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Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Two-year course of depressive and anxiety disorders: Results from the Netherlands Study of Depression and Anxiety (NESDA)

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ARTICLE INFO

Article history:

Received 9 December 2010

Received in revised form 12 March 2011

Accepted 12 March 2011

Available online 14 April 2011

Keywords:

Depression

Anxiety

Course

Comorbidity

Cohort study

Longitudinal

ABSTRACT

Background: Whether course trajectories of depressive and anxiety disorders are different, remains an important question for clinical practice and informs future psychiatric nosology. This longitudinal study compares depressive and anxiety disorders in terms of diagnostic and symptom course trajectories, and examines clinical prognostic factors.

Methods: Data are from 1209 depressive and/or anxiety patients residing in primary and specialized care settings, participating in the Netherlands Study of Depression and Anxiety. Diagnostic and Life Chart Interviews provided 2-year course information.

Results: Course was more favorable for pure depression ($n = 267$, median episode duration = 6 months, 24.5% chronic) than for pure anxiety ($n = 487$, median duration = 16 months, 41.9% chronic). Worst course was observed in the comorbid depression–anxiety group ($n = 455$, median duration >24 months, 56.8% chronic). Independent predictors of poor diagnostic and symptom trajectory outcomes were severity and duration of index episode, comorbid depression–anxiety, earlier onset age and older age. With only these factors a reasonable discriminative ability (C -statistic 0.72–0.77) was reached in predicting 2-year prognosis.

Limitation: Depression and anxiety cases concern prevalent – not incident – cases. This, however, reflects the actual patient population in primary and specialized care settings.

Conclusions: Their differential course trajectory justifies separate consideration of pure depression, pure anxiety and comorbid anxiety–depression in clinical practice and psychiatric nosology.

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1. Introduction

Depressive and anxiety disorders have an enormous impact on public health for a large part because both disorders often present a chronic-intermittent course and consequently have sustained impact over the life-cycle. As from Kraepelin's time, a disorder's prognosis has been an important criterion to validate clinical entities: when naturalistic course differs across disorders, their distinction could be useful in clinical practice and psychiatric nosology. For depressive disorders, longitudinal, naturalistic cohort studies indicate that the median duration of episodes ranges between 3 and 6 months, whereas approximately 20% of episodes becomes chronic (Keller et al., 1992; Ormel et al., 1993; Spijker et al., 2002). In anxiety disorders the few large-scale prognostic studies indicate an at least similarly poor or even worse course trajectory. Two reviews estimated that the course of panic disorder shows little to no improvement in 36–40% of the subjects (Keller and Hanks, 1993; Pollack and Otto, 1997). The HARP study showed that only 35% of the patients with social phobia recovered over 10 years, while the recurrence rate after recovery was 34% (Keller, 2006). Although these results depict anxiety disorders as insidious with a less favorable course compared to depressive disorders, comparison is hampered since few prior studies directly compared the course of depressive and anxiety disorders within the same study design and with the same instruments. Given the well-documented high levels of comorbidity, and the effect this may have on prognosis (Bruce et al., 2005; Merikangas et al., 2003; Ormel et al., 1993), any study comparing the prognosis of anxiety and depression should consider those with comorbid conditions separately to avoid confounding results. This issue has not always been adequately addressed.

In addition, proper insight into clinical determinants of the naturalistic course of depressive and anxiety disorders is of great importance for a better scientific and clinical understanding of these disorders. Most prognostic studies have found that basic clinical factors, such as severity and duration of the index episode are among the most consistent and strongest predictors (Spijker et al., 2002, 2004; Vuorilehto et al., 2009). Also, specific type of disorder may provide important course information since it, for instance, has been reported that the course is more favorable for panic disorder than for social phobia (Yonkers et al., 2003). For socio-demographics such as age, female gender and low education, which are all confirmed determinants of the onset of anxiety and depressive disorders (Bijl et al., 1998a; Kessler et al., 1994; Seedat et al., 2009), the role in course prediction has been less consistent (Ramsawh et al., 2009; Spijker et al., 2002; Yonkers et al., 2003). This may indicate that once the disorder has become established, not the factors predicting the onset, but the clinical features of the disorder itself are most important for prognosis. This study examines the 2-year course in a large cohort of depressed and/or anxious persons from both primary care and specialized mental health care and directly compares course outcome between subjects with pure depression, pure anxiety and comorbid depression–anxiety. In addition, it will be determined to what extent course outcome is dependent on basic demographic and clinical factors.

