview had an immediate relapse. Those with previous MDEs (OR 5.15, 95% CI 1.14-23.24, P=.03) and those aged ≥40 years (OR 3.19, 95% CI 1.01-10.11, P<.05) more often had relapses. The median length of relapse during the follow-up was 2.2 months.

During the 18-month follow-up, 76 (38%) of the 198 patients had a recurrence (return of symptoms sufficiently severe to satisfy criteria for an MDE after at least two consecutive months of partial or full remission). The median time to the first relapse or recurrence was 4.3 months (95% CI 2.93-5.67 calculated without time with full MDE criteria after baseline), and the median length of recurrence was 1.5 months. The median score on the BDI during relapses or recurrences was 19.0 (combined due to low numbers; only those with BDI scores available [N=56] included). The BDI scores during the relapses/recurrences were significantly lower than the respective patients' scores at baseline (t=5.502, df=55, P<.001).

In univariate LR analyses, several baseline factors predicted recurrence either significantly or as a trend (Table 5). However, severity of MDD (OR 1.06, 95% CI 1.00-1.11, P=.04) and a higher number of comorbid psychiatric disorders (OR 1.25, 95% CI 1.03-1.51, P=.02) were the two most significant predictors in the backward stepwise multivariate LR models, when age, gender, duration of MDE before entry, number of prior MDEs, somatic disorders, comorbid psychiatric disorders, melancholic and psychotic subtypes of depression, mean score on the HAM-D, size of social network, and the time at risk for recurrence were entered as predictors. Partial remission from the index episode was significantly associated with risk of recurrence during follow-up (OR 2.14, 95% CI 1.06-4.31, P=.03). However, when partial remission was added as a predictor in the multivariate models, it did not remain significant after adjusting for the other predictors, and was thus not included in the final multivariate models.

Table 5. Univariate analyses of all possible predictors of time with full criteria, time to full remission, and recurrences in the VDS

Predictors	Time with full MDE criteria [a]			Time to full remission [a]			Recurrences [b]		
(at entry)	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age, yrs	1.01	1.00-1.02	-	1.01	1.00-1.03	.073	1.00	0.98-1.03	-
Gender (male)	0.97	0.71-1.33	-	0.83	0.56-1.24	-	0.92	0.47-1.78	-
Outpatient status	0.90	0.62-1.29	-	1.05	0.65-1.70	-	0.78	0.34-1.76	-
Age at onset, yrs	1.01	0.99-1.02	-	1.01	0.99-1.03	-	0.98	0.95-1.02	-
Longer MDE prior to entry	1.30	0.98-1.72	.069	1.30	0.91-1.84	-	1.78	0.97-3.26	.061
No. of previous episodes	1.02	0.97-1.08	-	1.03	0.96-1.10	-	1.12	0.98-1.28	.083
17-item HAM-D score	1.03	1.01-1.06	.011	1.04	1.01-1.07	.013	1.07	1.01-1.03	.018
21-item BDI score	1.03	1.01-1.05	.001	1.03	0.01-1.06	.006	1.05	1.01-1.09	.014
Beck Anxiety Inventory score	1.02	1.00-1.03	.015	1.03	1.01-1.04	.004	1.02	0.99-1.05	-
Beck Hopelessness Scale score	1.05	1.02-1.08	.003	1.05	1.01-1.09	.018	1.10	1.03-1.18	.006
Scale for Suicidal Ideation score	1.01	1.00-1.03	-	1.03	1.01-1.06	.010	1.06	1.02-1.11	.004
SOFAS score [c]	1.02	1.00-1.03	.019	1.02	0.97-1.00	.076	1.01	0.98-1.04	-
Axis I comorbidity									
Dysthymia	0.89	0.56-1.42	-	1.52	0.79-2.91	-	1.89	0.70-5.09	-
Anxiety disorders	0.81	0.62-1.07	-	0.87	0.62-1.23	-	1.59	0.87-2.90	-
Alcohol use disorders	1.01	0.72-1.43	-	1.15	0.75-1.75	-	1.35	0.65-2.79	-
Axis II comorbidity									
Personality disorders	1.46	1.10-1.93	.008	1.44	1.01-2.05	.043	1.84	1.00-3.38	.049
Cluster A	1.47	1.01-2.15	.044	1.28	0.80-2.04	-	1.99	0.90-4.38	.089
Cluster B	1.24	0.83-1.85	-	1.12	0.68-1.85	-	2.27	0.94-5.48	.069
Cluster C	1.54	1.13-2.09	.006	1.79	1.20-2.68	.005	1.41	0.74-2.71	-
No. of psychiatric disorders	1.04	0.97-1.13	-	1.06	0.96-1.18	-	1.27	1.06-1.53	.009
Axis III comorbidity									
No. of current somatic diseases	1.11	0.98-1.26	-	1.18	0.99-1.40	.071	1.05	0.82-1.36	-
No. of all axis I-III disorders	1.06	0.99-1.14	.071	1.09	1.00-1.18	.051	1.19	1.03-1.38	.020
Psychotic MDD	1.00	0.59-1.69	-	0.71	0.39-1.33	-	0.68	0.20-2.36	-
Psychosocial and personality factors									
Size of social network [c]	1.03	0.99-1.06	-	1.04	0.99-1.09	.093	0.98	0.90-1.07	-
PSSS-R score [e]	1.02	1.01-1.03	<.001	1.02	1.00-1.03	.038	1.02	0.99-1.04	-
Negative life events [d]	1.00	0.97-1.03	-	1.02	0.98-1.06	-	1.02	0.95-1.09	-
Neuroticism [e]	1.05	1.01-1.08	.016	1.05	1.01-1.10	.022	1.11	1.02-1.21	.020

[a] Cox proportional hazards models; all analyses controlled for age and gender, risk reported for increasing time,

[b] Logistic regression models; all analyses controlled for age, gender, and time at risk for recurrence

[c] Scales reversed in order to improve comparability,

[d] Interview for Recent Life Events; objectively measured negative impact of adverse life-events,

[e] Eysenck Personality Inventory; dimension of neuroticism

7.3 Stability and course of melancholic features (Study III)

7.3.1 Course of melancholic MDD

There were no statistically significant differences in the prospective course of depression between the subtypes (III: Table 4). In the Cox proportional hazards models adjusting for age and gender, time at full MDE criteria (OR 0.97, 95% CI 0.73-1.28, N.S.), time to partial remission (OR 0.94, 95% CI 0.70-1.25, N.S.), time to full remission (OR 1.07, 95% CI 0.75-1.52, N.S.), time to first relapse/recurrence (OR 0.89, 95% CI 0.56-1.40, N.S.), number of relapses (12.2% v. 8.9%, χ^2=0.55, N.S.), or recurrences (36.5% v. 39.5%, χ^2=0.18, N.S.) did not differ statistically significantly between melancholic and non-melancholic depressives. Neither there were any significant differences in duration of various symptom states (e.g. partial/full remission or MDE) analyzed by the Mann-Whitney test. However, the retrospective duration of MDE before entry into the cohort, with or without prodromal phase, was longer in non-melancholic than melancholic depression (OR 1.37, 95% CI 1.06-1.78, P=.02 and OR 1.31, 95% CI 1.02-1.67, P=.04, respectively).

