Chapter 3

The three-year naturalistic course of Major Depressive Disorder, Dysthymic Disorder and Double Depression

ABSTRACT

Background Recent studies support a distinction between acute and chronic forms of depression, which contrasts the single disease hypothesis for depressive disorders. Insight into the (determinants of) the 3-year naturalistic course of Major Depressive Disorder (MDD), Dysthymic Disorder and Double Depression may contribute to this debate.

Methods Data were derived from NEMESIS, an epidemiologic survey in the adult population of the Netherlands. 400 Respondents who met the Composite International Diagnostic Interview (CIDI) criteria of MDD and/or Dysthymic Disorder were selected. Cox proportional hazards analyses and Linear Mixed Models were conducted to examine 3-year course trajectories of MDD, Dysthymic Disorder and Dysthymic Disorder and determinants for course.

Results Adjusted analyses showed similar course trajectories for Dysthymic Disorder and Double Depression, which were significantly worse than the course for MDD. Determinants of unfavorable course were neuroticism and poor functioning.

Limitations Attrition was higher among persons with Dysthymic Disorder. However, since attrition is generally associated with poorer outcome, this would indicate that differences in course may even have been larger in reality.

Conclusions Dysthymic Disorder and Double Depression involve a similar course which is worse than the course of MDD only. These results do not support a distinction between Dysthymic Disorder and Double Depression. Duration of symptoms and level of functioning may serve as two clinically relevant classifying dimensions within the broad category of depressive disorders.

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INTRODUCTION

In 1980, Dysthymic Disorder was introduced in the DSM-III to replace neurotic depression and since then characterizes a mild, but chronic depressive disorder. Various studies have revealed high prevalence rates (Avrichir and Elkis, 2002; Bijl et al., 1998a; Kessler et al., 1994), a large impact on social functioning (Bijl and Ravelli, 2000; Wells et al., 1992) and high health care utilization (Howland, 1993) associated with Dysthymic Disorder. Many persons with a Dysthymic Disorder are faced with a comorbid Major Depressive Disorder (MDD), a phenomenon often called "Double Depression" (Keller and Lavori, 1984; Keller and Shapiro, 1982). Klein and colleagues (2000) found the percentage of a comorbid Major Depressive Disorder among Dysthymic outpatients even exceeding 90%. This enormous overlap in diagnoses between Dysthymic Disorder and MDD raised the question whether they could be seen as two distinct disorders. In the Zurich study, Angst and Merikangas (1997) found little diagnostic stability in patients with depressive disorders over time. There was a strong tendency for individuals to meet multiple depressive subtypes over time. This finding was also described by Judd et al. (2002): during the long-term course of depressive illness, major, minor, dysthymic and subsyndromal symptoms waxed and waned within the same person. In other reports, the more chronic course of Dysthymic Disorder over MDD has been emphasized as a distinguishing feature. Patients with Dysthymic Disorder and Double Depression exhibited significantly lower rates of improvement, compared to patients with MDD (Keller et al., 1983; Klein et al., 2006). Paucity of differences between various forms of chronic depression (McCullough et al., 2000, 2003) and similar patterns of course (Klein et al., 2006) raised the question whether these various forms of chronic depression reflect clinically or etiologically meaningful distinctions, or could better be viewed as a single, broad condition that can assume a variety of clinical courses. It was stated, that the chronic-nonchronic distinction could be an important source of heterogeneity in depression and should be taken into account in clinical and etiological research.

The evidence supporting this would require studies of the natural course of depressive disorders and factors that may predict the outcome in community based studies. Moreover, a study would require sufficient subjects with MDD, pure Dysthymic Disorder and Double Depression (MDD superimposed on a Dysthymic Disorder); sufficient follow-up time to determine the outcome and a broad range of putative predictors of the outcome. Most studies to date have been conducted among out-patients (Klein et al., 2006; McCullough et al., 2000, 2003), which hampers generalization to the general population. Furthermore, due to high prevalence of a (history of) Double Depression, insight into the course of pure Dysthymic Disorder is limited. In the current large community-based study, we compare the three-year course of pure Dysthymic Disorder, Double Depression and Major Depressive Disorder (MDD), and examine the most important determinants for the course of these depressive disorders.

METHODS

Study sample

The data of the current study were derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). This is a naturalistic, prospective, epidemiological survey among a representative sample (n=7076) of the general adult (aged 18 to 64 years) population in the Netherlands. Data were recorded in three waves: at baseline in 1996, after 12-month follow-up (1997) and after 3 years (1999). The sampling procedure consisted of a multistage, stratified, random sample. The method of recruitment was extensively described elsewhere (Bijl et al., 1998b). The fieldwork was done by 90 interviewers experienced in systematic data collection. All of them underwent a 3-day training course in recruiting respondents and computer-assisted interviewing, followed by a 4-day course of training at the WHO-CIDI training centre in Amsterdam (Bijl et al., 1998b). Procedures were approved by the ethics committee of the Netherlands Institute of Mental Health and Addiction and informed consent was obtained according to the prevailing Dutch law of 1996. In the first wave (T0), 7076 (69.7%) respondents could be included. At the second (T1) and third (T2) waves, 1458 (20.6%) and 822 (14.6%) respondents respectively were lost to attrition (Bijl et al., 1998b). After adjustment for sociodemographic factors, 12-month Social Phobia and Agoraphobia at T0 were associated with T1 attrition and 12-month MDD, Dysthymic Disorder and Alcohol Dependence at T1, were associated with T2 attrition (Graaf et al., 2000a,b).