2. Methods

2.1. Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing cohort study designed to investigate the course and consequences of depressive and anxiety disorders. A total of 2981 persons aged 18 through 65 years were included, consisting of healthy controls, persons with a prior history, and persons with a current depressive and/or anxiety disorder. To represent the entire range of settings and stages of psychopathology in which patients in the naturalistic (clinical) reality are seen, depressed or anxious subjects were recruited in three Dutch regions in three settings: the community, primary care, and secondary care. Community-based subjects with depressive or anxiety disorders were previously identified in two population-based studies (Nemesis (Bijl et al., 1998b) and Ariadne (Landman-Peeters et al., 2005)). Primary care patients were identified through a 3-stage screening procedure (involving the K10 and the CIDI short form (Donker et al., 2010)), among patients of 65 General Practitioners consulting for any reason in a 4-month period. In secondary care, patients were recruited when newly enrolled for a depressive or anxiety disorder at one of the 17 participating mental health organization locations. General exclusion criteria were a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder and not being fluent in Dutch. A detailed description of the NESDA design and sampling procedures is elsewhere (Penninx et al., 2008). We previously showed that non-response was not so much related to mental health status but was slightly higher among younger and male respondents (Penninx et al., 2008; van der Veen et al., 2009). The baseline assessment included assessment of demographic and personal characteristics, a standardized diagnostic psychiatric interview and a medical assessment. The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent. After two years, a face-to-face follow-up assessment was conducted with a response of 87.1% ($n = 2596$). Non-response was significantly higher among those with younger age, lower education, non-North European ancestry and depressive disorder, but was not associated with gender or anxiety disorder (Lamers et al., *in press*).

The presence of depressive (major depressive disorder, and dysthymia) or anxiety (panic disorder, social phobia, generalized anxiety disorder, and agoraphobia) disorders was established using the DSM-IV based Composite Interview Diagnostic Instrument (CIDI, version 2.1), a highly reliable and valid instrument for assessing depressive and anxiety disorders (Wittchen, 1994). For the present analysis, only subjects who were symptomatic in the month before baseline were included. Consequently, the sample was restricted to the 1456 subjects with a 6-month depressive or anxiety diagnosis who confirmed symptoms in the month prior to baseline at either the CIDI recency questions or the Life Chart Interview (see below). Of these, 1209 (83.0%) participated in the 2-year follow-up (median in-between time = 24 months) and all had complete data on the central outcome indicators (CIDI and LCA): 267 (22.1%) with a pure depressive disorder ('Dep'), 487 (40.2%) with a pure anxiety disorder ('Anx') and

455 (37.6%) with comorbid depressive and anxiety disorders ('Comorbid') at baseline.

2.2. Course of depressive and anxiety disorders

Course was determined using two sources of data collected during the 2-year follow-up assessment: 1) the CIDI interview and the 2) Life Chart Interview (LCI). The CIDI interview determined the presence of DSM-IV classified depressive and anxiety disorders during the time between baseline assessment and 2-year follow-up. Organic exclusion rules were used in defining diagnoses, and hierarchy-free diagnoses. For all persons with detected depressive or anxiety symptoms in the CIDI interview, the LCI was conducted by trained and supervised clinical research staff. Using a calendar method, life events are recalled to refresh memory after which the presence of depressive and anxiety symptoms – separately – at each month during this 2-year period was determined. In addition, for each month with reported symptoms, severity was assessed ranging from no or minimal severity, mild, moderate, to severe, or very severe. Earlier studies have described the method behind the LCI in detail (Lyketsos et al., 1994) and its methodology has shown high validity and reliability (Warshaw et al., 1994). Symptoms on LCI were only considered to be present when at least of mild severity. Using both the CIDI and LCI, the following course indicators were created:

(Time to) remission of index disorder was defined based on LCA as the occurrence and the first time-point at which no symptoms of the index disorder were reported for three consecutive months. For instance, remission of an anxiety disorder was considered present when no anxiety symptoms at all existed for 3 consecutive months during follow-up, and likewise a comorbid condition was considered remitted when no symptoms at all of both anxiety or depression existed for 3 consecutive months. This 3-month criterion is in line with that used before (Spijker et al., 2002) and was uniformly applied across all disorders to allow comparison of outcomes. No distinction was made between remission and recovery (Frank et al., 1991) because the data did not allow for such precision. Among subjects with a remission, the *recurrence and time to recurrence of index disorder* was assessed using LCA information and defined as the re-occurrence of symptoms with at least mild severity for at least one month under the condition that also the CIDI interview confirmed the presence of a depressive or anxiety disorder during follow-up.

Psychiatric status after 2 years was based on the presence of CIDI DSM-IV diagnosed anxiety or depressive disorders (6-month recency) at the time of the 2-year follow-up.

Clinical course trajectory of index disorder was defined by categorizing persons into four categories on the basis of both their depressive and anxiety symptoms over time. As done before (Beekman et al., 2002), distinction was made between: a) early sustained remission defined as remission of index disorder(s) within six months without recurrence of any symptoms during follow-up, b) late sustained remission defined as remission after six months without recurrence of any symptoms, c) remission with recurrence: those with remission but later recurrence of depressive and anxiety symptoms, and d) chronic course: those without remission

but enduring anxiety and/or depression symptoms of at least mild severity during the entire follow-up period.

Duration of symptoms during follow-up was calculated using LCA data as the percentage of time during follow-up with symptoms of at least mild severity. Duration of symptoms was calculated as (number of affected months/total number of follow-up months) * 100%, and ranged from 0% (no symptoms during follow-up) to 100% (symptoms during entire follow-up).