7.3.2 Stability of melancholic features

Altogether, 32 (27%) of the 117 non-chronic non-melancholic patients and 23 (34%) of the 67 non-chronic melancholic patients who completed the 18-month interview were in a new episode during the follow-up interviews. The original subtype of MDD persisted in 29 out of 55 cases (53%), while in almost as many cases it changed (47%, 26/55): non-melancholic MDD shifted to melancholic in eight out of 32 (25%) cases, and melancholic to non-melancholic in 18 out of 23 (78%) cases (χ^2=15.23, df=1, P<.001). Variation in severity of episodes during the follow-up did not explain the changes of subtype. At six months, 24% (13/55) of the depressed patients were melancholic, the proportion rising to 36% (16/45) at 18 months. There were no statistically significant differences in mean HAM-D scores between the patients with and without melancholic features either at six or 18 months (mean=17.7, S.D. 6.8 v. mean=19.9 S.D. 4.9, t=1.312, df=40, N.S.; and mean=18.2 S.D. 5.9 v. mean=18.7 S.D. 4.5, t=0.217, df=27, N.S., respectively). The median HAM-D score of the patients in a depressive episode at follow-up was 19.0 at both six and 18 months.

7.4 Antidepressant and psychosocial treatments in MDD (Study IV)

7.4.1 Antidepressants

7.4.1.1 Antidepressants received in the acute phase

At baseline most patients (88%, 174/198) received antidepressants, and for the majority (78%) the dosage level was adequate for the acute phase. More than half (57%, 112/198) of the study cohort patients received SSRIs alone at baseline, about one fifth (18%, 36/198) newer antidepressants (tetracyclics, NaSSA, SNRI, RIMA), only 8% (15/198) TCAs, and 6% (11/198) combination treatment, usually SSRI and TCA. While SSRIs and newer antidepressants were used inadequately in the acute phase in only about a tenth of cases (7% and 11%, respectively), TCAs were used inadequately in about half (47%) (χ^2=20.08, df=2, P<.001). However, only a few, and none without remission, received augmentation of pharmacotherapy (e.g. lithium or buspirone). Only 3% received ECT (Table 6).

7.4.1.2 Continuity of treatment

In contrast to generally adequate treatment in the early acute phase, the continuity of antidepressant treatment provision was far less complete, particularly in the continuation and maintenance phases (Table 7, Figure 5). Although the median time on antidepressant treatment was 55 (95% CI 34.7-75.3) weeks (Figure 5), premature termination of treatment was common. In about half (49%, 86/174) of patients antidepressant treatment was terminated before completion of a continuation phase, or in the early maintenance phase for those with three lifetime episodes. One third of antidepressants were terminated in the acute phase (33%, 57/174), i.e. while still in MDE or partial remission. About a quarter (28%, 49/174) of patients completed a continuation phase lasting at least four months. Only about a fifth (19%, 13/67) of those with three lifetime episodes proceeded to a maintenance phase.

7.4.1.3 Predictors of premature termination

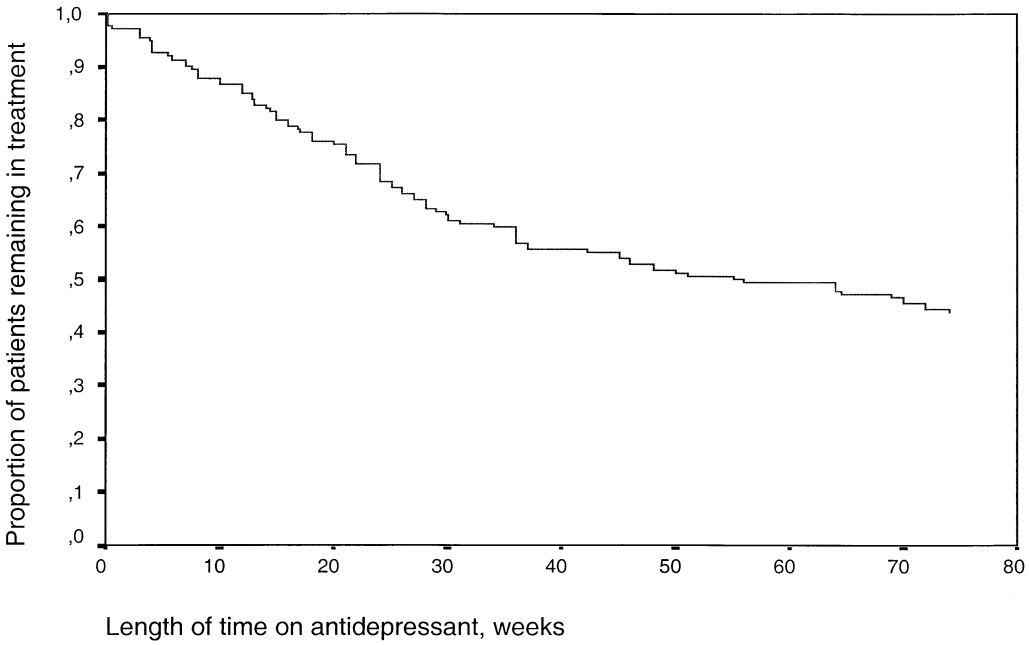
In stepwise backward LR analyses with premature termination of antidepressant treatment as a dependent variable, and factors significant in univariate analyses as independent variables, premature termination was significantly predicted by no earlier antidepressant treatment (OR 2.13, 95% CI 1.10-4.16, P=.026), and less severe depression (OR 1.58, 95% CI 1.00-1.13, P=.049). It also associated with negative treatment attitudes during the follow-up: 86% (18/21) of the patients with negative attitudes at six months, and 74% (20/27) at 18 months had premature termination of antidepressant treatment.