For the present study, respondents from NEMESIS with a 12-month MDD and/ or 12-month Dysthymic Disorder at baseline were included (n=536). Availability of data from the baseline assessment (T0) and at least one follow up (T1 or T2) were considered necessary to contribute to the analyses. 136 Subjects did not fulfill the latter criteria, resulting in a study population of exactly 400 respondents. Attrition rates, adjusted for confounding covariates, among the different depressive disorder subgroups differed (MDD as reference, Dysthymic Disorder (OR 1.68 [95% CI 1.00-2.83]), Double Depression (OR 0.67 [95% CI 0.40-1.11]) with slightly higher rates among those with Dysthymic Disorder and Double Depression.

Measurements

Depressive disorder diagnoses

Diagnoses of MDD, Dysthymic Disorder and Double Depression, in all three waves, were based on the Composite International Diagnostic Interview (CIDI), version 1.1 (Smeets and Dingemans, 1993). The CIDI, developed by the WHO (World Health Organization, 1990), is a structured interview with acceptable reliability and validity (Wittchen, 1994). The depressive disorder diagnoses served to select the study cohort, as well as to define the outcome variables in the longitudinal analyses on 3-year course. Organic exclusion rules were used in making diagnoses, but hierarchical exclusion criteria, as applied by the CIDI were ignored, thus allowing comorbidity of depressive diagnoses. The diagnosis of MDD and Dysthymia were defined based on DSM-III-R criteria. Based on the presence of 12-month MDD and

Dysthymia diagnoses at baseline, various baseline depression groups were defined. MDD only consisted of those fulfilling a MDD but not a Dysthymia diagnosis, whereas Dysthymic Disorder only consisted of those with a Dysthymia but not a MDD diagnosis. Double Depression was defined as Dysthymic Disorder with a comorbid MDD, ignoring the sequence of onset of Dysthymic Disorder and MDD. For disease course over time, the presence of any MDD and/or Dysthymic Disorder diagnosis over 3 years was evaluated in the 1-year and 3-year follow-up assessments using CIDI diagnoses. To be able to distinguish between remission and persistence of symptoms, minor depression as an outcome measure was also included in the analysis. A person met the criteria for minor depression if at least one of the key features of a MDD was met and up to three additional symptoms, resulting in a minimum of 2 to a maximum of four depressive symptoms.

SF-mental summary scale

In order to see, whether our results are consistent when outcome was defined using a continuous indicator, we conducted a longitudinal analysis with outcome defined as symptom severity measured by the SF-mental health summary scale. The mental health summary scale of the Short-Form 36 Health Survey (SF-36) (Ware and Sherbourne, 1992) is a widely applied questionnaire involving 4 subscales and consisting of role limitations due to mental health, vitality, social functioning, and mental health. Scoring was performed on a 0-100 scale, with 100 defined as maximum functioning. Good reliability and validity of this instrument has been demonstrated elsewhere (Aaronson et al., 1998; Burke et al., 1995; McHorney et al., 1993, 1994). In our study, the mental summary scale has sufficient internal reliability (Cronbach's α=0.81). It has been demonstrated elsewhere that there is no substantial loss of information, when summary scales are used (Ware et al., 1995).

Baseline characteristics

Characteristics of the subgroups of depressive disorders were recorded during the baseline interview. We included the following variables: gender, age, partner status, level of education and the number of comorbid somatic disorders. Age was included as a continuous variable. Partner status was dichotomized into having a relationship or not. Education was included to assess socio-economic status and dichotomized into lower (≤ 10 years of education) and higher level (≥10 years of education). The number of comorbid somatic disorders was defined as the number of somatic disorders during the last year. Only those somatic conditions that were reported to be treated or monitored by a doctor were included. This was assessed by means of a 32-item semi-structured list, based on the Health Interview Survey of Statistics Netherlands (Berg and Bos, 1989) and recorded as a continuous variable.

