Chapter 7:

Symptom Dimensions as Predictors of the Two-Year Course of Depressive and Anxiety Disorders

Abstract

Background, Because of the heterogeneity of known predictive factors, course-predictions for depression and anxiety are often unspecific. Therefore, it was investigated whether symptom-dimensions could be used as more specific course-predictors, on top of already known predictors, such as diagnosis and overall severity. *Methods,* A sample of 992 subjects with depressive and/or anxiety disorders was followed in a 2-year prospective cohort study. Dimensions of the *tripartite model* (general distress, anhedonic depression and anxious arousal) were assessed at baseline. Diagnostic and course information were assessed at baseline and 2-year follow-up. *Results,* Dimensional scores at baseline predicted diagnosis after two years and course-trajectories during follow-up. Increased general distress at baseline was associated with comorbid depression-anxiety at follow-up, increased anhedonic depression was associated with single depression and anxious arousal was associated with (comorbid) panic disorders at follow-up. Baseline general distress was associated with an unfavourable course in all patients. All associations were independent and added prognostic information on top of diagnosis and other predictive factors at baseline.
Limitations, Only prevalent patients were included at baseline and only three dimensions were measured. *Conclusions,* Symptom dimensions predict the future 2-year course of depression and anxiety. Importantly, the dimensions yield predictive information on top of diagnosis and other prognostic factors at baseline.

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7.1 Introduction

Although several predictive factors are known, course predictions for depression and anxiety are usually unspecific. Depression is known to be episodic and sometimes chronic (±20%) (e.g. Keller & Baker, 1992; Ormel et al., 1993; Piccinelli & Wilkinson, 1994), anxiety disorders are known to remit less often (e.g. Keller & Hanks, 1993; Pollack & Otto, 1997; Tiemens et al., 1996), and comorbid depression-anxiety are known to have a particularly unfavourable course (e.g. Shankman & Klein, 2002; Merikangas, 2003; Patten et al., 2010; Penninx et al., 2011). Other predictors of poor prognosis include old age (Penninx et al., 2011), young age-of-onset (Karlsson et al. 2008, Penninx et al. 2011), high severity (van Beljouw et al., 2010, Penninx et al. 2011) and long disorder duration (Conradi et al., 2008).

Still, prognosis varies between individuals with seemingly similar characteristics. To account for this heterogeneity, *symptom-dimensions* could be used as additional predictors, increasing homogeneity, circumventing comorbidity (Widiger & Samuel, 2005) and increasing statistical power (MacCallum et al., 2002). The tripartite model (Clark & Watson, 1991) describes well-validated common and specific dimensions for depression and anxiety (e.g. Keogh & Reidy, 2000; de Beurs et al., 2007). The common dimension of *'General distress (GD)'* covers psychological distress seen in both depression and anxiety and accounts for their comorbidity. The specific dimension of *'Anhedonic depression (AD)'* covers depression-specific anhedonia/energy loss and *'Anxious arousal (AA)'* covers anxiety/panic-specific somatic arousal. Each tripartite dimension was hypothesized to have specific prognostic value (Clark et al., 1995). Indeed, GD and AD were found to predict outcome of depression (Joiner et al., 2000; Lonigan et al., 2003) and generalized anxiety disorder (Chambers et al., 2004) and related dimensions made similar predictions (Geerts & Bouhuys, 1998; Clark et al., 2003). However, there were large methodological differences across studies and the AA-dimension was not often investigated. Moreover, anxiety and comorbid depression-anxiety patients were not accounted for in these studies, hampering the differentiation between the predictive abilities of GD, AD and AA. Importantly, the added value of dimensions on top of known predictors was not evaluated.

Therefore, we investigated the ability and added value of the tripartite dimensions in predicting the 2-year course and outcome of depression, anxiety and comorbid depression-anxiety in a large outpatient cohort (n=992).

