Insight into the heterogeneity of depressive disorders

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Chapter 11

Summary and General Discussion

The aim of this thesis was threefold: i) to gain insight into the heterogeneity of depressive disorders by examining the diagnostic categories of Major Depressive Disorder (MDD), Dysthymic Disorder and Double Depression on a broad range of socio-demographic, biological and psychological characteristics, course trajectories and consequences for general well-being; ii) to explore alternative models for depressive disorders, based on data-driven techniques, and iii) to examine the association between depression and anxiety, and its implications for the nosology of depressive disorders. In the present chapter, the main findings of this thesis will be integratively summarized and discussed within the framework of outcomes of previous studies. Next, methodological issues, relevant for this thesis, will be addressed and some notes on possible clinical implications of our findings will be given. Finally, some topics for future research are identified.

MAIN FINDINGS

Part I. Depressive disorders: carving nature at its joints?

Plato stressed the importance of dividing things into classes along the 'natural joints', instead of recklessly 'breaking any part' in order to create boundaries between categories (*Phaedrus 265e*- around 370 BC). To what extent are the current depressive categories divided along natural occurring boundaries? In Chapter 2 through 5 we examined MDD, Dysthymic Disorder and Double Depression on a broad range of socio-demographic, biological and psychological characteristics, course trajectories and consequences for general well-being. If MDD, Dysthymia and Double Depression represent distinct clinical entities, differences in these parameters might be expected. Since symptoms used to classify Dysthymic Disorder and MDD in DSM-III and further editions are similar, albeit of longer duration and less severity in Dysthymic Disorder, significant differences in pathophysiological processes between MDD and Dysthymia may be attributed to these core clinical features of depression (severity and/or duration).

Biology and Psychology

In a review on the biological and characterological features of Dysthymia, Griffiths et al. (2000) concluded that there is scattered information on differences in the biological underpinnings of MDD and Dysthymic Disorder and stressed the importance to distinguish between pure Dysthymia and Double Depression in studies on the biological aspects of Dysthymia. However, studies that compare pure Dysthymic Disorder with Double Depression are limited. In **Chapter 2**, we compared persons with a 6-month diagnosis of MDD (n=853), pure Dysthymic Disorder (n=43) and Double Depression (n=262) on i) biological characteristics (including cortisol, inflammation markers and serum Brain Derived Neurotrophic Factor (sBDNF)) and ii) psychological characteristics (including personality measures and cognitive vulnerability). No differences were found on biological parameters suggesting that outcomes on biological parameters seem to be unrelated to depressive subtypes of MDD, Dysthymia and Double Depression, and, thus, seem to be unrelated to

severity and/or duration of depressive symptoms. This is in line with other reports, based on NESDA-data, in which severity and duration were unrelated to cortisol (Vreeburg et al., 2009), inflammatory response- with the exception of higher levels of TNF-α in women with more severe depressive symptoms- (Vogelzangs et al., 2012), and BDNF (Molendijk et al., 2011). Broader literature on the importance of severity and chronicity of depressive symptoms on biological parameters conflicts with both present (Brouwer et al., 2005; Dowlati et al., 2010; Oldehinkel et al., 2001) and absent associations (Anisman et al., 1999; Aydemir et al. 2007; Bhagwagar et al., 2005; Nelson et al., 1997; Marques-Deak et al., 2007; Watson et al., 2002). Note, the lack of differences does not imply that similar pathophysiological processes underlie MDD, Dysthymia and Double Depression. Possibly our findings on cortisol, inflammation and BDNF represent the endpoints of a final common pathway, with heterogeneity in underlying processes. Another explanation of lack of differences might be the insufficient discriminant validity of the depressive categories. As Caroll (1989) said: 'No biological measure can in principle do better than the clinical independent variable against which it is compared'. Hence, possible flaws in the concepts of MDD, Dysthymia and/or Double Depression limit the detection of actual differences between these subgroups of depressive disorders.

Persons with MDD, Dysthymia and Double Depression showed different psychological profiles, with higher levels of neuroticism in the latter two, and an absence of differences in cognitive styles between Dysthymic Disorder and Double Depression, suggesting that personality and cognitive styles are associated with chronicity. This is in line with previous research (Wiersma et al., 2011). Unfortunately, causality cannot be inferred from our cross-sectional data. Cognitive theorists have proposed that maladaptive cognitive processing becomes more likely as more or chronic depressive episodes are experienced (Moulds et al., 2008). To what extent differences in personality and cognitive styles represent a state or trait effect is topic of debate. Ormel et al. (2004) previously demonstrated that persons with (a history of) MDD report higher levels of neuroticism when they are depressed than when they are not depressed, whereas others concluded that personality traits assessed during depressive episodes are a valid reflection of personality pathology rather than an artifact of depressed mood (Morey et al., 2010). Recently, NESDA researchers examined associations between specific personality dimensions and depressive disorders. They demonstrated that neuroticism, extraversion, and conscientiousness are not only predispositions of affective disorders, but they also appear to be subject to change with onset and recovery of depression (Karsten et al., 2012). Further, prospective research is needed to unravel the interplay between personality and depressive subtypes.

Course trajectories of depressive disorders and functioning

Longitudinal observations are of great importance for classifying mental disorders: when naturalistic course differs across disorders, their distinction could be useful in clinical practice and psychiatric nosology. In **Chapter 3,** we investigated the course trajectories of persons with a Composite International Diagnostic Interview (CIDI) diagnosis of Major Depressive Disorder (n=225), Dysthymic Disorder (n=62) or Double Depression (n=113) at baseline, with outcome defined as i) a CIDI diagnosis of depression after 3-year follow-up, and ii) the 3-year course of mental functioning, measured by the SF-36 mental subscale. Data were derived from NEMESIS-1. Cox proportional hazards analyses and Linear Mixed Models showed that Dysthymia and Double Depression had similar course trajectories, which were worse than the course trajectories of MDD only. These results do not support a distinction between Dysthymia and Double Depression. Multivariate analyses demonstrated the importance of neuroticism and global functioning in predicting the course of depressive disorders. What do these results add to the debate on the nosology of depressive disorders? Since the presence of a superimposed MDD does not alter the course of a pure Dysthymic disorder, the validity of a distinction between Dysthymia and Double Depression is not supported. However, both chronic disorders differed from MDD, representing non-chronic depression. To conclude, our findings are in line with Wells' proposal to differentiate between depressive disorders on the basis of functional status and chronicity (Wells, 1992), instead on stringent DSM-categories.

Chapter 4 further elaborates on the association between level of functioning and type of depressive disorder. It is well known that depressive disorders have a large impact on both social and physical domains of functioning and work performance (Coryell et al., 1993; Judd et al., 1996; Rapaport et al., 2005; De Graaf et al., in press), similar to or even exceeding the impact noted in common somatic illnesses (Buist-Bouwman et al., 2006; Merikangas et al., 2007; Ormel et al., 1994). Since persistence of a lower level of functioning predicts recurrence of a depressive episode, even after the symptoms of depression are alleviated (Faravelli et al., 1986; Judd et al., 2000; Judd and Akiskal, 2000; Solomon et al., 2004; Spijker et al., 2004), insight into the course of social and physical functioning of persons with depressive disorders, and into the determinants of an impaired recovery of functioning, may facilitate recurrence prevention, limit the burden of disease, and informs us on the nosological status of the concepts under study. If for example substantial differences between level of functioning between MDD, Dysthymia and Double Depression are encountered, this would support the validity of the distinction between these subtypes.