Predictors of course

In addition to the baseline characteristics, a range of putative predictors of course were included: childhood adversity, comorbid anxiety disorder, comorbid alcohol dependence, the presence of a MDD-episode prior to the current episode, a depressive disorder among first-degree family members, neuroticism and the level of global functioning. All these putative predictors were recorded during the baseline interview. Childhood adversity was assessed using a structured interview in which respondents were asked to retrospectively recall whether they had experienced emotional neglect, psychological abuse, physical abuse or sexual abuse before the age of 16. For more detailed information on the questions, we refer to previous reports (Afifi et al., 2007; Graaf et al., 2004). The ordinal responses to these inquiries were recorded as: never, once, sometimes, regularly, (very) often. Neglect, psychological abuse, and physical abuse were coded as present if abuse occurred at least sometimes. Sexual abuse was coded as present if the abuse occurred once or more (Afifi et al., 2007; Graaf et al., 2004). Comorbid anxiety disorder, comorbid alcohol dependence and the presence of a MDD prior to the current episode of a depressive disorder were assessed by means of the CIDI (Smeets and Dingemans, 1993). For comorbid anxiety disorder and alcohol dependence, 12-month diagnoses were applied. The presence of a MDD prior to the current episode was assessed differently for the three groups. For persons with a current MDD or Double Depression, a prior MDD was present if the persons met the CIDI criteria for a recurrent episode of MDD at baseline. For persons with a Dysthymic Disorder, a prior MDD was present, if a person met the CIDI criteria for a lifetime MDD at baseline. The presence of depressive disorders among the first-degree relatives (father, mother, brother, sister or child) of the respondent was based on self-report by the respondent. Neuroticism was assessed using the Groningen Neuroticism Questionnaire (Ormel, 1983; Ormel et al., 2001; Ormel and Wohlfarth, 1991), a 14-item, 3 point scale with sufficient internal reliability in the present study (Cronbach's α=0.80). An inversed scale was computed, resulting in high scores reflecting high levels of neuroticism. Global functioning was assessed using the physical summary scale of the Short-Form 36 Health Survey (SF-36) (Ware and Sherbourne, 1992). This summary scale covers 4 subscales including physical functioning, role limitations due to physical health, bodily pain, and general health. The physical summary scale has sufficient internal reliability in the present study (Cronbach's α=0.85). It has been demonstrated elsewhere that there is no substantial loss of information, when summary scales are used (Ware et al., 1995).

Statistical analyses

First, the baseline characteristics across depressive disorder groups were compared using two-tailed chi-square statistics (for categorical variables) and one-way-analysis of variance statistics (ANOVA for continuous variables). Second, the course of the three depressive disorders was described using cross tabulations of the various disorders at follow-up assessments. Third, it was analyzed which factors were associated with a more chronic

course, after adjustment for socio-demographic differences between the groups. Cox proportional hazards model was used to examine the association of type of depressive disorder at baseline (MDD, Dysthymic Disorder, Double Depression) and course. The dependent variable was time to first report of any depressive disorder, MDD or Dysthymic Disorder during the following three years. Persons with no depressive disorder both at T1 and at T2 were censored at their time of last interview. No depressive disorder was defined as not fulfilling the criteria of a MDD and/or Dysthymic Disorder or minor depression. The Hazard Ratio (HR) is the risk of having a depressive disorder during three years of follow up, incurred by the presence or absence of a prognostic factor, as compared to the reference category. Hazard Ratios (HRs) and 95% confidence intervals (CIs) were used as the measure for association, adjusted for confounding variables, including age, gender, education, partner and number of comorbid somatic diseases. The assumption of proportionality of hazard was checked and confirmed by tests of the interaction of time with exposure. To see, whether our results would be consistent when using a continuous indicator of mental health, an additional analysis was conducted with outcome defined as symptom severity measured by the SF-mental summary scale. Linear Mixed Models (LMM) were used to examine the association of type of depressive disorder at baseline (MDD, Dysthymic Disorder, Double Depression) and the continuous outcome measure, SF-mental summary score, during three years of follow-up. Estimated mean scores were calculated for the SF-mental summary scale, adjusted for confounding variables (age, gender, education, partner and number of comorbid somatic diseases). All variables were entered in the model as fixed factors. The only random factor entered in the model was the subject. Finally, we adjusted the Cox proportional hazards model and the Linear Mixed Model for possible predictors of course (childhood adversity, comorbid anxiety disorder, comorbid alcohol dependence, a prior episode of MDD, a positive family history of mood disorders, neuroticism and global functioning). All analyses were conducted using SPSS (version 15) (SPSS, 2006).

RESULTS

Of the 400 respondents at baseline, 56.3% met the CIDI criteria for 12-month MDD, 15.5% for a Dysthymic Disorder and 28.3% for a Double Depression. As presented in Table 1, the Dysthymia and Double Depression groups differed from the group with MDD at baseline. Subjects with Dysthymic Disorder or Double Depression were more often female, older and less educated and had more comorbid somatic diseases than persons with MDD at T0. Considering putative predictors of course, persons with Dysthymic Disorder or Double Depression had more often a comorbid (12-month) anxiety disorder and less often a prior episode of MDD than persons with MDD. In addition, persons with Dysthymic Disorder or Double Depression had more childhood adversity, a higher level of neuroticism and a lower level of global functioning. There were no significant differences in alcohol dependence and a positive family-history.

Table 1. Characteristics of persons with Major Depressive Disorder, Dysthymic Disorder and Double Depression at baseline.