2.3. Determinants of 2-year course

2.3.1. Sociodemographics

Information was included on age, gender and years of education.

2.3.2. Clinical characteristics

Severity of depressive symptoms was measured with the 30-item Inventory of Depressive Symptomatology (IDS, (Rush et al., 1996)). Severity of anxiety symptoms was measured using the 15-item Fear Questionnaire (Marks and Mathews, 1979) and the 21-item Beck Anxiety Inventory (BAI, (Beck et al., 1988)). Information on *duration of symptoms* prior to baseline was derived from LCA (Lyketsos et al., 1994) at baseline which assessed the percent of time the patient spent with depressive and/or anxiety symptoms in the prior four years. Based on CIDI data, the following specific types of baseline depressive disorder were differentiated to explore the role of type of disorder: first onset MDD, recurrent MDD, and dysthymia (without MDD). *Specific types of anxiety disorder* included social phobia, generalized anxiety disorder, panic disorder with or without agoraphobia, and agoraphobia without panic. *Age of onset* of the index disorder was assessed, and earliest age was used for those with comorbid disorders. *A history of a remitted depressive or anxiety disorder* – other than the index disorder – before baseline was determined in the CIDI interview. The presence of a *family history of depression or anxiety* among first degree relatives (not including offspring) was determined using the family tree method (Fyer and Weissman, 1999). *Comorbidity of alcohol use disorders* was determined using lifetime DSM-IV diagnoses in the CIDI interview. An indicator for *care setting* differentiated subjects receiving specialized mental health care vs those receiving care from general practitioners, the gatekeeper for care to Dutch citizens. *Medication use* was assessed based on drug container inspection of drugs used in the past month and coded using the Anatomical Therapeutic Chemical (ATC) classification. Use of antidepressants was considered when taken at least 50% of the time and included selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (N06AA) and other antidepressants (N06AF/N06AX). The receipt of *psychological treatment* (either formal psychotherapy or counseling as well as skills training) was based on self-reported information.

2.4. Statistical analyses

Characteristics and 2-year course outcomes were compared across baseline diagnostic status (Dep, Anx, Comorb) using chi-square statistics for categorical variables and analyses of variance for continuous variables. Time to

remission, time to recurrence, and duration of symptoms were compared using Mann Whitney tests because of the non-normal distributions of these outcomes. The cumulative probability of first remission was estimated with Kaplan–Meier product limit and survival curves were compared across baseline diagnostic groups using the log-rank test. Subjects with a duration greater than 24 months were censored at 24 months. Median survival time is the first recovery at which cumulative survival reaches 50%.

Subsequently, associations between sociodemographic and clinical factors with 2-year course were examined. Using Cox's proportional hazards analyses univariate and multivariate (adjusted for other covariates) associations between sociodemographic and clinical factors with time to first remission were examined. Logistic regression analyses determined associations with a 2-year diagnostic status. Finally, multivariate associations with the 4-category course trajectory indicator were determined in multinomial logistic regression analyses using early remission as the reference group and calculating risks for the outcome late remission, remission with recurrence and chronic course. As an overall indication of the ability to discriminate between patients with and without poor course outcome based on final multivariate models, the concordance-statistic (c-statistic, i.e. the area under the Receiver Operating Characteristic curve) was calculated. C-statistics between 0.7 and 0.8 are generally considered as acceptable and between 0.8 and 0.9 as excellent (Hosmer and Lemeshow, 2000).

3. Results

The study sample mean age was 42.1 years, and 66.0% was female. Of all 1209 participants, 39.1% received medication and 44.0% received psychological treatment at baseline (38.3% received no treatment at all, 40.3% received one and 21.4% received both forms of treatment). The index episodes of the Comorbid group were more severe and protracted and this group reported an earlier age of onset and more often receiving treatment (Table 1).

3.1. 2-year course of anxiety and depressive disorders

The majority of persons with depressive disorder remitted within 2 years: 79.5% of the Dep group and 74.5% of the Comorbid group (Table 2). Although these percentages did not differ, median time to remission was significantly shorter in the Dep group (6 months) than in the Comorbid group (12 months). Among depressed subjects who remitted, 22% developed a recurrent episode during follow-up. Recurrence rate was similar for the Dep and Comorbid groups.

Remission from anxiety disorder showed a less favorable picture: only 58.7% from the Anx group and 50.4% from the Comorbid group remitted, and median remission time was much higher than for depressive disorder: 16 months for Anx and 24 months for Comorbid. Among those who remitted, recurrence rates were comparable to those found for depression: 21.9% for Anx and 23.8% for Comorbid.

Time to first remission of the index disorder was significantly different for the Dep, Anx and Comorbid groups (log-rank $p < .001$, Fig. 1). For the Comorbid group, this was defined as remission when both anxiety and depression had

remitted. Since a symptom-free period of 3 months was defined as remission, first remissions could only occur at 4 months of follow-up. Half of the Dep group recovered within 6 months, which was 16 months in the Anx group. Over 2 years, less than half of the Comorbid group (44%) had recovered from both anxiety and depression.