7.2 Methods

Participants

Participants came from the Netherlands Study of Depression and Anxiety (NESDA), a large longitudinal cohort study (N=2981) of participants with (n=2329) or without (n=652) a lifetime depressive/anxiety disorder (see Penninx et al. (2008) for details). Exclusion criteria were: not being fluent in Dutch or a psychotic, obsessive-compulsive, bipolar or

severe addiction disorder. Ethical Review Boards of all participating universities approved the study-protocol. All participants signed informed consent.

At baseline, a face-to-face assessment was conducted (demographic/personal information, psychiatric interview, questionnaires) and 2596 (87.1%) participants were followed-up after 2-years. For this study, only current patients were included: 1495 participants had a 1-month diagnosis at baseline or had a 6-month diagnosis and were symptomatic in the month prior to baseline. Of these, 1209 (80.9%) completed the follow-up. Dropouts were younger and lower educated (Lamers et al., 2011). Of these patients, 992 (82.1%) provided all required data to compute dimensional scores and covariates. Incomplete data were associated with fewer years of education ($p<0.001$) but not with age or gender.

Instruments

The adapted Mood and Anxiety Symptoms Questionnaire

To measure the tripartite dimensions at baseline, participants completed the 30-item adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ-D30; Wardenaar et al., 2010; original: Watson et al., 1995) MASQ-D30-items were rated on a 5-point scale and added up to three subscales (GD, AD and AA). The MASQ-D30 was previously shown valid and reliable (Wardenaar et al., 2010).

The course of depression and anxiety

DSM-IV depressive disorders (MDD, Dysthymia) and anxiety disorders (Panic disorder, Social Phobia, GAD, and Agoraphobia) were diagnosed at baseline and follow-up with the Composite Interview Diagnostic Instrument (CIDI, WHO version 2.1; hierarchy-free diagnoses with organic exclusion rules). If participants reported any diagnosis during follow-up on the CIDI, the Life Chart Interview (LCI) was administered: using a calendar method, the presence and severity of depressive or anxiety symptoms was determined for each month during follow-up, using recalled life-events as memory-aids (Lyketsos et al., 1994). Symptom-severity was rated on a 5-point scale (no/minimal, mild, moderate, severe, very severe). The baseline LCI was used to determine the presence of symptoms in the month prior to baseline. The follow-up LCI was used to calculate course-indicators. Symptomatology was only considered present if at least mildly severe and remission was considered present after ≥3 symptom-free months.

Two course indicators were created. The *1-month CIDI diagnosis at follow-up* was defined as follows: (1) being healthy at follow-up, (2) MDD or dysthymia at follow-up, (3) anxiety at follow-up and (4) comorbid MDD and anxiety at follow-up. Additional dichotomous variables were created to test the specific prediction of social phobia, panic disorder, agoraphobia and GAD. The *course trajectory* was defined as follows: (1) early sustained remission (<6 months after baseline), (2) late remission (>6 months after baseline) or recurrence following remission, and (3) chronic course.

Covariates

Following Penninx et al (2011), sociodemographic covariates were age, gender and years of education. Clinical covariates at baseline were: the percentage of symptomatic months during the four years before baseline (based on LCI), the CIDI-based age-at-onset of the baseline disorder (youngest age for comorbid cases). Treatment was not included because a previous study in the same sample found no treatment effects of either antidepressant use or the receipt of psychological interventions on course in multivariate analyses (Penninx et al., 2011).

Statistical analyses

Multinomial regression analyses were used to investigate the associations between the dimensions at baseline on the one hand and diagnosis at follow-up (using 'no diagnosis' as reference) and course trajectory (using 'early-sustained remission' as reference) on the other hand. Additional anxiety-disorder specific associations were tested with logistic regression. Different models were used to investigate if dimensions predicted course independently from diagnosis and demographics. In *model 1*, baseline DSM-IV dummies were added (depression, anxiety and comorbidity). In *model 2*, demographic and clinical covariates were added. $P<0.05$ was considered significant. Analyses were done with SPSS-17 for Windows.