Using data from NEMESIS-1, we compared 3-year trajectories of functioning across depressive persons with MDD (n=102), Dysthymia (n=66) and Double Depression (n=73), who recovered during three year follow-up, and compared these with persons without any DSM-diagnosis. Functioning was assessed using the Groningen Social Disability Schedule (GSDS) (Wiersma et al., 1988) and the SF-36 physical health summary-scale (Ware et al.,

1995). Data were derived from NEMESIS-1. Linear Mixed Models showed that compared to persons without any diagnosis, all depressed groups were significantly impaired on social and physical functioning. Across depressive groups, Dysthymic Disorder and Double Depression had a lower level of post-morbid physical functioning compared to MDD. Determinants for impaired social functioning (neuroticism) and impaired physical functioning (older age, somatic comorbidity and neuroticism) were identified. To conclude, chronicity of symptoms appears to be associated with impaired recovery of functioning to a greater extent than severity of symptoms, since especially those with Dysthymia (either with or without a superimposed MDD) showed slower and less complete recovery of functioning.

Is Dysthymic Disorder worth the classification as a specific DSM-disorder?

The findings of Chapter 2 through 4 allude to the questionable discriminant validity of Dysthymic Disorder - and provide further fuel to the debate currently being considered for DSM-V that the term 'Dysthymia', 'Double Depression' and 'Chronic Major Depression' be abandoned and subsumed into an enveloping 'Chronic Depressive Disorder'. However, if this container concept overrides identification of intrinsically differing conditions that might argue for quite different interventions, its clinical relevance is compromised. Therefore, **Chapter 5** seeks to further elucidate the concept of Dysthymic Disorder, assuming it is a broad diagnostic domain subsuming multiple expressions of clinical, chronic depression, such as minor chronic as well as 'smouldering' depressive episodes, treatment resistant depressive conditions, and depression syndromes underpinned by psychological and social factors. 318 Patients, attending the Black Dog Institute Depression Clinic, Sydney, and fulfilling the MINI-criteria of Dysthymic Disorder, were examined on a broad range of characteristics, including socio-demographics, personality measures and clinical characteristics. Latent Class Analysis (LCA) and Latent Profile Analysis (LPA) were conducted, with the aim of detecting distinct classes within Dysthymic Disorder, based on depressive symptomatology and personality domains, respectively. However, due to large heterogeneity we could not identify distinct conditions (other than variation by severity). Finally, clinicians' formulations of the patients were examined. Remarkably, none of the clinicians diagnosed a Dysthymic Disorder. These findings further add fuel to the debates on the questionable discriminant validity and clinical utility of Dysthymia in a tertiary referral clinic.

Part II. Alternative models for depressive disorders

In Chapter 2 through 5, we examined current DSM-categories of MDD, Dysthymic Disorder and its composite- Double Depression. Since 1980, course was incorporated into the diagnostic criteria of these depressive subtypes, by requiring a minimum duration of depressive symptoms of two weeks for MDD and two years for Dysthymic Disorder. However, do DSM-categories of MDD, Dysthymic Disorder and Double Depression indeed adequately represent clinically relevant course trajectories of depression? Data-driven

techniques, free from any a priori assumptions or diagnostic categories, can help to detect naturally occurring course trajectories among persons with depression. In **Chapter 6,** we compare DSM-categories (MDD, Dysthymic Disorder and Double Depression) with empirically derived prognostic categories, using a prospectively followed cohort of depressed patients (n=804). Latent Class Growth Analysis (LCGA) identified five distinct course trajectories, ranging from mild severity and rapid remission to high severity and chronic course trajectory. These identified classes were compared with DSM-diagnoses. Contrary to expectations, over 50% of persons with Dysthymia and Double Depression were allocated to classes with favorable course trajectories, suggesting that current DSM-categories do not adequately represent clinical relevant course trajectories. The class with the most favorable course trajectory differed on a number of characteristics from other classes (younger age, more females, less childhood adversity, less somatic illnesses, lower neuroticism, higher extraversion). Older age, earlier age of onset and lower extraversion predicted poorest course trajectory.

Thus far, we have focused on specifiers of depressive disorders such as severity and duration, reflected in the diagnostic categories of MDD, Dysthymic Disorder and Double Depression. However, since DSM-III, other specifiers such as melancholic or atypical features are available for further differentiation of depressive subtypes. Over the past several decades, there has been substantial research devoted to the identification of depressive subtypes based on distinct symptom profiles, treatment response, and clinical correlates. Using Latent Class models in a large cohort (n=818) of subjects with depression, NESDA researchers previously demonstrated the importance of depression severity (moderate versus severe) and the nature of depressive symptoms (melancholic versus atypical) as differentiators between depressive subtypes (Lamers et al., 2010). However, few studies have investigated the stability of depressive subtypes, an essential requirement for the validity of the delineation of subtypes. Studies that examined the longitudinal stability of depressive subtypes have shown low to moderate stability of subtypes (Young et al., 1987; Coryell et al., 1994; Angst et al., 2007), with greater stability between adjacent episodes (Coryell et al., 1994). **Chapter 7** concerns the stability of depressive subtypes of a sample of 488 persons from NESDA who had a Major Depressive Disorder at both baseline and at the 2-year follow-up assessment. A Latent Transition Analysis (LTA) was applied to examine the stability of depressive subtypes across time-points. Overall LTA showed 76% stability across 2-year follow-up, with the greatest stability of the Severe Atypical class (79%). Persons hardly changed from Moderate to Severe Typical, and from Severe Typical to Severe Atypical. Transitions from the Severe Atypical to Severe Typical subtype may represent the phenomenon that endogenous/melancholic symptoms increase with increasing age (Brodaty et al. 1997; Parker et al. 2001). Analyses of correlates in stable subtypes showed a preponderance of women and more overweight and obesity in the Severe Atypical subtype, and a greater number of negative life events, and higher neuroticism and functioning scores

in the Severe Typical subtype. Subtypes of Major Depressive Disorder were found to be stable across 2-year follow-up and to have distinct determinants, supporting the notion that the identified subtypes are clinically meaningful.

Part III. Depression and Anxiety: same side of the coin?

Chapter 8 illustrates the importance of anxiety for course trajectories of depressive disorders. In this chapter, 303 respondents, who participated both in NEMESIS-1 and NESDA, with a depressive and/or anxiety CIDI-disorder were interviewed, examining the 7-year course of depression (n=141), anxiety (n=102) and their comorbid state (n=60) and possible prognostic factors. After 7 years, 60.7% of the subjects were free from a 12-month CIDI depression or anxiety diagnosis. The risk for a depression or anxiety at follow-up was higher for subjects with anxiety only or with comorbidity compared to subjects with depression only. Furthermore, low physical functioning and high neuroticism predicted the presence of a diagnosis after 7 years. During 7-years follow-up, 37.3% of the subjects were free from depressive and anxiety symptoms according to the Life Chart Interview (Lyketsos et al., 1994). Again, (comorbid) anxiety resulted in a poorer course. High neuroticism and childhood adversity predicted more follow-up time with symptoms.