Looking at psychiatric status at two-year follow-up, 47.6% and 46.0% of the Dep and Anx groups were without a disorder, which was only 25.1% in the Comorbid group ($p < .001$). Of the Dep group, 7.5% switched to anxiety and 16.1% developed anxiety comorbid to a sustained depression. Results in the Anx group were very similar: 7.0% switched to depression and 16.4% developed comorbid depression.

Using the clinical course trajectory indicator combining data on depression and anxiety symptoms, chronic course without remission was least common in the Dep group (24.5%), and most common among the Comorbid group (56.8%, $p < .001$), with the Anx group in an intermediate position (41.9%). This is further confirmed by the continuous symptom duration indicator from the LCA. The median percentage of time during follow-up with anxiety or depression symptoms was 38% in the Dep group, 63% in the Anx group and 92% in the Comorbid group ($p < .001$).

3.2. Determinants of 2-year course

Determinants of time to first remission of depression and/or anxiety were analyzed using Cox's survival analyses (Table 3). Univariately, both Anx and Comorbid groups showed a significantly lower risk for first remission – indicating a longer episode duration – as compared to the Dep group. Additional indicators associated with lower risk for first remission were first compared to recurrent MDD, panic disorder compared to GAD or agoraphobia, longer baseline symptom duration, higher symptom severity, early age of onset, no personal history of a remitted other depressive or anxiety disorder, and being in the mental health care setting or receiving treatment. In a multivariate model, seven predictors remained significant: pure anxiety and comorbid depression–anxiety as compared to pure depression, older age, longer baseline duration of the index disorder, earlier age of onset, more severe fear symptoms and no earlier personal (remitted) history were independently associated with lower risk to first remission. Trends were observed for more severe depressive symptoms with lower risk to first remission, and having agoraphobia with higher risk to first remission. The c-statistic of the final multivariate model was 0.73, indicating a reasonable discriminative ability in predicting first remission.

When examining the presence of a depressive or anxiety disorder (6-month recency) after two years using logistic regression analyses, a very similar picture of predictors emerged (Table 3). Comorbidity, longer symptom duration at baseline and more severe depressive and fear symptoms independently predicted the presence of disorders after two years. In addition, agoraphobia was associated with a better outcome, while older age and early age of onset were associated with worse outcome. The c-statistic of the final model was 0.72, indicating a reasonable discriminative ability.

When examining determinants of the 4-category clinical course trajectory outcome in multinomial regression analyses (Table 4), again worse outcome was more likely to occur in the Anx and Comorbid groups (as compared to the Dep

Table 1
Baseline characteristics according to baseline psychiatric status (n = 1209).

	Pure depression N = 267	Pure anxiety N = 487	Comorbid depression–anxiety N = 455	p ^a
<i>Sociodemographics</i>				
Age (mean years, SD)	42.2 (12.7)	41.8 (12.6)	42.3 (11.9)	.82
Sex,% female	63.7%	68.2%	65.1%	.40
Education (mean years, SD)	12.0 (3.2)	12.2 (3.3)	11.1 (3.2)	<.001
<i>Clinical psychiatric characteristics</i>				
Type of baseline disorder:				
First episode of MDDk	39.3%	–	49.2%	
Recurrent MDD	56.6%	–	44.6%	
Dysthymia	20.6%	–	37.1%	
Panic disorder	–	47.2%	50.1%	
Social phobia	–	50.1%	53.4%	
Generalized anxiety disorder	–	22.2%	48.8%	
Agoraphobia (without panic)	–	17.0%	13.0%	
Number of anxiety disorders (mean, SD)	–	1.4 (0.6)	1.6 (0.7)	
Duration of symptoms at baseline:				
% months with symptoms in past 4 years	42.2 (30.1)%	57.8 (37.6)%	66.7 (32.5)%	<.001
Severity of symptoms at baseline:				
Inventory of Depressive Symptoms (score, SD)	30.7 (10.5)	23.4 (9.9)	37.2 (10.8)	<.001
Beck Anxiety Inventory (score, SD)	13.6 (8.8)	15.6 (9.5)	22.3 (10.7)	<.001
Fear Questionnaire (score, SD)	23.8 (17.2)	33.4 (18.3)	40.6 (21.4)	<.001
Personal history of other remitted depressive or anxiety disorder	39.7%	67.8%	28.6%	<.001
Family history of depression or anxiety	82.4%	83.5%	86.8%	.21
Comorbid alcohol use disorder	29.6%	29.8%	32.7%	.54
Age of onset:				
Age on onset (mean years, SD)	25.4 (13.1)	19.9 (11.8)	19.5 (12.5)	<.001
Care setting:				
Primary care	41.6%	54.0%	34.9%	<.001
Specialized mental health care	58.4%	46.0%	65.1%	
Psychiatric treatment at baseline				
Medication	38.2%	30.4%	49.0%	<.001
Psychological treatment	43.8%	37.8%	50.8%	<.001

^a p-value based on chi-square statistics for categorical variables and analyses of variance for continuous variables.

group), and with more severe or protracted index episodes. Agoraphobia was associated with a more favorable course. Independent of differences in severity, duration and comorbidity across settings – the course of patients treated in specialized mental health care was worse than that in primary care, and was worse for those with an earlier age of onset. Persons with an earlier history of another remitted disorder had a lower risk of a chronic course. The c-statistic of the multivariate model was high for the chronic course outcome ($c=0.77$) indicating that the discriminative ability of the final model was good.