Table 6. Treatments received, and the highest level of remission achieved from the index episode of the VDS MDD patients followed for 18 months

Variables	Full remission (N=122)		Partial remission (N=61)		MDD (N=15)		Total (N=198)			
	N	(%)	N	(%)	N	(%)	N	(%)	χ^2/F	P
Antidepressant treatment										
Antidepressant at baseline	101	(83)	58	(95)	15	(100)	174	(88)	8.01	.018
Adequacy at first antidepressant trial: [a]										
Adequate	86	(71)	53	(87)	15	(100)	154	(78)	11.79	.019
Inadequate	15	(12)	5	(8)	-	(-)	20	(10)		
No antidepressant	21	(17)	3	(5)	-	(-)	24	(12)		
≥ 3 trials on antidepressants	13	(20)	13	(36)	10	(71)	38	(31)	14.70	.001
Antidepressant combination treatment	17	(14)	12	(20)	5	(33)	34	(17)		-
Buspirone augmentation	7	(6)	4	(7)	-	(-)	11	(6)		-
Lithium augmentation	-	(-)	-	(-)	-	(-)	-	(-)		-
Psychosocial treatments										
Psychotherapeutic support	119	(98)	60	(98)	15	(100)	194	(98)		-
Psychotherapy	20	(16)	11	(18)	-	(-)	31	(16)		-
All psychotherapeutic sessions, No, mean (SD) [b]	16.9	(15.7)	24.6	(26.6)	38.3	(17.6)	21.1	(20.7)	9.13	<.001
Duration of psychotherapeutic treatment, months, mean (SD) [c]	9.4	(6.5)	11.5	(6.0)	17.5	(3.6)	10.7	(6.5)	11.93	<.001
Visits to psychiatrist, mean (SD) [d]	2.9	(3.0)	5.3	(5.9)	8.6	(4.5)	4.1	(4.5)	29.69	<.001
ECT	1	(1)	3	(5)	1	(7)	5	(3)		-

[a] Antidepressant/s at adequate dosage level for at least four weeks in acute phase,
[b] Data missing for 4.0% of patients, N=190, [c] Data missing for 3.5% of patients; N=191; [d] Kruskal Wallis test

Figure 5. The probability of remaining on antidepressant treatment



7.4.1.4 Consequences of premature termination

Patients whose antidepressant treatment was terminated in MDE or partial remission achieved full remission more rarely 42% (24/57) vs. 66% (77/117) (χ^2=8.85, df=1, P=.003), in a longer time (mean±SD 14.0±5.6 vs. 9.7±6.8 months, OR 2.17, 95% CI 1.37-3.44, P=.001), and spent less time without any depressive symptoms (median 2.1 vs. 6.5 months, Z=-2.96, P=.003). About a fifth (19%, 19/98) of those who discontinued treatment had a new antidepressant trial during the follow-up, and most of them for a recurrence (74%, 14/19 vs. 36%, 56/155, χ^2=9.93, df=1, P=.002).

7.4.1.5. Self-reported reasons for terminating antidepressants

The most frequent self-reported reason for discontinuing the first antidepressant trial among those who dropped out of antidepressant use in the acute phase was "autonomous decision", which was the main reason for terminating treatment in 40% (21/52, missing N=5) of the patients. Other common self-reported reasons were side-effects in 25% (13/52), poor response in 21% (11/52), and subjective recovery in 12% (6/52).

Table 7. Continuity of antidepressant treatment in the index episode and lifetime number of MDEs among the VDS patients followed for 18 months

Variables	Single episode N=66		2 episodes N=65		≥ 3 episodes N=67		Total N=198			
	N	%	N	%	N	%	N	%	χ^2	P
No antidepressant (baseline)	16	(24)	2	(3)	6	(9)	24	(12)	14.73	.001
Antidepressant (baseline)	50	(76)	63	(97)	61	(91)	174	(88)		
Antidepressants ongoing for the index episode:	15	(23)	26	(40)	35	(52)	76	(38)	8.60	.014
In acute phase	8	(12)	14	(22)	21	(31)	40	(20)		-
In continuation phase	1	(2)	1	(2)	1	(2)	5	(3)		-
In maintenance phase	6	(9)	11	(17)	13	(19)	31	(16)		-
Antidepressants discontinued:	35	(53)	37	(57)	26	(39)	98	(49)	8.60	.014
In MDE	4	(6)	6	(9)	5	(7)	15	(8)		-
In partial remission	17	(26)	17	(26)	8	(12)	42	(21)		-
In continuation phase	7	(11)	9	(14)	7	(10)	23	(12)		-
In maintenance phase	7	(11)	5	(8)	6	(9)	18	(9)		-
Antidepressant discontinued and restarted	6	(9)	6	(9)	7	(10)	19	(10)		-

7.4.1.6 Self-reported antidepressant adherence

The majority of patients (77%, 109/142) reported taking antidepressants regularly when treatment was ongoing, about a tenth (11%, 16/142) somewhat irregularly, and a similar proportion (12%, 17/142) very irregularly or never. Of 142 patients interviewed, 29 (20%) reported non-adherence at both follow-ups. In stepwise backward LR models adjusting for age, gender, and severity of MDD, having no avoidant personality (OR 4.83, 95% CI 1.33-17.48, P=.017), or no anxiety disorder (OR 2.40, 95% CI 1.01-5.71, P=.047) persisted significant predictors for continued non-adherence. Two-thirds (60%, 74/124) of patients with no ongoing psychiatric treatment, and almost all (92%, 68/74) of those who had remained in treatment answered questions about adherence at 18 months.

7.4.2 Psychosocial treatments

7.4.2.1 Treatments received in the acute phase

Nearly all patients (98%) received psychotherapeutic support in the early acute phase, but only a few, and none without remission, had weekly psychotherapy (16%) (Table 6).

7.4.2.2 Continuity of psychosocial treatments

Not unexpectedly, patients with poorer outcome received psychosocial treatment for longer (Table 6). However, only two thirds (58%, 44/76) of the patients without full remission remained in psychiatric care, and a third of them (32%, 24/76) were without any follow-up treatment at 18 months. Most patients were already receiving psychosocial support at baseline, but weekly psychotherapy began about three months later (mean±SD 2.9±4.0 months), and lasted for about one year (mean±SD 11.0±6.0 months).