In Chapter 8, anxiety was broadly defined, hence limiting the insight into the impact of specific anxiety disorders on course trajectories. In **Chapter 9**, anxiety was defined as panic attacks, in accordance with DSM-V's proposal to rate panic as a dimension across all mental disorders. Since the main purpose of this thesis is to gain insight into the heterogeneity of depressive disorders, we here only consider the associations of panic with affective disorders. Results showed a considerable impact of current panic attacks, and- to a lesser extent- of a history of panic attacks on the prevalence, 3-year onset and persistence, and functioning of affective disorders. Further research is needed to unravel the nature of this association: Is panic a severity marker of depressive disorders, conceivably representing a distinct subtype (Kessler et al., 1998), or a comorbid condition? And is the occurrence of panic prior to the onset of depression a proxy for some underlying causal risk factor (Kessler et al., 1998), possibly a symptom of shared genetical vulnerability? Irrespective of the nature of the association between anxiety and depression, results of Chapter 8 and 9 strongly point at the relevance of anxiety for course trajectories of depressive disorders, and hence, its contribution to the heterogeneity of depressive disorders.

Finally, the recognition of the large comorbidity between depression and anxiety also questioned the validity of a categorical distinction between specific depressive and anxiety categories (Goldberg, 1996), in particular Generalized Anxiety Disorder (GAD) and depression. In **Chapter 10**, Latent Class Analysis was applied to anxious and depressive symptomatology of respondents, participating in i) three large, population based cohorts (NSMHWB-2007, NCS-R and NEMESIS-2) and ii) a multi-site naturalistic cohort of adults

(NESDA) to examine whether GAD and Dysthymic Disorder can be differentiated into an anxiety versus a depression symptom cluster based on data driven methodology. A three-class and two-class model respectively best fitted the data, reflecting mainly different levels of severity of symptoms. No division into specific anxious versus depressive profiles emerged. The absence of a clear demarcation of an anxiety versus depressive profile in empirically derived classes questions the current categories of GAD and Dysthymic Disorder.

IN SUMMARY

This thesis demonstrated the heterogeneity of depressive disorders and the role of anxiety on (course trajectories of) depressive disorders. It provided insight into the correlates of chronicity, and alternative models for the classification of depressive disorders were explored. We demonstrated that our current depression categories seem to exist in a kind of no man's land, disconnected from the underlying clinical entities and imposing artificial boundaries without clinical utility (McGorry et al., 2007). Illustration of the latter was the remarkable finding, that none of the clinicians in a tertiary referral clinic diagnosed Dysthymic Disorder in a population defined by the MINI as fulfilling the criteria of Dysthymia (Chapter 5). Furthermore, the limited discriminant validity of Dysthymic Disorder versus Double Depression was demonstrated; demarcation from MDD was more evident. Duration and severity of depressive symptoms and anxiety were identified as clinically relevant dimensions, in combination with assessment of correlates of chronicity, they may be preferable over the existing various diagnostic categories. These findings are in line with previous studies that found that basic clinical factors, such as severity and duration of the index episode are among the most consistent and strongest predictors of course (Spijker et al., 2002, 2004; Vuorilehto et al., 2009).

METHODOLOGICAL CONSIDERATIONS

In the following, we (re)consider the most important strengths and limitations of our conducted studies, such as thoughts on sampling and non-response, measurement of psychopathology and statistical methods.

Sampling and non-response

This thesis was based on several large, nationally representative surveys. In NEMESIS-1 and -2 a multistage, stratified, random sampling procedure was followed. Likewise, in the NSMHWB-2007, Australia, and the NCS-R, the United States, respondents were selected from a multistage clustered area probability sample of households. These sampling procedures enabled generalizability into the general population. The Netherlands Study of Depression and Anxiety (NESDA) is a multi-site naturalistic cohort study of adults (aged 18 to 65 years) recruited from the general population, general practices, and mental health organizations. The Black Dog Institute (BDI) sample included depressed out-patients,

recruited through a Depression Clinic, Sydney. In all surveys, long-term institutionalized persons and persons, who are not sufficiently fluent in Dutch (NEMESIS/ NESDA) or English (NSMHWB-2007/ NCS-R/ BDI), were excluded. Hence, generalizations towards institutionalized persons and some ethnic minorities are of limited legitimacy. In addition, as the subjects in these studies were adults, results have limited value for the elderly.

Non-reponse patterns in the baseline samples of NEMESIS-1 revealed a response rate at the baseline measurement of 70% (Bijl et al., 1998). In total 7076 persons participated; 5618 could be re-interviewed after one year (T_1) (79.4%) and 4796 after three year (T_2) (85.4% of T_1) (Graaf et al., 2000). Of NEMESIS-2 only baseline data were available for the present thesis, consisting of 6646 persons (response rate: 65%). The NSMHWB-2007 consisted of 8841 respondents (response rate: 60%); the total sample of NCS-R consisted of 9282 persons (response rate: 71%). Detailed analyses of non-response and attrition were provided in the previous chapters. In addition, Lamers et al. (2012) described attrition in NESDA in more detail. Overall, psychopathology only slightly increased the probability of loss to follow-up. Attrition rates in Chapter 8, presenting the results on 7-year follow-up of depression and anxiety, were considerable. This merits further attention: Of the 662 subjects approached, 359 (54.2%) refused to participate and 303 (45.8%) could be followed up. However, those who were followed up did not differ in terms of age (p=.77), gender (p=.79), or type of baseline disorder (anxiety, depression or comorbid disorder, p=.97) from those not participating. To conclude, we feel that our results on depressive subtypes are not appreciably affected by attrition.

Measurement of depression and anxiety

In all surveys, psychopathology was measured using standardized, diagnostic instruments, like Composite Interview Diagnostic Instrument (CIDI)- version 1.1; 2.1; and 3.0 (respectively: World Health Organization, 1990; 1998; Kessler et al., 2004) and Mini-International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997). The use of a structured instrument in large-scale epidemiological studies is a major strength. Inter-rater reliability for the two core concepts of this thesis, MDD and Dysthymic Disorder, has shown to be excellent (using the CIDI: k=0.97 for MDD; k=0.96 for Dysthymia (Wittchen et al., 1991; Wittchen, 1994); using the MINI: k=1.00 for MDD, Dysthymia: to our knowledge not available (Sheehan et al., 1998)). However, some have argued that the use of community-based diagnostic instruments, administered by lay interviewers (as the CIDI), instead of a clinical interview by a clinician, results in detection of subtreshold cases with limited clinical significance (Regier et al., 1998). Therefore, in this thesis, in addition to DSM-categories, course was additionally defined using a continuous mental health score (Chapter 2) or Life Chart Information (Chapter 6, Chapter 8) with similar results, illustrating that our results are unlikely due to the choice of our diagnostic instrument.