4. Discussion

This study described and compared the 2-year diagnostic and symptom trajectory outcome of depressive and anxiety disorders in a large naturalistic cohort of subjects from both primary and specialized mental health care settings. Its results – using similar measurements allowing for direct comparison – clearly indicate that anxiety disorders have a longer time to first remission and a more chronic course trajectory than depressive disorders. For example, the median episode duration to first remission was 6 months for the Dep group and 16 months for the Anx group, whereas a chronic course of symptoms was present in 24.5% and 41.9%, respectively. An even more distinctive group in terms of both the diagnostic and symptom trajectory outcomes were

those with comorbid depression–anxiety: their median episode duration was over 24 months and 55.3% developed a chronic course. The most consistent independent predictors of poor diagnostic or symptom trajectory outcomes were comorbid depression–anxiety, severity and duration of the index episode, early age of onset, and older age. A model based on these very basic sociodemographic and clinical prognostic factors showed quite reasonable discriminative ability to the course outcome over 2 years.

Compared to prior population-based studies or inception cohorts reporting episode durations between 3 and 4 months (Furukawa et al., 2000; Keller et al., 1992; Spijker et al., 2002) our median episode duration of depression is in the higher range, but results are in line with those from other clinical population studies (Ormel et al., 1993; Solomon et al., 1997; Tiemens et al., 1996). Also the finding that about 80% of the depressed subjects reach remission within 2 years is in line with earlier findings (Ormel et al., 1993). For anxiety disorders, the observed 46% without a disorder after two years, is in line with the reported 48% among social phobia patients in the HARP study (Keller, 2006). Time to first complete remission for subjects with comorbid depression–anxiety has not been clearly described before. Our findings indicate that the median episode duration for comorbid subjects is extensive, as it stretches beyond the 24 months.

We did not find evidence for extensive diagnostic ‘instability’ across depression and anxiety disorders, as

Table 2

Two-year course indicators according to baseline psychiatric status (N = 1209).

	Pure depression N = 267	Pure anxiety N = 487	Comorbid depression–anxiety N = 455	p ^a
<i>Remission from depressive disorder</i>				
Depression remission	79.5%	NA	74.5%	.13
Median time to remission, in months (IQR)	6.0 (18.0)	NA	12.0 (20.0)	.01
Among those with remission:				
Recurrence of depression	21.5%	NA	22.3%	.83
Median time to recurrence, in months (IQR)	6.0 (6.0)	NA	5.0 (5.0)	.06
<i>Remission from anxiety disorder</i>				
Anxiety remission	NA	58.7%	50.4%	.01
Median time to remission, in months (IQR)	NA	16.0 (20.0)	24.0 (20.0)	.03
Among those with remission:				
Recurrence of anxiety	NA	21.9%	23.8%	.62
Median time to recurrence, in months (IQR)	NA	4.0 (5.0)	4.0 (9.0)	.28
Psychiatric status after 2 years				
No depressive or anxiety disorder	47.6%	46.0%	25.1%	<.001
Depressive disorder	28.8%	7.0%	15.2%	
Anxiety disorder	7.5%	30.6%	20.2%	
Depressive and anxiety disorder	16.1%	16.4%	39.6%	
Clinical course trajectory of combined depression and anxiety symptoms				
Early remission (≤ 6 months)	34.7%	29.3%	14.0%	<.001
Late remission (> 6 months)	15.1%	11.8%	13.5%	
Remission with recurrence	25.7%	17.1%	15.8%	
Chronic course without remission	24.5%	41.9%	56.8%	
Duration of symptoms during follow-up				
Percent time (median, IQR) with depression	32 (68)	0 (12)	50 (72)	<.001
Percent time (median, IQR) with anxiety	0 (12)	60 (89)	80 (89)	<.001
Percent time (median, IQR) with depr. or anx.	38 (76)	63 (84)	92 (57)	<.001

IQR = interquartile range.

^a p-value based on chi-square statistics for categorical variables and Mann Whitney non-parametric statistics for continuous variables.

described before (Merikangas et al., 2003). About 7% of the pure depression group switched to an anxiety disorder over 2 years, which was similar to the corresponding switch from anxiety to depression. It is interesting to point out that pure depression and anxiety groups did not differ significantly in terms of diagnostic status after 2 years: about 47% was diagnosis-free. This finding illustrates that it can be misleading to limit focus on diagnostic status alone, since one then wrongly would have concluded that prognosis was similar. Integrating the in-between symptomatology – as in the present study – showed that the 2-year course trajectory was

different: anxiety patients reported longer episode duration, more time with symptoms and a more chronic course than depressed patients.