In stepwise backward LR analyses with receiving weekly psychotherapy as a dependent variable, the most significant predictors for having psychotherapy were fewer DSM-IV current comorbid psychiatric disorders (OR 1.37, 95% CI 1.02-1.82, P=.034), larger social network (OR 1.12, 95% CI 1.00-1.25, P=.046), and more severe suicidality (OR 1.08, 95% CI 1.02-1.14, P=.004). Moreover, patients with personality disorder had psychotherapy more infrequently than those without personality disorder (9%, 8/85 vs. 20%, 23/113, χ^2=4.40, df=1, P=.036). This result remained significant (OR=2.88, 95% CI 1.11-7.44, P=.029) when entered simultaneously with age, gender, and other significant factors like size of social network, neuroticism, and more severe suicidality into stepwise backward LR models.

7.4.2.3 Self-reported psychosocial treatment adherence

Nearly all patients (92%, 68/74) still in psychiatric care, and about two thirds (56%, 69/124) of those without ongoing treatment, answered questions about adherence at 18 months. Nearly all who had received weekly psychotherapy (96%, 27/28) reported attending sessions regularly. Most patients (75%, 82/109) with psychotherapeutic support also reported attending sessions regularly, about a fifth (17%) somewhat irregularly, and 7% very irregularly or never.

7.4.3 Attitudes towards treatments

At baseline, the majority (85%, 223/262), and two-thirds (61%, 164/268) of patients, respectively, had positive attitudes towards psychosocial and antidepressant treatments. Among study cohort patients, attitudes towards psychosocial treatments remained positive, and in most (82%, 56/68) cases negative attitudes towards antidepressants became positive during the follow-up. The factors explaining negative attitudes towards antidepressants at baseline were younger age (OR 1.03, 95% CI 1.00-1.05, P=.031), lower score on BAI (OR 1.04, 95 % CI 1.01-1.07, P=.019) and HAM-D (OR 1.08, 95% CI 1.03-1.14, P=.003), longer duration of MDE (OR 1.05, 95 % CI 1.00-1.10, P=.050), and having no current alcohol use disorder (OR 2.00, 95% CI 1.00-3.99, P=.050), while the factors explaining negative attitudes about psychosocial treatment were male gender (OR 4.25, 95% CI 1.84-9.80, P=.001) and dysthymia (OR 3.22, 95% CI 1.22-8.48, P=.018) (IV: Table 3).

Among those with reservations/negative attitudes about antidepressants the most frequently reported reasons for these attitudes were fears of dependence and side-effects, which were reported by nearly half of the patients (43% and 41%, respectively) at baseline. No belief in getting any help from the treatment (43%), and unwillingness to confide in a stranger (33%) were the most frequently reported reasons for negative attitudes towards psychotherapeutic treatments. Patients with negative attitudes about antidepressants at entry tended to terminate them in the acute phase more often (43%, 22/51 vs. 29%, 34/119, df=1, χ^2=3.43, P=.064). Those with negative attitudes to antidepressants or psychosocial treatments at 18 months also reported non-adherence to them more often (79%, 19/24 vs. 20%, 26/130, χ^2=34.29, df=1, P<.001, and 75%, 6/8 vs. 24%, 33/140, χ^2=10.31, df=1, P=.001, respectively).

8. DISCUSSION

8.1 Main findings

A typical psychiatric patient with MDD in psychiatric care suffered from many comorbid disorders; over half had current comorbid anxiety disorders (57%), nearly half personality disorders (44%), and a quarter alcohol use disorders (25%). Only one fifth (21%) had pure depression without any comorbid disorder.

Achieving full remission took about eight months, so despite the use of new antidepressants the outcome of MDD appears not to be improved in psychiatric care. Although patients typically responded early to the treatment (most in 4-8 weeks), the major problem was the long period with only partial remission. In addition, about 40% of the patients had a recurrence of MDD during the 18 months of follow-up. Numerous factors predicted the duration of MDE to some extent, but more severe depression and presence of current comorbidity were the two most robust predictors. More severe depression was also a significant predictor of recurrence. There were no major differences in current comorbidity or course of depression between melancholic and non-melancholic patients. Moreover, the consistency of DSM-IV melancholic features across episodes appeared weak.

Most depressive patients in psychiatric care received adequate antidepressant (88%) and psychotherapeutic treatments (98%) in the early acute phase, and had favourable attitudes towards them. Nevertheless, over time antidepressants were terminated too early in about half of the patients, often following their autonomous decision. About a third of the patients not achieving full remission were without any psychosocial treatment by the end of follow-up. Negative treatment attitudes were more common towards antidepressants than psychosocial treatments, and tended to predict premature termination. The main challenge in psychiatric care appears to be continuity of treatments.

8.2 Methods

8.2.1 Representativeness of the cohort sample

Clinical studies conducted on representative unselected samples of commonly met, highly comorbid, depressive patients are extremely sparse. However, the familiar tendency for patients to have undergone many prior treatments in studies conducted in tertiary-level treatment centres may produce bias towards more chronic, severe and recurrent illnesses compared with more unselected cohorts of MDD patients (Spijker et al., 2002; Furukawa et al., 2000; Roy-Byrne et al., 2000). Moreover, the most influential outcome studies were undertaken during the past era of tricyclic antidepressants and before the recommendation of continuation and maintenance treatments. In addition, only a few recent psychiatric care studies have reported how treatments, especially after the immediate acute phase, are carried out, and which factors predict treatment inadequacy, premature termination and non-adherence among depressive patients (Ramana et al., 1999; Sirey et al., 1999; Simon et al., 2001; Cuffel et al., 2003; Kennedy et al., 2003).

The present naturalistic study (I-IV) involved a relatively large (N=269) cohort of both outpatients and inpatients with MDD, effectively representing psychiatric patients with a new episode of MDD in the city of Vantaa; and it took place during the era of modern antidepressants in 1997-1999 in a community psychiatric setting. On the basis of an epidemiological survey, two thirds of all depressed subjects in the general population of Vantaa seeking treatment from psychiatrists are treated in the PMCD (Rytsälä et al., 2001).