Furthermore, this thesis was mainly longitudinal in its approach, with follow-up periods ranging from 2 to 7 years. In the course of time, some changes were made in the different versions of the CIDI. However, the diagnostic criteria for MDD and Dysthymic Disorder remained largely unchanged. In DSM-IV, criterion C was added, requiring that the depressive symptoms should have an impact on social and occupational functioning, hence, the threshold for fulfilling the criteria of either MDD or Dysthymic Disorder became somewhat higher in DSM-IV. In addition, some changes were made in course specifiers for MDD, and the specifier of primary versus secondary Dysthymic Disorder was abandoned. However, these changes in specifiers did not influence the criteria for fulfilling either a MDD or Dysthymic Disorder, and, therefore, did not influence the findings of this thesis. Relevant for Chapter 9 was the modification of the criteria for panic disorder in CIDI 2.1, requiring recurrent unexpected panic attacks accompanied by a month or more of persistent concern of having attacks or about the implications of an attack, whereas in CIDI 1.1, based on DSM-III-R, either four attacks in 4 weeks, or one attack followed by a month of persistent fear for having another attack, was required (WHO 1990, 1998). These changes resulted in a stricter definition of panic disorder at follow-up and might, therefore, result in an underestimation of the long-term persistence of anxiety disorders. Hence, our conclusion that a (comorbid) anxiety disorder resulted in a poorer course trajectory would have been stronger when the same diagnostic criteria would have been used.

In our search for predictors of course, we were able to use an extensive assessment battery, facilitating multivariate analyses on a range of potential risk factors. However, treatment was not included in our multivariate analyses, although it may be associated with course trajectories. In our naturalistic study designs, the effect of treatment on course cannot be adequately evaluated. In addition, adjustment for treatment effect is complex because of the bias, that patients with the most severe problems receive the most treatment. Hence, a spurious relation between treatment and outcome can be found and its interpretation becomes very difficult.

Statistical methods

Various data-driven methods were applied in order to explore alternative models for the classification of depression. Chapter 6 presents one of the largest studies to date, that longitudinally investigates the existence of depressive course types in a cohort of depressed subjects by data-driven methods (LCGA). In addition, to our knowledge, Chapter 7 is the first to evaluate the prospective stability of depressive subtypes by Latent Transition Analysis. Finally, Chapter 10 relies on the aggregation of three major, general population samples from three different continents, enabling us to perform Latent Class Analysis on a sufficient number of participants. Despite these innovative procedures, when interpreting the results of these studies, several limitations should be taken into consideration. It should be noted that data-driven methods draw upon mathematical models that cannot account for a great

variety of fluctuations in symptom levels. There is evidence that depressive symptoms wax and wane within the same patient and that these symptomatic periods are interspersed in the overall course within times when patients are remitted and symptom free (Judd and Akiskal, 2000). This pleiomorphic course cannot completely be described by LCGA. Also, some potential limitations of the LTA should be noted. We used 2 time-points and had relative stable subtypes. Although two time points suffice for LTA analysis, it is possible that if we had had more follow-up measurements, more transitions would have occurred, and that the current results are therefore an overestimation of the true stability. Second, we evaluated course trajectories (Chapter 6) and transitions (Chapter 7) across a rather short period of two years. Although it has been reported that most symptom changes generally occur in the first year after the start of an episode (Penninx et al., 2011), future research should evaluate whether the course trajectories of symptomatology is indeed similar when longer time periods are used.

IMPLICATIONS FOR CLINICAL PRACTICE AND THEORY

What are the possible implications of our findings for clinical practice? The most important message of this thesis concerns the lack of validity and utility of our current diagnostic system. This has great implications for (the organization of) mental health care, since diagnostic categories are the back and bone of patient care and clinical management. For example, many mental health organizations have organized their out-patients care along the lines of DSM-diagnostic groups, such as mood disorders or anxiety disorders, artificially drawing a line between depression and anxiety. Likewise, clinical guidelines and studies into intervention strategies, such as randomized clinical trials, strictly adhere to diagnostic categories.

We demonstrated that dimensions of duration and severity of depressive symptoms, and possibly an additional, dimensional rating of panic across mental disorders, may be preferable over the existing depressive categories. This requires a major shift in psychiatric thinking, since it undermines current clinical taxonomy and provides fuel for the development of alternative clinical models. We elaborate on possible models in the next paragraph, but what is its impact on patient care? Currently, Procrustean diagnostic concepts guide clinical practice. The knowledge gained in this thesis showed that, instead of counting the number of diagnostic criteria to see which DSM-category fits the complaints of individual patients, a more prominent role for rating scales of severity of depression and panic, and a thorough assessment of the psychiatric history, including assessment of duration and recurrence of symptoms, may be more useful to identify persons at risk for chronic course trajectories.

Currently, similar strategies are already in use in mental health care. For example, clinical guidelines for Bipolar Disorder (Nolen et al., 2008) propagate the use of a so-called ‘action

plan' (Perry et al., 1999) in which the nature and timing of prodromal symptoms of a manic or depressive relapse are elicited in order to seek earlier treatment and to reduce the time to next relapse. In this action plan, dimensions of severity and duration of symptoms guide interventions. This personalized intervention strategy has proven to be very effective in relapse prevention of manic episodes and improved social functioning and performance in employment (Perry et al., 1999). Likewise, a patient oriented approach, with input of severity measures (such as Hamilton Depression Rating Scale) and a thorough assessment of psychiatric history providing insight in the age of onset, relapse rate and duration of symptoms thus far, may provide a framework for individualized 'action plans' for depressed persons and facilitates the identification of persons at risk for chronic course trajectories.

However, severity and duration dimensions alone might not suffice. Shankman and Klein (2002) demonstrated that a combination of symptom severity and prior course provided only a minimal increase in predictive power over and above DSM diagnoses of Major Depressive Disorder and Dysthymia. They propagated inclusion of additional features, like personality and cognitive measures, functioning or biological correlates. We identified some correlates of poor course trajectories that may ameliorate the predictive power of dimensional models, such as older age (Chapter 6), early age of onset (Chapter 6), lower level of functioning (Chapter 3, 8), somatic illnesses (Chapter 4, 6), high neuroticism and low extraversion (Chapter 4, 6, 8) and childhood adversity (Chapter 6, 8). Most correlates were previously also identified as predictors for chronicity (see also Sargeant et al., 1990; Ormel et al., 1993, Keitner et al., 1992; Wiersma et al., 2009). The diversity in correlates of chronic course illustrates, that treatment focused on depressive symptoms only will not suffice to reduce risk of recurrence or chronicity and to enhance functioning of depressed individuals. Successful treatment must go beyond ameliorating signs and symptoms to address the broader issue of restoration of health. Among others, in clinical care, attention should be paid to personality dimensions, level of functioning and childhood adversity as significant predictors of chronic course trajectories of depression in the general population.

Theoretical implications: an alternative model for depression?

After Michelangelo finished his masterpiece, the Pieta, in 1499, he commented: "I saw the angel in the marble and carved until I set him free." In psychiatry, during the last decades, researchers sought to detect clinical entities hidden behind symptoms of disturbed mood, anxiety, delusions and so on, and to create classification systems for psychopathology. A challenging endeavor. Some mental disorders were defined, to be abandoned again several years later. In this thesis we navigated trough the landscape of depression using triangulation of data and methods and demonstrated the flaws in current DSM-categories. Where to go next? Instead of endlessly searching for our own Pieta's, we might as well wonder: Is there a Pieta hidden behind the symptoms of disturbed mood? Or should we adhere to a more dimensional approach?