With regard to prognostic factors, demographics were not consistently among the most important predictors. Although female gender and low education have shown to predict onset of anxiety and depression (Bijl et al., 1998a; Kessler et al., 1994; Seedat et al., 2009), our findings indicate that they are not as important in determining prognosis. Older age predicted poorer course outcome over 2 years, which is in line with studies suggesting that the course of depression in old age may be less favorable than that of younger adults (Licht-Strunk et al., 2009). Clinical characteristics were clearly the most important predictors of the ensuing prognosis. Consistent determinants were severity and duration of the index episode and comorbid depression–anxiety. It is important to emphasize that these predictive factors exerted their effect independent of each other. In other words, the poorer course outcomes among comorbid patients remained after controlling for baseline differences in severity and duration of symptoms. The reason why the comorbid group has such an unfavorable prognosis remains to be uncovered and may be sought in both the genetic and environmental realms. Another interesting finding was that a history of an earlier remitted disorder – other than the index disorder – predicted an earlier remission and a lower risk of chronic course. This could be explained by the fact that those with remissions in the past may identify persons who suffer more from intermittent course trajectories characterized by rather unstable, short-termed and switching conditions.

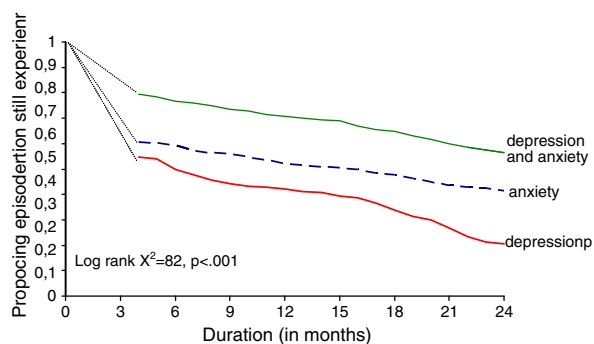


Fig. 1. Survival curve illustrating time until first remission across baseline psychiatric status (n = 1209). The dotted lines (.....) are projected lines since by definition no remission could have occurred within the first 3-month period.

Table 3

Univariate and multivariate determinants of time to first remission (episode duration) and presence of a depressive or anxiety disorder at 2-year follow-up (N = 1209).

	Time to first remission of depression and/or anxiety disorder		Presence of a depressive or anxiety disorder at 2-year follow-up	
	Univariate ^a	Multivariate ^a	Univariate ^b	Multivariate ^b
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Baseline psychiatric status				
Pure depression	Ref	Ref	Ref	Ref
Pure anxiety	0.66 (0.55–0.79) ‡	0.68 (0.51–0.89) ‡	1.07 (0.79–1.44)	1.13 (0.71–1.79)
Comorbid depression–anxiety	0.43 (0.35–0.52) ‡	0.60 (0.46–0.77) ‡	2.71 (1.97–3.74) ‡	1.70 (1.11–2.55) ‡
Sociodemographics				
Age (per 10 years increase)	0.96 (0.90–1.02)	0.92 (0.86–0.99) ‡	1.09 (0.99–1.19) †	1.16 (1.03–1.31) ‡
Female gender	1.13 (0.96–1.33)	1.12 (0.95–1.33)	1.01 (0.79–1.30)	1.07 (0.80–1.42)
Education (per year increase)	1.02 (1.00–1.04) †	1.00 (0.97–1.02)	0.97 (0.94–1.01) †	1.03 (0.98–1.07)
Specific psychiatric indicators				
Type of depressive disorder				
First episode MDD	Ref	Ref	Ref	Ref
Recurrent MDD	1.29 (1.05–1.58) ‡	1.05 (0.85–1.36)	0.78 (0.56–1.08)	0.98 (0.68–1.40)
Dysthymia	1.09 (0.69–1.71)	0.99 (0.62–1.58)	0.78 (0.39–1.56)	0.85 (0.40–1.81)
Type of anxiety disorder				
Panic disorder	Ref	Ref	Ref	Ref
Social phobia	0.97 (0.78–1.21)	0.93 (0.74–1.16)	0.78 (0.57–1.06)	0.79 (0.56–1.13)
GAD	1.32 (1.02–1.72) ‡	1.21 (0.92–1.60)	0.65 (0.44–0.98) ‡	0.75 (0.47–1.17)
Agoraphobia (without panic)	1.54 (1.14–2.10) ‡	1.35 (0.98–1.85) †	0.38 (0.23–0.63) ‡	0.55 (0.32–0.94) ‡
Symptom duration at baseline				
Per 10% duration increase	0.91 (0.89–0.93) ‡	0.94 (0.92–0.97) ‡	1.14 (1.10–1.18) ‡	1.08 (1.04–1.13) ‡
Severity of symptoms				
IDS (per SD increase) ^c	0.79 (0.73–0.85) ‡	0.90 (0.80–1.02) †	1.89 (1.65–2.16) ‡	1.41 (1.15–1.72) ‡
BAI (per SD increase) ^c	0.78 (0.72–0.85) ‡	0.97 (0.87–1.09)	1.72 (1.51–1.97) ‡	1.11 (0.92–1.33)
Fear Q (per SD increase) ^c	0.75 (0.69–0.81) ‡	0.90 (0.82–0.99) ‡	1.74 (1.52–1.98) ‡	1.29 (1.10–1.51) ‡
Age of onset				
Per 10 years increase	1.12 (1.06–1.18) ‡	1.08 (1.00–1.16) ‡	0.84 (0.77–0.92) ‡	0.87 (0.77–0.98) ‡
Personal history of other remitted depressive or anxiety disorder				
Family history depression/anxiety	0.96 (0.78–1.18)	0.97 (0.79–1.09)	1.06 (0.77–1.46)	0.91 (0.64–1.29)
Comorbid alcohol use disorder	0.91 (0.77–1.08)	0.98 (0.82–1.16)	1.32 (1.02–1.70) ‡	1.26 (0.95–1.69)
Care setting:				
Primary care				
Mental health care	0.79 (0.68–0.92) ‡	0.90 (0.75–1.09)	1.53 (1.21–1.93) ‡	1.17 (0.86–1.61)
Treatment				
Medication	0.85 (0.73–0.99) ‡	0.98 (0.82–1.16)	1.38 (1.09–1.76) ‡	0.96 (0.72–1.28)
Psychological treatment	0.92 (0.79–1.07)	1.00 (0.84–1.18)	1.29 (1.02–1.63) ‡	1.06 (0.80–1.40)
C-statistic (95% CI)		0.73 (0.70–0.76)		0.72 (0.69–0.75)