		MDD n=225	Dystymia n=62	Double Depression n=113	Analysis		
Socio-demographics		%	%	%	X^2	df	p
Sex	*Female*	60.9	71.0	74.3	6.8	2	.03
Partner	*No*	48.4	37.1	46.9	2.5	2	.28
Education	*Low*	40.9	59.7	68.1	24.3	2	<.001
		Mean (±SD)	Mean (±SD)	Mean (±SD)	F	d	p
Age (years)		38.5	45.7	41.8	12.3	2	<.001
Number of somatic diseases		1.0	2.2	1.7	15.9	2	<.001
Psycho-social characteristics		%	%	%	X^2	df	p
Childhood adversity	*Yes*	58.2	75.8	64.6	6.6	2	.036
Comorbid anxiety disorder	*Yes*	47.1	62.9	63.7	10.8	2	.005
Comorbid alcohol Dependence	*Yes*	7.1	4.8	8.0	0.61	2	.74
History of MDD	*Yes*	53.8	24.2	26.5	32.0	2	<.001
Positive family history	*Yes*	48.0	53.2	59.3	3.9	2	.14
		Mean (±SD)	Mean (±SD)	Mean (±SD)	F	df	p
Neuroticism		67.6 (5.7)	70.9 (5.9)	70.9 (6.3)	15.2	2	<.001
Functioning (SF-physical summary)		77.4 (20.2)	65.5 (26.0)	68.9 (23.1)	10.1	2	<.001

3-Year course

The distribution of diagnoses at T1 and T2, 1 and 3 years after baseline, is shown in Table 2. At T1, 5.6% of the original group of 400 respondents met the 12-month criteria for minor depression, 20.0% for MDD, 5.1% for Dysthymic Disorder and 8.6% for Double Depression. A considerable percentage (60.8% of the baseline population) did not meet the criteria for minor depression nor MDD nor Dysthymic Disorder nor Double Depression at T1. This was significantly higher for respondents with a pure MDD at T0 (70.9%) than for those with Dysthymic Disorder at T0 (50.0%) or Double Depression at T0 (46.4%) (p<.001). At T2, 2.2% met the criteria for minor depression, 12.8% for MDD, 5.3% for Dysthymic Disorder and 5.3% for Double Depression. Considering remission rates, again a significantly different course between the three groups was demonstrated: 77.6% of the respondents with a MDD at T0 did not meet the criteria of a depressive disorder at T2, versus 70.8% of the group with pure Dysthymic Disorder at T0 and 69.1% of the respondents with Double Depression at T0 (p=.001). Cross-sectional comparisons across depressive groups indicated that the rate of depressive diagnoses at follow-up was significantly different for Dysthymic Disorder and Double Depression as compared to MDD. Dysthymic Disorder and Double Depression groups, however, did not differ in the rate of depressive diagnoses at follow-up (at T1 p=.25; at T2 p=.70).

Table 2. Prevalence of depressive disorders after one and three years of follow-up according to baseline depressive disorder status.

	No Depressive Disorder	Minor Depression	Pure Major Depressive Disorder	Pure Dysthymic disorder	Double Depression	p across all groups	p between groups
	n (%)	n (%)	n (%)	n (%)	n (%)		
T1 (after one year) n=395[1]							
MDD n=223	158 (70.9)	14 (6.3)	39 (17.5)	4 (1.8)	8 (3.6)		MDD vs Dysth <.001
Dysth n=60	30 (50.0)	3 (5.0)	12 (20.0)	9 (15.0)	6 (10.0)	<.001	MDD vs DD <.001
DD n=112	52 (46.4)	5 (4.5)	28 (25.0)	7 (6.3)	20 (17.9)		Dysth vs DD .25
Total n=395	240 (60.8)	22 (5.6)	79 (20.0)	20 (5.1)	34 (8.6)		
T2 (after three years) n=321[2]							
MDD n=192	149 (77.6)	6 (3.1)	27 (14.1)	5 (2.6)	5 (2.6)		MDD vs Dysth <.02
Dysth n=48	34 (70.8)	0 (0)	5 (10.4)	6 (12.5)	3 (6.3)	.001	MDD vs DD .01
DD n=81	56 (69.1)	1 (1.2)	9 (11.1)	6 (7.4)	9 (11.1)		Dysth vs DD .70
Total n=321	239 (74.5)	7 (2.2)	41 (12.8)	17 (5.3)	17 (5.3)		

[1] At T1, 1.3% (n=5) were lost to attrition, but could be traced at 3-year follow up and were included in the analysis. [2] At T2, 19.8% (n=79) were lost to attrition. Abbreviations: MDD= Major Depressive Disorder, Dysth= Dysthymic Disorder, DD= Double Depression.

Predictors of 3-year course

We analyzed possible associations between the type of depressive disorder at baseline and differences in course, adjusted for confounding covariates. None of these confounders was significantly associated with course. As presented in Table 3, the Cox proportional hazards model, adjusted for age, gender, partner, education and number of somatic diseases, showed that the type of depressive disorder at baseline (MDD, Dysthymic Disorder or Double Depression) predicted outcome. Dysthymic Disorder at baseline was associated with a 2.32-fold increased risk for any depressive disorder (MDD, Dysthymic Disorder, Double Depression or Minor Depression) during three years of follow up (95% CI 1.53-3.53) and Double Depression with a 2.40-fold increased risk (95% CI 1.71-3.37), as compared with MDD (reference). If the outcome 'any depressive disorder' would have been defined solely as MDD, Dysthymic Disorder and Double Depression with exclusion of minor depression, the Hazard Ratios would have been similar. The risk for any depressive disorder was somewhat reduced after full adjustment of the Cox proportional hazards model for potential predictors (childhood adversity, comorbid anxiety disorder and comorbid alcohol dependence, prior episode of MDD, positive family-history, neuroticism and global functioning), resulting in a Hazard Ratio of 1.88 [95% CI 1.18-2.99] for persons with Dysthymic Disorder and a Hazard Ratio of 2.24 [95% CI 1.53-3.28] for persons with Double Depression.