8.2.2 Study refusals and drop outs

The rate of drop-outs from the main follow-ups was quite low, as 87% of the cases could be interviewed at least once after baseline. The patients whose diagnosis switched to bipolar I or II disorder during the 18-month follow-up (5%) were excluded from the analyses. As the factors associating with dropping out included both positive (younger age) and negative (living alone, neuroticism, dysthymia) outcome predictors, the small percentage of drop-outs is unlikely to have biased findings. In some analyses, however, only those who completed the whole 18-month follow-up could be included. In these cases, the rate of drop-outs was 23% (N=58; including eight patients who died during the follow-up), which is likely to have somewhat biased findings towards better adherence to treatments (Study IV).

8.2.3 Diagnostic measures

The patients were diagnosed using semi-structured interviews with excellent reliability (kappa=0.86) for the diagnosis of MDD. However, the reliability of comorbid disorder and melancholic MDD diagnoses is unknown, and the distinction between melancholic and non-melancholic depression was based solely on the SCAN-interview and DSM-IV criteria. Moreover, diagnoses of axis III disorders were based on self-report, although only diseases diagnosed by a physician were included.

Axis II diagnosis were assessed using the semi-structured SCID-II interview for DSM-III-R, as the SCID II for DSM-IV was not yet available in February 1997. Differences between DSM-III-R and DSM-IV were taken into account by excluding masochistic PD. Passive-aggressive PD was included because it belongs to the personality disorder NOS in DSM-IV. Patients were also interviewed with the SCID-II during their depression, which may (Stuart et al., 1992; Peselow et al., 1994; Ferro et al., 1998), or may not (Loranger et al., 1991) have inflated the prevalence of personality disorders. This, as well as the inclusion of patients with current alcohol use disorders, was done deliberately in order to investigate the persistence and effects of these disorders in the follow-up. Patients with eating disorders and those who have experienced acute psychological traumas are probably underrepresented in the VDS. Only 4% of the patients admitted to occasional misuse of sedatives, or use of illicit drugs.

8.2.4 Life-chart and definitions for outcome

Many approaches to the longitudinal measurement of psychopathology have been developed. Probably one of the most influential measurements is the Longitudinal Interval Follow-up Evaluation (LIFE) methodology, first used to investigate the outcome of depression in the NIMH-CDS (Keller et al., 1987). The LIFE is a semi-structured interview and rating system for assessing the longitudinal course of psychiatric disorders in sufficient detail to provide the basis for calculating length of episodes and time to remission (Keller et al., 1987). In the VDS the outcome of MDD was investigated by using a graphic life chart, which is similar, but not identical, to the LIFE. As is done with the LIFE, change points in the psychopathologic state were inquired about using probes related to important events. Moreover, all patient records and monthly BDI-ratings (for the first 6 months) were available. Unlike the LIFE, patients' follow-up time was classified into periods of DSM-IV MDE, or partial (1-4 criteria symptoms) or full (no symptoms) remission. The major advantage of this classification is that it counts episodes and defines recurrences precisely, as does any clinician when using the DSM-IV.

However, comparison of the findings with studies using the LIFE can be undertaken only with some caution. For example, it appears that criteria for full remission in the VDS were more stringent than those used for recovery in the CDS (Psychiatric Status Ratings,

1-2; no symptoms or 1 to 2 symptoms to a mild degree). The mean±SD HAM-D scores at the 18-month interview were 2.7±2.8 for those with full remission, 8.3±4.3 for those with partial remission, and 18.5±4.8 for those with an MDE. In practice, if those with only one or two symptoms were also included in the full remission grouping, 76% of patients would have a recovery (instead of 63%); this percentage is comparable with the number of patients fully recovered in the CDS within two years (81%) (Keller et al., 1992).

Unfortunately, there is currently no universally accepted definition of remission (Keller, 2003), despite significant efforts (Frank et al., 1991). Nevertheless, in most longitudinal studies, recurrence/relapse follows a period of remission, which is relatively consistently defined as the presence of only one or two minimal symptoms of major depression to a mild degree, or complete absence of symptoms for at least two months (Keller, 2003). So, having used the same criteria for duration for remission, it is likely that the findings from the VDS are comparable to other studies.

8.3 Current comorbidity of psychiatric disorders in MDD (Study I)

When presenting for treatment for a new depressive episode, a typical psychiatric patient with MDD suffered from one to three comorbid axis I or II disorders; only one fifth had pure depression without any comorbid disorder. As expected, comorbid disorders also varied markedly by a number of relevant background factors, such as gender, in- vs. outpatient status, type of residential area, and somewhat by lifetime number of depressive episodes.

Current comorbidity in MDD was extremely common; anxiety disorders were prevalent in 57%, alcohol use disorders in 25%, and personality disorders in 44%, which is more in line than expected with earlier, mostly tertiary level studies (Van Valkenburg et al., 1984; Kocsis et al., 1986; Alnaes & Torgersen, 1988; Coryell et al., 1988; Sanderson et al., 1990; Stuart et al., 1992; Flick et al., 1993; Grunhaus et al., 1994; Golomb et al., 1995b; Pepper et al., 1995; Sato et al., 1996; Alpert et al., 1997; Pini et al., 1997; Schatzberg et al., 1998; Fava et al., 2000; Zimmerman et al., 2000; McDermut et al., 2001). However, when considering the representativeness of the VDS cohort, and the fact that all comorbid patients with MDD were deliberately included, this finding is less surprising.

Current comorbidty in MDD was also highly concentrated; anxiety and personality disorders were commonly complicated by current alcohol abuse or dependence, particularly among subjects with cluster B PD. Moreover, social phobia, specific phobia and agoraphobia without panic disorder in cluster C PDs, and panic disorder in cluster B PDs, were frequently found. These findings accord with the studies reporting high prevalence of comorbid anxiety disorders in borderline PD (Zanari et al., 1998; Zimmerman & Mattia, 1999), cluster B or C PDs (Oldham et al., 1995), different axis I disorders (Alnaes & Torgersen, 1988; McGlashan et al., 2000), or in MDD (Alpert et al., 1997).

Comorbidity varied by gender, in-vs. outpatient status, type of residential area, and somewhat by lifetime number of depressive episodes. Not surprisingly, males had twice the prevalence of current alcohol use disorders as females (39% vs. 19%), which is consistent with a study (Fava et al., 1996a) reporting more lifetime alcohol use disorders among males. One crucial neglected area of research has been the difference in clinical features between in- and outpatients. Inpatients not only had more severe and more common melancholic or psychotic depression than outpatients, but also a higher prevalence of alcohol use disorders (39% vs. 22%), cluster B personality disorders (26% vs. 12%), and panic disorder with agoraphobia (17% vs. 5%). It was also found that the more recurrent the depression, the lower the prevalence of pure MDD. This accords with earlier prospective outcome studies reporting a negative impact of multiple disorders on MDD outcome (Keller et al., 1984; Sargeant et al., 1990; Coryell et al., 1992; Mueller et al., 1994; Paykel et al., 1995; Alnaes & Torgersen, 1997).