Based on the work of Fava and Kellner (1993), a clinical staging framework as an alternative model for current DSM-classification has been previously proposed (Fava and Tossani, 2007; McGorry, 2007; Hetrick et al., 2008). Clinical staging, already a proven strategy in the treatment of malignancies, defines the progression of disease in time and where a person lies along this continuum of the course of illness (McGorry, 2007). Defining discrete stages according to the progression of disease creates a prevention-oriented framework. This requires an accurate understanding of the broad social, biological and personal risk and protective factors that influence movement across stages (McGorry, 2007). Fava and Tossani (2007) developed an initial clinical staging framework for depression. This model was still based on current depressive categories (see Table 1).

Table 1. Stages of primary unipolar depression proposed by Fava and Tossani (2007).

Stages
1. Prodromal phase (anxiety, irritable mood, anhedonia, sleep disorders)
a. No depressive symptoms
b. Minor Depression
2. Major Depressive Disorder
3. Residual Phase
a. No depressive symptoms
b. Dysthymia
4. a. Recurrent Depression
b. Double Depression
5. Chronic Major Depressive Episode (lasting at least 2 years without interruptions)

(Source: Fava and Tossani, 2007)

Our findings demonstrated the lack of validity and clinical utility of the current depressive categories, hence questioning the model of Fava and Tossani (2007), since this model was based on these traditional concepts. A clinical staging model, incorporating duration and severity dimensions, as well as an additional dimension of anxiety, in association with correlates of chronicity, such as neuroticism and level of functioning may be more valid. Hetrick et al. (2008) provided a heuristic model for unipolar depressive disorders (see Table 2). This model employs a more dimension-based approach, including depression severity and functional status. In addition, the role of anxiety is reckoned, at least in stage o and 1.

Table 2. Clinical staging model framework for unipolar depressive disorders proposed by Hetrick et al. (2008).

Stages	
0.	Increased risk of anxiety or depressive disorder. No symptoms currently.
1.	a. Mild or non-specific symptoms of anxiety or depression, including neurocognitive deficits of severe mood disorder. Mild functional change or decline. b. Ultra high risk: moderate but subthreshold symptoms of anxiety or depression, with moderate neurocognitive changes and functional decline to caseness (Global Assessment of Functioning [GAF] < 70)
2.	First episode of Major Depressive Disorder. Full threshold disorder with moderate to severe symptoms, neurocognitive deficits and functional decline (GAF 30-50)
3.	a. Incomplete remission from first episode of care. Could be linked or fast-tracked to Stage 4. b. Recurrence of relapse of depressive disorder which stabilizes with treatment at a level of GAF, residual symptoms, or neurocognition below the best level achieved following remission from first episode c. Multiple relapses, provided worsening in clinical extent and impact of illness is objectively present.
4.	Severe, persistent OR unremitting illness as judged on symptoms, neurocognition and disability criteria.

Note: The clinical staging model also includes target populations for recruitment, potential interventions and indicative biological and endophenotypic markers (see Hetrick et al., 2008).

According to the findings of this thesis, we would promote the inclusion of correlates of chronicity like personality measures (high neuroticism, low extraversion), older age, earlier age of onset, somatic comorbidity and childhood adversity as markers for further differentiation of persons at risk for progression from stage 2 to 3 or 4. Future research may further refine the clinical staging model for mood disorders, and may result in clearly quantifiable stages guiding the use of appropriate stage-specific, evidence-based treatment (Hetrick et al., 2008). First results are promising: Fournier et al. (2010) showed that the magnitude of benefit of antidepressant medication with placebo increases with the severity of depression symptoms, demonstrating the benefits of dimensional approaches above stringent DSM-categories.

Finally, the prominent role of anxiety in the classification of depression merits further attention. This thesis suggests that dimensionally rating anxiety, in casu panic, across all mental disorders might be of great value for clinical care. This approach is not new. In 1960s and 1970s depressed patients were subtyped according to the presence or absence of anxiety symptoms rather than being given separate diagnoses (Paykel, 1972; Overall et al., 1966). Recently, others have argued for a 3-dimensional structure (Clark and Watson, 1991) or a 2-dimensional structure of an internalizing dimension, encompassing Major Depressive Disorder, Dysthymia and anxiety disorders, and externalizing dimension (Krueger, 1999; Vollebergh et al., 2001; Olino et al., 2012). Chapter 10 contributes to this debate by showing that at least GAD and Dysthymic Disorder belong to one diagnostic domain. To what extent a dimensional rating of panic across mental disorders, including mood disorders, suffices, or

a reclassification of psychopathology into a tripartite model, or an internalizing versus externalizing dimensional model is needed, merits further research. Recently, Wardenaar et al. (2012) demonstrated the predictive value of dimensions of the tripartite model (general distress, anhedonic depression and anxious arousal) (Clark and Watson, 1991) on 2-year course trajectories of depression and anxiety on top of diagnosis and other prognostic factors. These findings warrant further replication. Knowledge to be gained by this research should be integrated into the staging framework for affective disorders.

FUTURE RESEARCH

To date, the practical application of clinical staging of mood disorders largely eluded psychiatry (Hetrick et al., 2008). Hence, future research should further refine a clinical staging framework for mood disorders, and examine its validity and utility for clinical practice and research. Thorough knowledge on broad social, biological, genetic, and personal risk and protective factors, that influence progression from one stage to the next, is needed. The more information is included in the model, the stronger its predictive value (Fava et al., 2012). Brietzke et al. (2012) recently proposed a predictive algorithm for bipolar disorders integrating genetic (i.e. family history), environmental (e.g. childhood maltreatment) and biological markers (i.e. BDNF, inflammatory and oxidative stress markers). Similar proposals should be developed for unipolar depressive disorders. Furthermore, we need to know the relative potency of the identified risk factors and which of them may be responsive to current interventions. Some factors may operate across several or all stages, others may be stage specific (McGorry et al., 2007). For example, socio-demographics such as age, female gender and low education are all confirmed determinants of the onset of depressive disorders (Kessler et al., 1994; Seedat et al., 2009). However, their role in course prediction has been less consistent (Ramsawh et al., 2009; Spijker et al., 2002; Yonkers et al., 2003).

In oncology, clinical staging depends on the type of malignancy. For example, lung cancers are broadly classified into two types: small cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC). This classification is based upon the microscopic appearance of the tumor cells themselves. These two types of cancers grow and spread in different ways and may have different treatment options, so a distinction between these two types is important. To what extent distinction between typical and atypical depression (Chapter 7), or a division into melancholic versus non-melancholic depression (Parker et al., 2010), warrants distinct clinical staging models, merits further research. Likewise, the subjects in this thesis were adults, participating in general population studies or out-patients settings. Knowledge from severely depressed in-patients as well as depressed elderly is needed to assess whether a clinical staging framework fits all types of depression, at all ages.