Table 3. Risk for depressive disorder during three years of follow up by baseline depressive disorder status, with and without adjustment for psychosocial characteristics.

	Model 1[1] HR (95% CI)	Model 2[1] (HR (95%CI)
Outcome: any depressive disorder during three years of follow up (no. of events= 192; 48.0%)		
MDD only	Ref	Ref
Dysthymia only	2.32 (1.53-3.53)	1.88 (1.18-2.99)
Double Depression	2.40 (1.71-3.37)	2.24 (1.53-3.28)
Childhood adversity	-	1.05 (0.73-1.50)
Comorbid anxiety disorder	-	1.30 (0.91-1.86)
Comorbid alcohol dependence	-	1.47 (0.84-2.58)
Prior MDD	-	0.83 (0.59-1.17)
Positive family history	-	1.07 (0.77-1.47)
Neuroticism	-	1.05 (1.02-1.08)
Functioning	-	0.99 (0.98-0.99)
	Model 1[1] HR (95% CI)	Model 2[2] (HR (95%CI)
Outcome: Major Depressive Disorder during three years of follow up (no. of events= 146; 36.5%)		
MDD only	Ref	Ref
Dysthymia only	1.96 (1.18-3.24)	1.59 (0.94-2.70)
Double Depression	2.44 (1.66-3.58)	2.11 (1.41-3.15)
Childhood adversity	-	1.07 (0.73-1.57)
Comorbid anxiety disorder	-	1.17 (0.80-1.71)
Comorbid alcohol dependence	-	1.77 (0.97-3.23)
Prior MDD	-	0.84 (0.59-1.21)
Positive family history	-	1.03 (0.73-1.45)
Neuroticism	-	1.06 (1.02-1.09)
Functioning	-	0.99 (0.98-0.99)
	Model 1[1] HR (95% CI)	Model 2[2] (HR (95%CI)
Outcome: Dysthymic Disorder during three years of follow up (no. of events= 75; 18.8%)		
MDD only	Ref	Ref
Dysthymia only	6.34 (3.26-12.33)	3.95 (1.95-8.00)
Double Depression	5.67 (3.14-10.25)	4.10 (2.20-7.66)
Childhood adversity	-	1.40 (0.77-2.56)
Comorbid anxiety disorder	-	1.72 (0.97-3.06)
Comorbid alcohol dependence	-	1.54 (0.75-3.20)
Prior MDD	-	0.76 (0.44-1.31)
Positive family history	-	1.38 (0.83-2.29)
Neuroticism	-	1.04 (1.00-1.09)
Functioning	-	0.99 (0.97-1.00)

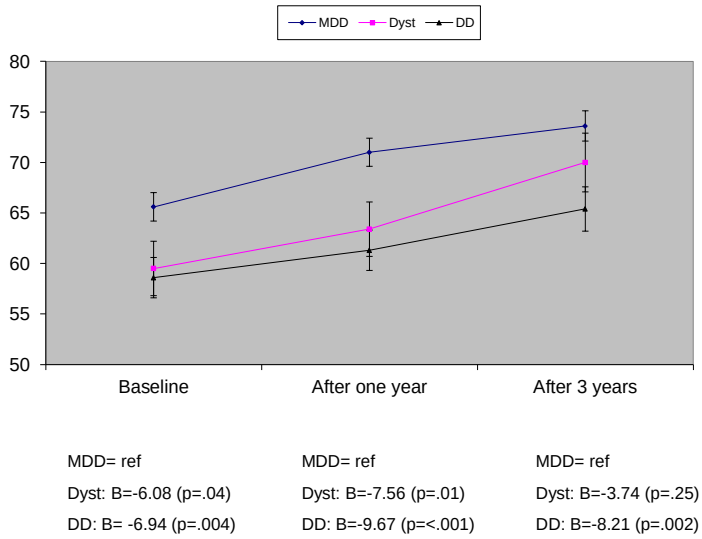
[1] Adjusted for age, sex, education, partner and number of comorbid somatic diseases.

[2] Adjusted for age, sex, education, partner and number of comorbid somatic diseases and the additional variables mentioned in the table.

Of the potentially explanatory variables, only neuroticism (HR 1.05 [95% CI 1.02-1.08]) and functioning (HR 0.99 [95% CI 0.98-0.99]) predicted course. Similar analyses were conducted with outcome defined as the presence of MDD during three years of follow up. When compared to MDD only, Dysthymic Disorder was associated with a 1.96-fold increased risk (95% CI 1.18-3.24) and Double Depression with a 2.44-fold increased risk (95% CI 1.66-3.58) for having a MDD during the 3-year follow up. Again, this risk reduced somewhat after full adjustment. When the outcome was defined as Dysthymic Disorder during three years of follow up, Dysthymic Disorder at baseline predicted a 6.34-fold increased risk (95% CI 3.26-12.33) and Double Depression with a 5.67-fold increased risk (95% CI 3.14-10.25), as compared to MDD at baseline (reference), which reduced slightly but remained significant after full adjustment. Again, only neuroticism and global functioning predicted the presence of MDD or Dysthymic Disorder over three years.