‡ p < .05, † p < .10.

^a Based on Cox's proportional survival analyses.

^b Based on logistic regression analyses.

^c SD for IDS = 12.3, SD for BAI = 10.4, SD for Fear Q = 20.1.

Some other predictors emerged. Subjects with agoraphobia without panic had a more favorable course than those with panic disorder or other anxiety patients. This is consistent with the idea that agoraphobia alone may identify persons with rather mild anxiety. In addition, earlier age of onset increased the risk of poor course, which adds to the recent suggestion (Kendler et al., 2009) that early onset disorders typify a subset of patients with a distinct etiological profile in which genetic vulnerability and early developmental aspects play a larger role. Our study adds that early onset disorders – apart from severity and duration – seem to result in poorer prognosis as well.

With regard to treatment setting, in most multivariate analyses adjusting for differences in severity, duration and other clinical aspects, course differences between patients in primary vs specialized mental health care did not retain. However, for the late recovery and chronic course outcomes

those in the mental health care setting remained to have a significantly higher risk. This may indicate that additional underlying differences – such as care seeking behavior (Verhaak et al., 2009) or personality (Spinhoven et al., 2009) – across treatment settings may exist and play a role in course prediction. Although significant in univariate analyses, treatment was not a significant course determinant anymore in multivariate analyses containing clinical information on e.g. severity and duration of symptoms, as found before (Ormel et al., 1993; Spijker et al., 2002). This, however, does not imply that treatment is unimportant. Treatment may well influence the course of the disorders, but since clinical indicators also determine receipt of treatment, an observational study may end up finding no association. Only experimental studies can examine the effect of treatment.

Using basic sociodemographic and clinical indicators, we were able to achieve a reasonable discriminative ability to

Table 4Multivariate^a determinants of the clinical course trajectory of depressive and anxiety symptoms (N = 1209).