Research into intervention strategies can greatly benefit from this alternative approach. Thus far, our official diagnostic systems have impeded the search for neurobiological, genetic and psychosocial risk factors, and treatment. In clinical practice, dissemination of a clinical staging approach, such as treatment algorithms and 'action plans', can help to prevent mood disorders to progress, and to personalize treatment for individual patients along the lines indicated by the staging model.

In this thesis, data-driven methods, such as LCGA and LTA, were applied. Distinct course trajectories and depressive subtypes were identified. To examine whether these identified subtypes represent clinical relevant entities or dimension, an examination of these subtypes on a broad range of socio-demographic, biological, genetic and psychological characteristics, course trajectories and consequences for general well-being is needed. For example, in Chapter 6, our fifth class (chronic, severe) was characterized by greater severity, an early age of onset and a higher familial loading, possibly identifying a genetically more homogenous group. Lyons et al. (1998) and more recently Kendler et al. (2009) also suggested that early age-of-onset does typify a subtype of depressive disorders, with poorer course trajectories. This may be informative for etiological research. Likewise, Vogelzangs et al. (2012) for example demonstrated immune dysregulation has a role in a subgroup of depressed persons, in particular in men with a late-onset depression. Selection of persons, characterized by an early onset depression and a high familial loading for depressive disorders, for research into the pathophysiology and genetic background of mood disorders may facilitate the identification of etiological processes and genetic vulnerability.

EPILOGUE

Knowledge gained by this thesis resulted in a critical appraisal of current depressive categories of MDD, Dysthymic Disorder and Double Depression. We demonstrated the possible benefits of dimensional approaches, with two cross-cutting dimensions of severity and duration of depressive symptoms, a dimension of anxiety, and additional features, such as functioning, personality measures and childhood adversity, above stringent DSM-categories. Findings provided the 'bricks' for building alternative models for depression, like the clinical staging framework. Psychiatry should move beyond our customary clinical taxonomy, and develop alternative models to differentiate between patients, who otherwise seem to be deceptively similar, since they share the same psychiatric diagnosis (Fava et al., 2012). Much is still there to be learned about the nature of depression, paraphrasing Father Sebastian Englert of Rapa Nui, Easter Island: "When the subject is depression, no man's knowledge is either complete or secure".

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Nederlandse Samenvatting

Depressies, ofwel 'depressieve stoornissen', zijn veel voorkomende ziektebeelden met een grote impact op het leven van patiënten en op de samenleving als geheel. De Wereldgezondheidsorganisatie (WHO) verwacht dat in 2030 depressie op de eerste plaats staat van ziekten met de hoogste ziektelast. Twintig procent van de Nederlandse bevolking krijgt in zijn of haar leven te maken met een stemmingsstoornis en per jaar lijdt lijdt ongeveer 6% van de volwassenen aan een stemmingsstoornis. Dit zijn enorme aantallen. Omgerekend betekent het dat rond 650 duizend volwassenen in Nederland in 2011 last hadden van een stemmingsstoornis. Inzicht in depressies is dan ook van groot belang.

Sinds 1980 wordt in de psychiatrie wereldwijd gebruik gemaakt van het 'Diagnostic and Statistical Manual' (DSM), een classificatiesysteem om psychiatrische ziektebeelden te ordenen. Dit classificatiesysteem heeft onder meer onderzoek naar het ontstaan, beloop en behandeling van depressies gefaciliteerd. De huidige versie van de DSM maakt onderscheid tussen een depressieve stoornis, gedefinieerd als een depressieve stemming of interesseverlies gedurende tenminste twee weken; een dysthyme stoornis, gedefinieerd als een depressieve stemming, milder van aard dan de depressieve stoornis, maar van langere duur (tenminste twee jaar); en een depressie 'niet anderszins omschreven'. In dit proefschrift onderzoeken wij de heterogeniteit van depressies. In het bijzonder verkennen wij de concepten 'depressieve stoornis' en 'dysthyme stoornis'.

Epidemiologische studies tonen aan dat een depressieve stoornis en dysthyme stoornis vaak tegelijkertijd voorkomen- in sommige onderzoeken heeft zelfs meer dan 90% van de patiënten met een dysthyme stoornis tevens een depressieve stoornis. Dit gelijktijdig voorkomen van beide stoornissen wordt 'dubbele depressie' genoemd. Tevens blijken de (chronische) depressieve stoornis en de dysthyme stoornis nauwelijks van elkaar te verschillen in socio-demografische en klinische kenmerken. Dit voedt de twijfel over de validiteit van beide concepten. Met het oog op de DSM-V, de nieuwe versie van de DSM die naar verwachting in mei 2013 uit zal komen, zijn alternatieve classificaties voor depressies voorgesteld. Hierin worden beide stoornissen samengevoegd en wordt er slechts een onderscheid gemaakt tussen een chronische en niet-chronische depressieve stoornis. De dysthyme stoornis zou dan uit de DSM verdwijnen.

Niet alleen wordt het onderscheid tussen de depressieve en de dysthyme stoornis betwist, ook de afgrenzing tussen depressies en angststoornissen is onderwerp van discussie. Al sinds de oude Grieken wordt erkend dat depressies vaak gepaard gaan met angstklachten. Desondanks worden sinds de DSM-III (1980) angst en depressie apart geclassificeerd. Een grote mate van comorbiditeit- het gezamenlijk voorkomen- van angst en depressie leidt echter tot de vraag of het huidige onderscheid tussen angst en depressie wel gerechtvaardigd is.

Gezien de hoge prevalentie van depressies in de bevolking en de grote ziektelast, is het van groot belang dat er helderheid wordt verkregen in de heterogeniteit van depressieve stoornissen. In dit proefschrift trachten wij dan ook i) inzicht te verkrijgen in de heterogeniteit binnen het grote containerbegrip 'depressie' en dan in het bijzonder in het onderscheid tussen de depressieve stoornis, de dysthyme stoornis en de combinatie van beide, de zogenaamde 'dubbele depressie'; ii) alternatieve modellen voor het indelen van depressieve stoornissen te verkennen, en iii) het belang van angst(stoornissen) op de classificatie van depressieve stoornissen te onderzoeken.

Deel I: Classificatie van depressieve stoornissen

De eerste vier hoofdstukken van dit proefschrift onderzoeken de huidige onderverdeling van depressies in de depressieve stoornis, de dysthyme stoornis en de 'dubbele depressie'. In *hoofdstuk 2* wordt de vraag gesteld of er verschillen zijn in biologische en psychologische kenmerken van mensen- deelnemers aan de Nederlandse Studie naar Depressie en Angst (NESDA)- met een depressieve stoornis, dysthyme stoornis of 'dubbele depressie'. Er werden geen verschillen gevonden in biologische kenmerken, bestaande uit cortisol, ontstekingsparameters en serum Brain Derived Neurotrophic Factor (sBDNF). Personen met een dysthyme stoornis en 'dubbele depressie' hebben wel een ander psychologisch profiel. Zij zijn onder andere neurotischer en minder consciëntieus dan personen met een depressieve stoornis. Dit doet vermoeden dat chroniciteit van depressieve symptomen geassocieerd is met dergelijke persoonlijkheidskenmerken.