The catchment area in the VDS was divided into East and West-Vantaa, based on the established service areas in Vantaa healthcare. East-Vantaa includes some socio-economically disadvantaged areas, and overall has about 10% lower average per-capita income, 25% higher unemployment, 20% fewer university graduates, and 40% more persons from ethnical minorities than West-Vantaa. On the basis of clinical experience within the community health care system, higher rates of alcohol use and personality disorders among MDD patients living in the more socioeconomically disadvantaged areas of East Vantaa were expected. Markedly higher PD prevalences and a somewhat less striking trend of heavy drinking in the East were indeed found. This suggests that current comorbidity of MDD may vary even by the type of residential area.

8.4 Outcome of MDD (Study II)

The duration of the index episode in our representative secondary-level cohort, comprising predominantly (85%) outpatients, was no shorter than in previous studies despite more extensive (88%) and more adequate use of the new antidepressants in the acute phase. This finding contrasts with results from a Japanese sample (Furukawa et al., 2000), but accords with a more recent tertiary-level long-term outcome study (Kennedy et al., 2003). Surprisingly, no differences between outpatients and inpatients regarding length of the MDE or rates of recurrence were found.

The rates of remission from the index episode in the VDS were comparable with those reported in older studies. Within three months, 22% of our cohort reached full remission, versus 41% (Keller et al., 1992), 30% (Myers et al., 2002) and 33% (Ramana et al., 1995) in other studies. The same percentages for full remission within six months were 42% in the VDS versus 54% (Keller et al., 1992), 50% (Ramana et al., 1995) and 43% (Kennedy et al., 2003) in other studies. However, only two-thirds (63%) of the patients reached strictly defined full remission within 18 months, taking a relatively long median time of

eight months. Although patients typically responded early to treatment, the major problem was the long period with only partial remission, which is partly explained by the strict definition of full remission used. Also, unlike other studies (Ramana et al., 1995; Myers et al., 2002), all comorbid patients with MDD were deliberately included in the VDS. When all the subjects with a concurrent major psychiatric or physical illness (Ramana et al., 1995; Myers et al., 2002) were excluded from the data, the median time to full remission somewhat decreased (from 8.1 to 7.2 months). Thus, a representative psychiatric cohort of MDD patients who typically have multiple current comorbid disorders may also include subjects with many known risk factors for poor outcome of MDD.

More severe depression, and longer duration of MDE before entry were found to predict longer episode, in line with earlier prospective studies (Keller et al., 1982; 1984; 1992; Sargeant et al., 1990; Wells et al., 1992; Ramana et al., 1995; Mueller et al., 1999; Parker et al., 2000b; Myers et al., 2002). However, it was somewhat unexpected to find that severe MDD was such a robust predictor among all other theoretically relevant risk factors. The finding that anxiety symptoms and personality disorders associated with longer duration of depression accords with earlier studies investigating the effects of either comorbid anxiety (Coryell et al., 1988; 1992; Clayton et al., 1991) or personality disorders (Sato et al., 1993; Greenberg et al., 1995; Ilardi et al., 1997; Viinamäki et al., 2002; 2003) on the outcome of MDD.

Social support, as objectively measured by the size of the social network at entry and by the negative impact of preceding adverse life-events, had little or no effect on time to remission, which accords with some earlier studies (Andrew et al., 1993; Paykel et al., 1996). In contrast, social support as subjectively perceived was strongly related to the duration of depression. Subjectively perceived social support and neuroticism, however, were strongly correlated with the level of depressive symptoms or presence of comorbid personality disorders and were therefore not included in the final multivariate models. No association between adequacy of pharmacotherapy in the early acute phase and episode duration was found, probably due to homogeneity in the amount and adequacy of the treatment received, and possibly because of the known tendency for sicker patients to receive more treatment in a naturalistic study (Sturm, 1999).

The recurrent nature of depression is one of its fundamental features, and has major treatment implications. During the follow-up, about 40% of patients suffered a recurrence, which is consistent with the rates reported in speciality settings (Keller et al., 1983; Ramana et al., 1995; Keller & Boland, 1998; Mueller et al., 1999; Kennedy et al., 2003). However, it seems that although the rate of recurrence in the VDS was similar to older studies, the episodes during the follow-up were milder and shorter (Solomon et al., 1997). In this respect, findings from the VDS support those from a Japanese sample (Furukawa et al., 2000) in which the index episode duration was calculated to be 25% - 50% shorter than in older literature. The findings that number of prior MDEs, older age, longer duration of MDE before entry, personality disorders or neuroticism, hopelessness,

and achieving only partial remission from the index episode are associated with the risk of relapse/recurrence are convergent with previous studies (Keller et al., 1982; 1983; Coryell et al., 1991; Maj et al., 1992; Surtees & Barkley, 1994; Ramana et al., 1995; Alnaes & Torgersen, 1997; Ilardi et al., 1997; Keller & Boland, 1998; Lin et al., 1998; Mueller et al., 1999). Partial remission as a predictor in the multivariate models did not remain significant, which supports the interpretation of partial remission as an intermediate symptom state that is effectively predicted by more important predictors of outcome. The rate of recurrence ranged from 27% among those with a mild index episode to 58% among those with a severe one, and from 31% among those with no comorbid disorder to 54% among those with three or more current comorbid psychiatric disorders. Thus, severe depression and high number of comorbid disorders appear to be the major factors influencing the medium-term risk of recurrence.

Severity of MDE was found to be strongly associated with the risk of recurrence in medium-term follow-up. In previous studies severity of depression has either predicted recurrences (Ramana et al., 1995) or not (Keller et al., 1983; Sherrington et al., 2001). In studies (Keller et al., 1983; Sherrington et al., 2001) that found no association between severity and recurrences, most subjects were inpatients with severe and recurrent melancholic depression. However, severity of depression also predicted recurrence in the study by Ramana et al. (1995), in which the clinical severity of MDD varied from mild to severe, and the proportion of patients with melancholic features - as in our study (36%) - was somewhat lower (63%). So, it appears that at least in cohorts of less melancholic MDD outpatients with less severe depression in medium-term follow-up, the severity of depression might be a more useful predictor of recurrence than the number of prior MDEs.