As presented in Figure 1, the Linear Mixed Model, adjusted for age, gender, partner, education and number of somatic diseases, also showed that the type of depressive disorder at baseline predicted the 3-year course trajectory of mental health summary score. Both Dysthymic Disorder as well as Double Depression at baseline were associated with a lower mental health summary score during three years of follow up compared to MDD (reference) (Dysthymic Disorder: B=-6.08, p=.04; Double Depression: B=-6.94, p=.004). After three years of follow-up, a similar pattern was seen. Dysthymic Disorder had a lower level of mental health summary score, albeit not significant (B=-3.74; p=.25). Double Depression showed a significantly lower level of SF-mental summary score compared to MDD (B=-8.21, p=.002). Predictors of the 3-year course in SF-36 mental health summary score were very consistent of those found for diagnostic status over time. When all putative predictors of course were included in Linear Mixed Models, only neuroticism (B=-1.08, p<.001) and physical functioning (B=0.39, p<.001) predicted the course.

Figure 1: SF-mental summary score during three years of follow-up by baseline depressive disorder status, with adjustment for psychosocial characteristics, age, sex, education, partner and number of comorbid somatic diseases.



Abbreviations: MDD= Major Depressive Disorder, Dyst= Dysthymic Disorder, DD= Double Depression.

Post-hoc analyses

The course trajectories of the Dysthymic Disorder and Double Depression subcohorts were similar. However, 24.5% of the persons with 12-month Dysthymic Disorder at baseline had an episode of MDD during life time. Since information on the time of onset of Dysthymic Disorder and MDD was missing, these persons might have met the criteria of Double Depression or chronic MDD in partial remission. Therefore, post-hoc analyses with exclusion of these persons were conducted. Again, we found no differences between persons with pure Dysthymic Disorder and Double Depression. In addition, treatment might influence course trajectory. However, in naturalistic studies, adjustment for treatment effect is complex because of the bias for patients with the most severe problems to receive the most treatment. Spurious relation between treatment and outcome can be found and its interpretation becomes very difficult. In our sample, only 17.0% did receive antidepressant medication. In post-hoc analyses treatment did not predicted outcome and thus cannot explain the observed differential course trajectories across depression groups. Since Linear Mixed Models can handle missing data, we finally conducted a post-hoc analysis that included all 536 initial subjects in order to examine the result that attrition may have had on our results. This analysis showed, that both Dysthymic Disorder as well as Double

Depression had a lower SF-36 mental health score during three years of follow up as compared with MDD (at baseline: Dysthymic Disorder: B=-4.7; p=.05; Double Depression: B=-8.7; p<.001, at T1: Dysthymic Disorder: B=-9.3, p=.002; Double Depression: B=-13.5, p<.001 and at T2: Dysthymic Disorder: B=-6.1; p=.05, Double Depression: B=-11.8, p<.001). So Linear Mixed Models results with imputed data for those dropping out after baseline, confirm- and even provide stronger evidence- for a differential course trajectory across baseline depression groups.

DISCUSSION

Our primary aim was to examine the 3-year course of MDD, Dysthymic Disorder and Double Depression and possible determinants for course, providing some insight into whether a single diagnostic category (depressive disorder) with two clinically relevant dimensions (severity and duration) may be preferable over the existing diagnostic categories.

During the three years of follow up, we found a relatively high recovery rate for all three depressive disorders. The recovery rate for MDD was 70.9% after one year, rising to 77.6% after three years, for Dysthymic Disorder respectively 50.0% and 70.8% and for Double Depression respectively 46.4% and 69.1%. These recovery rates are higher than in previous studies (Klein et al., 2000; Wells et al., 1992). However, these prior studies have mainly focused on out-patient populations in which the recovery rates are likely to be lower than in community studies.

Both for persons with pure Dysthymic Disorder as well as for persons with Double Depression a higher hazard was found of having any depressive disorder, a MDD or a Dysthymic Disorder during three years follow up as compared to persons with pure MDD. In addition, both for persons with pure Dysthymia as well as for persons with Double Depression a lower level of the SF-mental health summary score during three years of follow-up was found as compared to persons with pure MDD. This additional analysis, in which outcome was measured using a continuous indicator of mental health, underlines the poorer prognosis among Dysthymic Disorder and Double Depression subjects compared to MDD only subjects. Analyses revealed similar course trajectories for persons with Dysthymic Disorder and persons with Double Depression. This illustrates the validity of the distinction between MDD and Dysthymic Disorder/ Double Depression.

The more favorable course trajectory for the group with MDD at baseline, in comparison to persons with Dysthymic Disorder or Double Depression, contributes to current debates on nosology of depressive disorders. Dysthymic Disorder and Double Depression show significantly poorer course trajectories than MDD. Klein et al. (2006) also demonstrated that out-patients with Dysthymic Disorder, with or without a superimposed MDD, exhibited significantly lower rates of improvement, compared to persons with MDD. Both Klein and

colleagues (2006) and McCullough et al. (2000, 2003) found that the chronic versus nonchronic distinction constitutes an important source of heterogeneity in depression. Thus, chronicity may be a predictor for a worse course trajectory and may serve as an important distinguishing feature in classifying depressive disorders.