Het beloop van een ziekte verschaft veel informatie over een ziektebeeld. In *hoofdstuk 3* en *4* wordt dan ook respectievelijk i) het 3-jaars beloop van depressies en ii) het 3-jaars beloop van het dagelijks functioneren van mensen met een doorgemaakte depressie beschreven. Beide hoofdstukken zijn gebaseerd op de Netherlands Mental Health Survey and Incidence Study (NEMESIS). Opnieuw werden drie groepen- depressieve stoornis, dysthyme stoornis en 'dubbele depressie'- met elkaar vergeleken. Beide hoofdstukken tonen aan dat er welliswaar een verschil is tussen de depressieve stoornis en de dysthyme stoornis of 'dubbele depressie', maar dat de beide chronische vormen (de dysthyme stoornis en de 'dubbele depressie') nauwelijks van elkaar te onderscheiden zijn. Een onderverdeling in niet-chronisch versus chronisch- zoals voorgesteld voor de DSM-V lijkt dan ook gerechtvaardigd.

Tenslotte wordt in *hoofdstuk 5* de 'dysthyme stoornis' nader onder de loep genomen. Met diverse methoden wordt getracht het concept te ontrafelen, vanuit de gedachte dat dit wellicht een conglomeraat is van verschillende depressieve subtypes. 318 Depressieve patiënten, verwezen naar het 'Black Dog Institute Depression Clinic' in Sydney, Australië, werden geselecteerd. Statistische methoden (Latente Klasse Analyse en Latente Profiel Analyse), die zonder vooronderstellingen kijken of er bepaalde patronen of klassen in de data voorkomen, werden toegepast. Verschillende klassen werden geïdentificeerd. Echter, deze klassen bleken dermate verschillend, dat er geen eenduidige subtypes geïdentificeerd

konden worden, behoudens subtypen verschillend in ernst van de depressieve symptomen. Tenslotte werd onderzocht welke psychiatrische diagnoses psychiaters stelden bij een subgroep patiënten, die voldeden aan de criteria van een pure 'dysthyme stoornis' (n=42). Geen van de psychiaters stelde de diagnose 'dysthyme stoornis'. Deze resultaten bevragen de discriminante validiteit en klinische utiliteit van het concept dysthyme stoornis.

In dit eerste deel van het proefschrift baseren wij ons op DSM-definities. Het is echter zeer wel mogelijk dat onze resultaten tot dusver beïnvloed werden door de gehanteerde DSM-definities. Immers, indien er geen verschillen worden gevonden tussen de verschillende depressie-groepen, kan dit wijzen op ofwel een afwezigheid van diversiteit binnen de depressieve stoornissen, ofwel op een foutieve definiëring van de depressie-groepen. Werkelijke verschillen tussen de groepen worden dan niet gevonden - een gebrek aan validiteit van de gehanteerde diagnoses. Om dit nader te onderzoeken worden in deel 2 van het proefschrift alternatieve onderzoeksmethoden toegepast waarmee wordt gezocht naar een andere indeling voor depressies dan de huidige DSM-classificatie.

Deel II. Alternatieve classificatiemodellen voor depressies

In het tweede deel van dit proefschrift hanteren we niet de DSM-classificatie om de heterogeniteit van depressieve stoornissen te onderzoeken, maar laten we de data spreken. *Hoofdstuk 6* toont de resultaten van een 'Latent Class Growth Analysis' (LCGA)- een extensie van de traditionele Latente Klasse Analyse, waarmee latente beloopstypen geïdentificeerd kunnen worden. Met behulp van het Life Chart Interview (LCI) werden gedurende twee jaar depressieve symptomen geregistreerd van een groep depressieve patiënten (n=804), die participeerden in NESDA. De LCI is een methode om het beloop van depressieve of angst klachten in kaart te brengen. Personen plaatsen allereerst belangrijke levensgebeurtenissen op een kalender. Vervolgens wordt gekeken of er in de afgelopen jaren sprake was van angst of depressieve klachten. De levensgebeurtenissen helpen om het geheugen op te frissen en daarmee tot een goede registratie van angst of depressieve klachten te komen. De LCGA identificeerde vijf verschillende beloopstypen van depressieve klachten. De beloopstypen varieerden in ernst en duur van de symptomen. Het was opmerkelijk, dat meer dan 50% van de personen met een dysthyme stoornis of 'dubbele depressie' bleken te behoren tot de gunstige beloopstypen, terwijl deze depressies in de DSM gedefinieerd worden als chronische depressies van tenminste twee jaar of langer. Dit doet vermoeden dat de DSM-diagnoses niet goed in staat zijn het beloop te voorspellen. Nader onderzoek van de verschillende beloopstypen liet zien, dat i) oudere leeftijd, ii) een op jongere leeftijd ontstaan van depressies en iii) minder extraversie voorspellend waren voor een slechter beloop.

Hoofdstuk 7 presenteert de resultaten van een tweede data-gestuurde methode, de Latente Transitie Analyse (LTA). Hier werd gekeken naar de stabiliteit van depressieve subgroepen, geclassificeerd naar ernst en aard- vitale kenmerken versus atypische kenmerken- van de

depressieve symptomen. Vitale kenmerken zijn onder meer vroeg ontwaken en afname van eetlust en gewichtsverlies. Atypische kenmerken zijn onder meer toegenomen slaapbehoefte en gewichtstoename. De LTA toonde aan dat de subtypes stabiel waren gedurende 2 jaar follow-up, hetgeen een indicatie is dat classificatie naar ernst en kenmerken van de depressieve symptomen (vitale kenmerken versus atypische kenmerken) een klinisch relevant onderscheid markeren.

Deel III. Depressie en angst, of angstige depressie?

Het laatste deel van het proefschrift verkent de rol van angst bij depressies. In *hoofdstuk 8* worden 303 mensen, met een depressie en/of angststoornis, participerend in zowel NEMESIS als NESDA, gedurende 7 jaar gevolgd. Na 7 jaar bleek ruim 60% geen DSM-diagnose van een depressie of angststoornis meer te hebben. Het risico op het persisteren van de stoornis bleek vergroot bij mensen met een angst stoornis- al dan niet met een comorbide depressie- bij aanvang van het onderzoek, bij slechter lichamelijk functioneren en bij meer neuroticisme. Tevens werd gekeken naar het persisteren van depressieve en angstklachten, geregistreerd middels het 'Life Chart Interview' in plaats van DSM-diagnoses. Ook hier bleek dat (comorbide) angst een slechter beloop voorspelde. Een grote mate van neuroticisme en traumatische ervaringen in de jeugd waren geassocieerd met meer symptomen gedurende follow-up.

In DSM-V wordt de rol van angst op het ontstaan en beloop van diverse psychiatrische aandoeningen erkend. Het voorstel is 'paniek' als een overkoepelende dimensie bij elke vorm van psychopathologie te scoren. In *hoofdstuk 9* onderzoeken wij de rol van paniek op het ontstaan en persisteren van psychopathologie en op het dagelijks functioneren. Aangezien wij in dit proefschrift de heterogeniteit van depressies onderzoeken, bespreken we hier alleen het effect van paniek op depressies. Zoals verwacht bleek paniek een aanzienlijke invloed te hebben op het ontstaan en beloop van depressieve stoornissen en het dagelijks functioneren van mensen met een depressie. Dit gold voor huidige paniek aanvallen, maar ook- zij het in mindere mate- voor een voorgeschiedenis van paniekaanvallen, zonder huidige klachten.