8.5 Stability and course of melancholic features (Study III)

The hypothesis that the prevalence of current comorbidity of axis II disorders and neuroticism would be higher among the non-melancholic patients was tested, and found not to be the case. The finding of no significant differences in rates of axis II disorders or neuroticism between melancholic and non-melancholic patients is consistent with some earlier studies (Zimmerman et al., 1986 [RDC criteria]; Shea et al., 1987; Tedlow et al., 2002), including a recent entirely outpatient study (Tedlow et al., 2002) with about the same prevalence of melancholic patients (39%) as in the VDS (36%). However, it is discordant with most of the studies on inpatients (Charney et al., 1981; Davidson et al. 1985; Zimmerman et al., 1986 [DSM-III-R criteria]; Parker et al., 1998), or non-clinical populations (Kendler et al., 1997). Nevertheless, some methodological disparities between studies need to be considered. Patients were interviewed with the SCID-II during their depression, and, unlike many other studies, alcohol use disorders and serious suicide risk were not exclusions in the VDS, which probably led to the higher prevalences of personality disorders. Because melancholic patients had a clinically more severe index episode than non-melancholic patients, the effect of severity was controlled for in the

multivariate models. However, the finding that DSM-IV melancholia was not associated with lower rates of personality disorders, or any personality disorder cluster, replicated the result of Tedlow and colleagues (2002), who also used semi/structured interviews for both MDD and comorbid personality disorders, and controlled for the effects of additional comorbid disorders and age. It is also noteworthy that psychotic features in the VDS population only moderately clustered in the melancholic depression group, thus not strongly supporting the hierarchical model of Parker (2000).

Also tested was the hypothesis that episode subtype would be consistent for the subsequent episodes, and again this was not the case. The results indicate a low level of subtype stability for subsequent episodes, which in fact is highly consistent with most earlier studies (Kendell, 1974; Paykel et al., 1976; Young et al., 1987), including a very recent one reporting not only instability of subtypes but also instability of symptoms in MDD (Oquendo et al., 2004). Instability of subtypes did not reflect differences in the severity of episodes during follow-up, although after the index episode the recurrent episodes were milder and shorter in this study, probably due to the treatment received. Despite the lack of difference in symptom severity between melancholic and non-melancholic episodes during the follow-up phase, the theoretical possibility that the treatment received benefited melancholic more than non-melancholic episodes, perhaps resulting in relatively fewer melancholic recurrences and therefore lower consistency across episodes, cannot be excluded. In order to explore the possibility that presence of psychomotor symptoms might better differentiate between the postulated subtypes, the data were reanalyzed by dichotomizing the patients according to presence or absence of psychomotor symptoms. Consistent with the presented findings, no significant subgroup differences emerged. Nevertheless, these findings have to be treated with caution due to the limited number of new episodes, the only medium-term follow-up, and the fact that the CORE measure (Parker et al., 1994; Parker & Hadzi-Pavlovic, 1996) for psychomotor symptoms was not used. Moreover, the possibility cannot be excluded that using a more sophisticated measure of psychomotor symptoms such as CORE (Parker et al., 1994; Parker & Hadzi-Pavlovic, 1996) would have produced different findings.

When comparing the course of depression in melancholic and non-melancholic MDD, no differences in prospective course between the subtypes were found. The duration of index episode, time to first subsequent MDE, number of recurrences/relapses, and duration of different symptom states did not significantly distinguish melancholic and non-melancholic depression. This finding is consistent with most earlier inpatient studies reporting no differences in outcome between melancholic and non-melancholic depression (Keller et al., 1984; 1986; Kiloh et al., 1988; Parker et al., 1992; Paykel et al., 1995; Brodaty et al., 2001; Kennedy et al., 2003), but not all (Lee & Murray, 1988; Duggan et al., 1991). The retrospective finding that melancholic patients had MDE of shorter duration prior to baseline seems to be explained by the factors associating with treatment facilities.

Melancholic patients with more severe depressive symptoms and lower functional capacity appear to be more easily recognized by primary care and occupational health services than non-melancholic patients, and thus more promptly referred to secondary level psychiatric care.

8.6 Antidepressant and psychosocial treatment in MDD (Study IV)

In contrast to the generally adequate treatment in the early acute phase, continuity of antidepressant treatment was far less complete in the later acute, continuation and maintenance phases. About half (49%) of the patients terminated antidepressant treatment prematurely, and only about a quarter (28%) completed a continuation phase of at least four months. Patients with less severe depression and those without previous antidepressant treatment were more likely to terminate medication prematurely. Those who did so while still in the acute phase achieved full remission significantly less often (42% vs. 66%), and in a longer time than other patients.

Premature termination of antidepressants was predicted by negative attitudes at entry. Underlying these attitudes most frequently were fears of dependence (43%) or side-effects (41%). Many depressive patients also reported having taken an active, autonomous role in the decision to terminate antidepressants. "Patient's autonomous decision" was a more common reason than all perceived side-effects of antidepressants, poor response or subjectively perceived recovery. These results accord with findings in the population of the UK Defeat Depression campaign (Paykel et al., 1998) as well as with other recent studies, which reported factors such as stigma, health-beliefs, and negative attitudes to be important risk factors for non-adherence (Melfi et al., 1998; Demyttenaere & Haddad, 2000; Demyttenaere et al., 2001; 2003; Sirey et al., 2001; Keller et al., 2002; Lingam & Scott, 2002; Lin et al., 2003).

Continuity of psychotherapeutic treatments was associated with more severe and more prolonged depressive symptoms. Noteworthy, however, was the finding that about a third (32%) of the patients not achieving full remission during the follow-up were without any psychosocial treatment at 18 months. Less than a fifth (16%) of the patients received weekly psychotherapy during the follow-up, which was somewhat surprising because about third (34%) of the attending professionals in the PMCD were qualified and certified therapists in specific psychotherapy, and the mean number of sessions was high enough for brief psychotherapy. The patients who received psychotherapy were either those able to form a good treatment alliance, and thus probably more able to benefit from therapy, or suicidal patients who needed more intensive treatment in the acute phase and also received it more promptly. Despite recommendations in practice guidelines (Schulberg et al., 1998; Anderson et al., 2000; APA, 2000; Bauer et al., 2002; Suomen Psykiatriyhdistys, 2004) for more intensive treatment, patients with personality disorders were the least likely to receive weekly psychotherapy.