Considering the various covariates included in our multivariate models, in addition to type of depressive disorder at baseline, we only found neuroticism and global functioning to be significantly associated with course. Reports differ on their identification of predictors for a more chronic course. Low level of functioning as well as initial depression severity (Ormel et al., 2004; Spijker et al., 2002) were previously identified as a predictors for poor outcome. On the other hand, Keller et al. (1983) have examined various predictors (among others age, marital status, number of episodes of MDD and duration), but could not identify predictors of recovery from Dysthymic Disorder among patients with Double Depressions. Similarly, Klein et al. (1998) analyzed the contribution of other variables to the variability in outcome of MDD and Double Depression: age, gender, education, age of onset, lifetime history of MDD, substance dependence and a concurrent anxiety disorder or personality disorder. None of the variables made a significant independent contribution to the prediction of recovery during a 30-months follow-up (Klein et al., 1998). This same study, however, showed some significant results after a follow-up of 5 years, in which family history of psychopathology, childhood adversity, cluster C features, high level of neuroticism, history of anxiety and history of eating disorders all predicted higher levels of depression at follow up (Hayden and Klein, 2001). Different length of follow-up, different study populations, different outcome measures as well as different predictor variables may account for differences in results. Hayden and Klein (2001) only included out-patients and used different outcome measures for the course (the Longitudinal Interval Follow-Up Evaluation (LIFE) as well as Hamilton depression scale). Childhood adversity and neuroticism were not significantly associated with depression outcome as measured by LIFE, but were significantly associated with a more severe Hamilton depression scale, illustrating the influence of differences in outcome measure. More comprehensive models, with different outcome measures are necessary to identify prognostic factors (Hayden and Klein, 2001).

Strengths and limitations

A strength of this study is its prospective design and its follow-up of three years with follow-up evaluations blind to diagnosis at baseline. In addition, this study is population based and an extensive assessment battery was used, which enabled us to perform multivariate analyses on a wide range of potential risk factors. Although the numbers at baseline were considerable, we were faced with attrition limiting the power to detect small effects at follow up. After adjustment for various risk factors, attrition was differential with respect to baseline type of depressive disorder. Higher attrition was found among persons with Dysthymic Disorder. Since attrition is generally associated with poorer outcome, this would

indicate that differences in course trajectories may even have been larger in reality. Considering the course of Dysthymic Disorder, a long term follow up is especially important because chronicity is one of its defining characteristics and a key feature in distinguishing it from MDD. In this study, follow-up was limited to 3 years. However, as Klein, Shankman and Rose (2006) also stated, most recoveries occurred within the first 3 years of follow up and after 6 years the probability of recovery was low. Considering this, we can assume, that the 3-year follow-up of this study can provide considerable information on differences in course trajectories. Another limitation of our paper regards to our definition of Double Depression. We defined Double Depression as fulfilling the criteria of Dysthymic Disorder as well as MDD, irrespective of what was first. Unfortunately, the CIDI interview did not provide accurate information on timing of the various depressive subtypes. This means that an unknown number of respondents with Double Depression may have been classified as chronic MDD in partial remission, when we had accurate information on the time of onset of both disorders. The use of a structured instrument, such as the CIDI, in large-scale epidemiological studies is a major strength. Inter-rater reliability for diagnosing both Dysthymia and MDD using the CIDI has shown to be excellent (Dysthymic Disorder: k=0.96; MDD: k=0.97 (Wittchen et al., 1991; Wittchen, 1994). In addition, consistent findings were present when course was defined using a continuous mental health score illustrating that our results are unlikely due to the choice of our diagnostic instrument. Finally, treatment may be associated with course trajectories. However, in this naturalistic study design, the effect of treatment on course cannot be adequately evaluated.

In conclusion, our results demonstrate the importance of duration of symptoms and global functioning in predicting the course of depressive disorders. Furthermore, since the presence of a superimposed MDD does not alter the course of a pure Dysthymic Disorder, the validity of a distinction between these subtypes of chronic depressions is challenged. Our findings support Wells' proposal to differentiate between depressive disorders on the basis of functional status and chronicity (Wells, 1992). In DSM-V, a single diagnostic category (depressive disorder) with two clinically relevant dimensions (severity and duration) may be preferable over the existing various diagnostic categories. Considering the high prevalence of depressive disorders and its great impact on wellbeing, this finding is of great clinical and public health significance. Prevention and intervention programs should aim at identifying persons with chronic depressions and low level of functioning and optimizing their treatment. In clinical practice, in addition to psychiatric diagnosis, a thorough assessment of functioning is therefore needed.

REFERENCES

Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. Journal of Clinical Epidemiology 1998; 51: 1055-1068.

Afifi TO, Enns MW, Cox BJ, Graaf R de, Have M ten, Sareen J. Child abuse and health-related quality of life in adulthood. Journal of Nervous and Mental Disease 2007; 195: 797-804.

Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. Journal of Affective Disorders 1997; 45: 31-39.

Avrichir BS, Elkis H. Prevalence and underrecognition of dysthymia among psychiatric outpatients in Sao Paulo, Brazil. Journal of Affective Disorders 2002; 69: 193-199.

Berg J van de, Bos GAM van de. Het (meten van het) voorkomen van chronische aandoeningen 1974-1987. Maandbericht Gezondheid (CBS) 1989; 8: 4-21.

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

Bijl RV, Zessen G van, Ravelli A, de Rijk C, Langendoen Y. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Social Psychiatry and Psychiatric Epidemiology 1998b; 33: 581-586.

Bijl RV, Ravelli A. Current and residual functional disability associated with psychopathology: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Psychological Medicine 2000; 30: 657-668.

Burke JD, Burke KC, Baker JH. Test-retest reliability in psychiatric patients of the SF-36 Health Survey. International Journal of Methods in Psychiatric Research 1995; 5: 189-194.

Graaf R de, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). American Journal of Epidemiology 2000a; 152: 1039-1047.

Graaf R de, Bijl RV, Vollebergh WA. Response and non-response third wave: the Netherlands Mental Health Survey and Incidence Study (NEMESIS) Technical Report no 11. 2000b. Utrecht, Trimbos-institute.

Graaf R de, Bijl RV, Have M ten, Beekman AT, Vollebergh WA. Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. Journal of Affective Disorders 2004; 82: 461-467.

Hayden EP, Klein DN. Outcome of dysthymic disorder at 5-year follow-up: the effect of familial psychopathology, early adversity, personality, comorbidity, and chronic stress. American Journal of Psychiatry 2001; 158: 1864-1870.

Howland RH. General health, health care utilization, and medical comorbidity in dysthymia. International Journal of Psychiatry in Medicine 1993; 23: 211-238.

Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. Psychiatric Clinics of North America 2002; 25: 685-698.

Keller MB, Lavori PW. Double depression, major depression, and dysthymia: distinct entities or different phases of a single disorder? Psychopharmacology Bulletin 1984; 20: 399-402.

Keller MB, Lavori PW, Endicott J, Coryell W, Klerman GL. “Double depression": two-year follow-up. American Journal of Psychiatry 1983; 140: 689-694.

Keller MB, Shapiro RW. "Double depression": superimposition of acute depressive episodes on chronic depressive disorders. American Journal of Psychiatry 1982; 139: 438-442.

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

Klein DN, Norden KA, Ferro T, Leader JB, Kasch KL, Klein LM, Schwartz JE, Aronson TA. Thirty-month naturalistic follow-up study of early-onset dysthymic disorder: course, diagnostic stability, and prediction of outcome. Journal of Abnormal Psychology 1998; 107: 338-348.

Klein DN, Schwartz JE, Rose S, Leader JB. Five-year course and outcome of dysthymic disorder: A prospective, naturalistic follow-up study. American Journal of Psychiatry 2000; 157: 931-939.

Klein DN, Shankman SA, Rose S. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. American Journal of Psychiatry 2006; 163: 872-880.

McCullough JP, Klein DN, Keller MB, Holzer CE, Davis SM, Kornstein SG, Howland RH, Thase ME, Harrison WM. Comparison of DSM-III-R chronic major depression and major depression superimposed on dysthymia (double depression): validity of the distinction. Journal of Abnormal Psychology 2000; 109: 419-427.

McCullough JP, Klein DN, Borian FE, Howland RH, Riso LP, Keller MB, Banks PL. Group comparisons of DSM-IV subtypes of chronic depression: validity of the distinctions, part 2. Journal of Abnormal Psychology 2003; 112: 614-622.

McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Medical Care 1993; 31: 247-263.

McHorney CA, Ware JE, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Medical Care 1994; 32: 40-66.

Ormel J. Neuroticism and well-being inventories: measuring traits or states? Psychological Medicine 1983; 13: 165-176.

Ormel J, Oldehinkel AJ, Brilman EI. The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. American Journal of Psychiatry 2001; 158: 885-891.

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

Ormel J, Wohlfarth T. How neuroticism, long-term difficulties, and life situation change influence psychological distress: a longitudinal model. Journal of Personality and Social Psychology 1991; 60: 744-755.

Smeets RMW, Dingemans PMAJ. Composite International Diagnostic Interview (CIDI), version 1.1. 1993. Amsterdam/ Geneva, World Health Organization.

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

SPSS. SPSS for Windows: version 15.0. 2006. Chicago, SPSS.

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical Care 1992; 30: 473-483.

Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Medical Care 1995; 3(4 Suppl): AS264-AS279.

Wells KB, Burnam MA, Rogers W, Hays R, Camp P. The course of depression in adult outpatients. Results from the Medical Outcomes Study. Archives of General Psychiatry 1992; 49: 788-794.

Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. British Journal of Psychiatry 1991; 159: 645-53, 658.

Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. Journal of Psychiatric Research 1994; 28: 57-84.

World Health Organization. Composite Diagnostic Interview (CIDI), version 1.0. 1990. Geneva, World Health Organization.