	Late remission (vs early remission)	Remission + recurrence (vs early remission)	Chronic course (vs early remission)
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Baseline psychiatric status			
Pure depression	Ref	Ref	Ref
Pure anxiety	0.74 (0.39–1.40)	1.10 (0.53–2.26)	2.57 (1.34–4.75) ‡
Comorbid depression–anxiety	0.48 (0.26–0.87) ‡	1.28 (0.68–2.40)	2.22 (1.26–3.82) ‡
Sociodemographics			
Age (per 10 years increase)	1.16 (0.97–1.38) †	0.93 (0.77–1.12)	1.15 (0.99–1.34) †
Female gender	0.72 (0.48–1.07)	1.13 (0.72–1.78)	0.77 (0.53–1.11)
Education (per year increase)	1.07 (0.95–1.07)	1.00 (0.93–1.06)	1.00 (0.95–1.06)
Specific psychiatric indicators			
Type of depressive disorder			
First episode MDD	Ref	Ref	Ref
Recurrent MDD	0.90 (0.54–1.51)	1.73 (1.03–2.96)	1.18 (0.74–1.82)
Dysthymia	0.42 (0.12–1.49)	1.17 (0.39–3.53)	1.04 (0.41–2.62)
Type of anxiety disorder			
Panic disorder	Ref	Ref	Ref
Social phobia	0.95 (0.54–1.64)	1.51 (0.86–2.63)	1.25 (0.79–1.98)
GAD	0.74 (0.37–1.45)	0.95 (0.48–1.84)	0.67 (0.38–1.17)
Agoraphobia (without panic)	0.52 (0.24–1.12) †	0.67 (0.30–1.54)	0.48 (0.28–0.91) ‡
Symptom duration at baseline			
Per 10% duration increase	1.02 (0.96–1.08)	1.01 (0.95–1.08)	1.12 (1.07–1.18) ‡
Severity of symptoms			
IDS (per SD increase) ^b	1.37 (1.03–1.83) †	1.34 (0.99–1.82) †	1.48 (1.15–1.92) ‡
BAI (per SD increase) ^b	0.82 (0.62–1.07)	0.82 (0.61–1.09)	0.92 (0.73–1.16)
Fear Q (per SD increase) ^b	1.23 (0.97–1.55) †	1.38 (1.08–1.76) ‡	1.35 (1.10–1.65) ‡
Age of onset			
Per 10 years increase	0.89 (0.75–1.05)	0.97 (0.80–1.17)	0.82 (0.71–0.96) ‡
Personal history of other remitted depressive or anxiety disorder			
Family history depression/anxiety	0.82 (0.55–1.23)	1.11 (0.72–1.71)	0.56 (0.39–0.80) ‡
Comorbid alcohol use disorder	1.09 (0.67–1.78)	1.02 (0.60–1.74)	1.08 (0.69–1.69)
Care setting	0.94 (0.62–1.42)	1.10 (0.71–1.71)	1.08 (0.74–1.56)
Treatment			
Primary care setting	Ref	Ref	Ref
Mental health care setting	1.79 (1.14–2.81) ‡	1.08 (0.67–1.73)	1.56 (1.05–2.33) ‡
Medication			
Psychological treatment	1.06 (0.70–1.61)	0.95 (0.61–1.47)	1.04 (0.72–1.50)
C-statistic (95% CI)	0.73 (0.48–1.10)	1.38 (0.89–2.12)	0.96 (0.66–1.38)
	0.69 (0.65–0.74)	0.71 (0.65–0.76)	0.77 (0.74–0.81)

‡ $p < .05$, † $p < .10$.^a Based on multinomial logistic regression analyses.^b SD for IDS = 12.3, SD for BAI = 10.4, SD for Fear Q = 20.1.

predict time to remission, 2-year diagnostic status and chronic course trajectory: c-statistics were 0.72, 0.73 and 0.77, respectively. Refinement and validity checks of a risk profile for course prediction were beyond the scope of this study, but deserve further research. The development of such a risk profile is never based on one single study, and the effects of implementing such a risk profile in clinical practice should be tested in further research. However the ingredients that deserve consideration in such a risk profile become apparent: our findings illustrate that – although there is some room for improvement – rather simple clinical characteristics provide good tools to identify people at risk for a poor outcome.

The present study included prevalent depression and anxiety cases as they were residing in primary care or when newly enrolled in specialized mental health care. Their course may not be directly comparable (and is likely somewhat more severe) to that of incident cases. Nevertheless, the clinical reality is that presenting patients often already have a history of symptoms, so our findings are generalizable to standard clinical settings. In addition, although longer-term follow-up

provides more information on episode and symptom recurrence beyond 2 years, it is known that the largest course variation takes place within this time period. Study strengths are its large well diagnosed sample from primary and specialized mental care settings in which we applied both a diagnostic and a symptom trajectory approach.

Our findings have several potential clinical implications. First, they support the importance of a full diagnostic approach covering the entire depressive and anxiety spectrum since this provides useful predictive information. Second, they suggest that rather simple clinical characteristics provide good tools for course prediction. Third, they lend support for individualized care approaches in which the least intensive treatment strategies (e.g. watchful waiting) are provided to those at lowest chronicity risk reserving more intensive treatment strategies (e.g. combined medication and psychotherapy) for those at the highest chronicity risk. Although such individualized treatment approaches have clear face value, future research should evaluate whether such 'stepped care approaches' in clinical practice are indeed effective. Our findings indicate that based on various rather

simple clinical characteristics it appears possible to predict the course risk of individual patients.

In sum, our findings indicate that pure anxiety had a much longer time to first remission and a more chronic symptom trajectory than pure depression. Depression–anxiety comorbidity results in even more persistence of diagnostic and symptom trajectory outcomes. Their differential course trajectory justifies separate consideration of pure depression, pure anxiety and comorbid anxiety–depression in clinical practice and psychiatric nosology.

Role of funding source

The NESDA study is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations. These sponsors have not had any role in the conducted analyses, writing the manuscript and the decision to publish these results.

Conflict of interest

Nolen has received grants from Astra Zeneca, Eli Lilly, GlaxoSmithKline and Wyeth, received consultation fees from Astra Zeneca, Pfizer, Servier and Wyeth and served on boardmembership for Astra Zeneca, Pfizer, Servier. Hoogendijk received grants from Ely Lilly, Lundbeck, Servier, Bristol-Meyers Squibb and Organon and has received consultation fees from Ely Lilly, Lundbeck, Servier, Bristol-Meyers Squibb and Organon. Other authors have no conflicts of interest.

Acknowledgments

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), and Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos)). All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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