Negative treatment attitudes at baseline were more common towards antidepressants than psychotherapeutic treatments, but in most (82%) cases these attitudes became positive during the treatment. The fact that MDD patients with negative attitudes were not those with comorbid personality or alcohol use disorder did not support the primary hypothesis. On the contrary, patients with alcohol use disorders had more positive attitudes towards antidepressants. Men and MDD patients with dysthymia (double depression) needed more encouragement before accepting psychotherapeutic treatments. The main reasons given for negative attitudes about psychosocial treatments were unwillingness to confide in a stranger, and patients believing they would not be helped by the treatment. Younger age, less severe and longer-lasting depression, and milder anxiety symptoms also associated with negative treatment attitudes.

Non-adherence is rarely an "on-off" phenomenon. Treatments may occur more or less irregularly, and it may be unclear whether this significantly affects achieving treatment goals or not. In contrast to the hypotheses, those with continued self-reported non-adherence to antidepressants were more often those without comorbidity, expecially if they were without anxiety and avoidant personality disorders. So it seems that presence of perceived distress is also a major factor that motivates continuation with treatment.

9. CONCLUSIONS AND FUTURE IMPLICATIONS

9.1. Conclusions

The recognition of comorbidity has important clinical significance in psychiatric care. Comorbidity of MDD is not only highly prevalent, but often also multiple and concentrated. It appears to predict a longer duration of MDE, and is associated with greater risk of recurrence.

The outcome of MDD appears not to be improved in psychiatric care. Achieving full remission takes a relatively long time, and although patients typically respond early to treatment, the major problem is the long period with only partial remission. Moreover, the rate of recurrence seems to be high. Severity of MDE and comorbidity are the two most significant predictors for the duration of MDE and risk of recurrence.

The descriptive validity of the DSM-IV melancholic features specifier may be questionable in MDD. There appear to be no major differences in current comorbidity or course of depression between melancholic and non-melancholic patients. Also, the consistency of DSM-IV melancholic features across episodes appears weak.

Problems of psychiatric care in MDD are mostly related to continuity of treatment. Many depressive patients take an active, autonomous role in the decision to terminate antidepressants. Premature termination not only associates with patients' negative attitudes, and fears of addiction and side-effects, but also appears to reflect their willingness or demands to cope without medicine. Negative treatment attitudes seem to be more common towards antidepressants than psychotherapeutic treatments, but these attitudes tend to become positive during the treatment. Less than a fifth of MDD patients receive weekly psychotherapy in psychiatric care. This is somewhat surprising, because quite a large proportion of professionals are qualified and certified therapists in specific psychotherapy, and the number of sessions is high enough for brief, focused psychotherapy. Patients with personality disorders appear to be very unlikely to receive weekly psychotherapy.

9.2 Clinical implications

It is likely that greater diagnostic precision, and better recognition of comorbid disorders will improve depression outcome. More complete and accurate diagnostic practice may serve as a better predictor of course and outcome, and may impact on patients' satisfaction with treatment, their alliance with treating professionals, selection of medication, and recommendation for psychotherapy. Comprehensive diagnostic evaluation also provides essential information to patients. It is always important to consider the effect of comorbidity on the outcome when interpreting findings from naturalistic outcome studies, as well as in planning and operating treatment facilities for psychiatric patients with MDD.

Severity of depression should influence clinical decision-making regarding the need for maintenance therapy, particularly among patients who are having their first or second MDE, when maintenance therapy is not usually recommended. Use of observer / self-report scales measuring severity of depression are recommended for routine clinical practice.

Providing psychoeducation to all depressive patients (and their families) seems essential. Psychoeducation should include information on antidepressants - not only their side-effects but also their non-addictiveness, and mechanisms of action. This might prove an effective way to improve continuity of treatments and outcome of depression. Moreover, it is important to motivate patients at least to try antidepressants, and to regularly ask about their treatment attitudes in order to recognize those at risk of non-adherence. Depression also seems to be pleomorphic in its manifestations across episodes. Considering treatment, instability of the MDD subtype across subsequent episodes suggests that the medication used in previous episodes is not necessarily always optimal in a recurrence.

From secondary and tertiary preventive perspectives, improving the continuity of treatment appears a crucial task for improving the outcome of psychiatric patients with MDD. Providing specific psychotherapies more often in psychiatric care, especially for MDD patients with personality disorders, could also enchance the quality of care.

Both professionals and patients face difficulties in complying with treatment guidelines, and the treatment eventually provided is the result of their interaction and compromises. Despite the unquestionably important role of practice guidelines in psychiatric care, clinicians should also keep in mind that evidence-based information on treatments in common, highly comorbid MDD patients is still lacking. While awaiting further studies to provide this information, the challenges in psychiatric care include providing better and more comprehensive diagnostic evaluations, and more structured and focused treatments. More comprehensive psychoeducation would enhance respect for the autonomous role of the patient as well as the treatment alliance.

9.3 Implications for future research

More research on depression as a heterogeneous, comorbid disorder is needed. Studies on comorbid MDD using both the dimensional and categorical models, and investigating factors from several potentially relevant domains including genetic, biological, developmental and environmental risk factors, should be carried out. Such studies would help us to better understand the nature of the mechanisms underlying comorbidity, and to discover the potential neurobiological and structural variations in MDD according to patterns of comorbidity. Further prospective longitudinal studies are needed to search for any logical pattern in the symptom progression, subtypes or comorbidity of MDD, over long time periods. Ideally, child, adolesenct and adult psychiatry will collaborate in future longitudinal research to the benefit of all.

Randomised controlled trials on both drug and psychosocial treatments should be carried out among ordinary, highly comorbid depressive patients, including beyond the acute phase. Ordinary psychosocial and drug treatments for MDD in various health care settings should be investigated and compared. Information is needed to help to develop better and more effective treatments and treatment facilities, as well as to improve co-operation between various treatment settings. More research is also urgently needed on specific psychotherapies.

More research needs to be conducted on the contributors to nonadherence and discontinuity of treatments, in order to better identify patients at particular risk. Future research should also include intervention studies and investigations of perceived interaction between patients and treating professionals, in order to clarify these dimensions of adherence.

Finally, studies are needed to determine whether semistructured diagnostic evaluations improve the outcome of depression.

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