Tenslotte presenteert *hoofdstuk 10* de resultaten van een Latente Klasse Analyse, waarin gekeken werd of mensen met een gegeneraliseerde angststoornis en een dysthyme stoornis verschillen in hun symptoomprofielen. Als beide stoornissen voldoende verschillen pleit dit voor een onderscheid in twee stoornissen in de DSM. Het blijkt uit deze studie dat de symptomen grotendeels overlappen en er geen sprake is van een duidelijk 'angst' profiel versus een 'depressief' profiel. Veeleer lijkt er sprake van 'sombere piekeraars' ofwel 'piekerende depressieven'. Deel 3 van dit proefschrift toont aan dat angst een grote rol speelt in het ontstaan en beloop van depressie en dat het dikwijls moeilijk is angst van depressie te onderscheiden. In de classificatie van depressie dient angst dan ook een evidente rol te krijgen.

Dit proefschrift eindigt met een algemene discussie (*hoofdstuk 11*) van de belangrijkste bevindingen en methodologische overwegingen. Samenvattend pleiten de resultaten voor een aanpassing van de huidige DSM classificatie voor depressieve stoornissen. Het onderscheid van depressies in een depressieve stoornis versus dysthyme stoornis lijkt niet gerechtvaardigd. Daarentegen lijken de parameters 'ernst' en 'duur' van de depressieve klachten wel onderscheidend te zijn voor depressieve subtypes. Tevens dient angst een meer prominente rol in de classificatie van depressies te krijgen. Hoofdstuk 11 presenteert een alternatief voor het huidige classificatiemodel geïnspireerd door stageringsmodellen, zoals reeds toegepast in onder meer de oncologie. Bij longkanker bijvoorbeeld wordt gekeken naar de grootte van de tumor, de mate van uitzaaiingen in lymfklieren en/of uitzaaiingen elders in het lichaam. Op grond hiervan wordt het stadium van de longkanker, en daarmee de behandeling en prognose, bepaald. Voor depressies kan een dergelijk stageringsmodel, met stadia gekenmerkt door verschillende mate van ernst en duur van depressieve klachten en angst, leidraad zijn voor klinisch handelen. Verdere identificatie van predictoren voor slechter beloop, zoals oudere leeftijd, jongere leeftijd van ontstaan van klachten, persoonlijkheidskenmerken (zoals neuroticisme), trauma en slechter functioneren- allen geïdentificeerd in dit proefschrift als voorspellers voor slechter beloop- en mogelijk biologische of genetische parameters, dienen in het model geïncorporeerd te worden. Zo zou men tot snellere identificatie van personen met een groot risico voor een slechter beloop kunnen komen. Dit zou snel en doelgericht ingrijpen kunnen faciliteren en daarmee leiden tot preventie van het ontstaan of chronisch worden van depressieve stoornissen. Mogelijk zijn, zoals in de oncologie, verschillende stageringsmodellen nodig voor bijvoorbeeld melancholische depressie, of voor bepaalde depressies op oudere leeftijd. In hoeverre slechts één stageringsmodel voldoende blijkt voor het grote container begrip 'depressie' dient dan ook nader onderzocht te worden.

Dankwoord

En dan het dankwoord. Dit proefschrift was niet tot stand gekomen dankzij... Meer dan waar! Maar: het voelt persoonlijker dan deze standaard zin. Mijn weg door onderzoeksland is niet zonder pieken of dalen geweest. Jonglerend met de tijd tussen kliniek en onderzoek. En dan: balans vinden tussen moederschap en deadlines. Het is niet alleen een wetenschappelijke uitdaging geweest, maar tevens een ontdekkingstocht in wat ik wil. Daar heb je steun bij nodig. Praktische steun (datamanagement en automatisering: bedankt!), inhoudelijke steun en een sterk wetenschappelijk kader (NEMESIS en NESDA-consortium: bedankt!), en een sterke dataset (alle respondenten: dank!), maar bovenal persoonlijke steun.

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Gordon: It was a great pleasure to work together, both in clinical care and research. I admire your passion for patients, your warmth, your excellent research and writing skills. Thanks for welcoming me in your institute and in your house; for sharing your thoughts with me. Be warned: I think I need a third visit to practice the art of both 'provocative' and poetic writing! Bec, thanks for your patience, guiding me through the datasets of the BDI. I really loved working with you, your humor, and your conscientiousness during the endless revisions of the paper (I counted 13 versions…). We'll keep in contact and hopefully, we'll finally have a 'diner' together ☺! Christine and Will, Karlyn and Pauline, all RAs, Matt, and all the others of the BDI: thanks for your great hospitality! You made my stay in Sydney unforgettable! Woof woof.

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En tenslotte: allerliefste PD en allerliefste kleine kookaburra. Wat heeft dit proefschrift jullie gebracht? De computer op tafel, maar niet om Mega Mindy te kijken. Uit je vertrouwde huis gehaald worden om kangaroos te aaien. Maar jullie liefde is grenzeloos; mijn liefde voor jullie is grenzeloos. Jullie zijn de beste remedie tegen werkstress. Na een drukke dag 2 meisjes op schoot tegen mij aangeplakt. ’s Avonds even kijken als jullie liggen te slapen. En wat is er nu mooier dan jullie lach? Dit proefschrift telt meer dan 80.000 woorden. Niet genoeg om te beschrijven hoeveel ik van jullie hou.

Curriculum Vitae

Didericke (Didi) Rhebergen was born on February 8, 1973 in Groningen, the Netherlands. After graduation from high school (Christelijk Gymnasium, Leeuwarden), she joined a student exchange program and lived for one year in Jakarta, Indonesia. Since 1992, she studied Medicine at the VU University, Amsterdam and conducted a study into the knowledge, attitudes and practices of leprosy patients in Nepal. Since 1994, she combined her study Medicine, with a study Cultural Anthropology- specialization Medical Anthropology- at the VU University, Amsterdam. For her master thesis Anthropology, she spent six months in Surabaya, Indonesia, to study possible ways to empower female street sex workers in Surabaya. After she finished her medical internship cum laude, she started her residency in psychiatry at GGZ inGeest in 2002. Since 2007, she is working as an old age psychiatrist at an elderly in-patients ward of GGZinGeest. In 2006, she started working as a part-time PhD-student at the department of Psychiatry and EMGO+ at the VU University Medical Center, Amsterdam. She investigated the heterogeneity of depressive disorders, in particular the long-term course trajectories of various depressive subtypes. During her research, she finished her master in Epidemiology at the VU University. From October 2011 to April 2012 she visited the Black Dog Institute, Sydney, Australia, the Clinical Research Unit for Anxiety and Depression (CRUfAD) at the University of New South Wales in Sydney, Australia, and the University of Fremantle, Perth, Australia. Currently she is working as an old age psychiatrist, GGZ inGeest, Amsterdam, and combines clinical work and research in her daily practice. She is happy together with Duco Roolvink and they are the proud parents of Mare en Amaya.

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