7.3 Results

Baseline characteristics

Of the sample, 66.2% was female and the mean age was 42.5 years (s.d.=12.3, see Table 7.1). Of the participants 227 (22.9%) had a single depressive disorder, 400 (40.3%) had single anxiety, and 365 (36.8%) had comorbid depression-anxiety. At baseline, mean age-at-onset was 20.9 (s.d.=12.5), the mean percentage of months with symptomatology prior to baseline was 31.6 (s.d.=20.1) and 384 participants (38.7%) used antidepressants. AD and AA were weakly correlated (r=0.31) and GD was moderately correlated with both AD (r=0.58) and AA (r=0.48).

Diagnoses at follow-up

At follow-up, 118 participants (11.9%) had single depression, 224 (22.6%) had single anxiety, 178 (17.9%) had comorbid depression-anxiety and 472 (47.6%) had no disorder (see Table 7.2). Only increased baseline AD was associated with increased odds of single depression at follow-up (OR=1.24). Both increased baseline GD and AA were associated with increased odds of comorbid depression-anxiety at follow-up after adjustment (OR=1.25 and OR=1.37). Only increased baseline AA was associated with increased odds of single anxiety after adjustment (OR=1.32). In the analyses with separate anxiety disorders at follow-up (see Table 7.1 for frequencies), baseline AA was only associated with the risk of a panic disorder at follow-up, even when adjusted for panic disorder at baseline (OR=1.66 [95% CI, 1.37-2.02]). In addition, associations between AA and other

anxiety disorders (OR=1.11 to 1.28), overall single anxiety (OR=1.12 [95% CI, 0.93-1.36]) and comorbid depression-anxiety (OR=1.13 [95% CI, 0.92-1.39]) all disappeared when panic-patients were excluded (n=842), indicating that the initially observed predictions of anxiety (and comorbidity) by AA were all driven by AA's specific predictive value for panic disorder.

Course trajectories during follow-up

During follow-up, 252 participants (25.4%) went into early-sustained remission, 324 participants (32.7%) went into late remission or into remission followed by recurrence, and 416 participants (41.9%) had a chronic course (see Table 7.2). Only increased GD was associated with increased odds of unfavorable course.

7.4 Discussion

The current study showed that common and specific dimensions of depression and anxiety, each add specific prognostic information on top of baseline DSM-diagnosis and other prognostic factors. Increased baseline GD was associated with increased odds of comorbid depression-anxiety at follow-up. Increased AD was associated with increased odds of single depression and increased AA was associated with increased odds of anxiety. In addition, increased GD predicted unfavourable course trajectories. These results showed the added value of using three (common GD; specific AD and AA) instead of two (depression and anxiety) dimensions, because each of the former had different implications for prognosis, which would go unnoticed when looking solely at depression and anxiety severity, without accounting for their heterogeneity and overlap. Thus, the results further empirically supported the tripartite model assumptions.

As in previous studies (e.g. Joiner et al., 2000; Lonigan et al., 2003; Clark et al., 2003) AD predicted risk of future depression. Also, AA predicted risk of future anxiety, particularly panic disorder. All associations of AA with other anxiety disorders, but also with comorbid depression-anxiety at follow-up disappeared when participants with a panic disorder were excluded. These results suggest that the prognostic value of AA is limited to panic disorders. Thus, more dimensions are needed to cover all anxiety disorders (e.g. Mineka et al., 1998).

In line with its presumed common role, increased GD only predicted increased risk of future comorbid depression-anxiety. Previously, general distress was also found to be associated with later comorbidity (Chamber et al., 2004). Thus, other findings of associations between GD and depression (Joiner et al., 2000; Lonigan et al., 2003; Clark et al., 2003) were most likely driven by both depression and anxiety in these groups. These findings confirm the idea that comorbidity is mostly accounted for by overlapping symptoms of depression and anxiety, and not by disorder-specific symptom-domains, showing the added value of the tripartite dimensions to increase prognostic differentiation. GD also was the only dimension to predict unfavourable course trajectories; probably because the trajectories were pooled across depressive, anxious and comorbid cases to limit the number of specific trajectory subgroups (5 instead of 12).

Table 7.1: Baseline characteristics of the study group

Baseline variable	Study Group
N	992
% female	66.2%
Mean years of age (s.d.)	42.5 (12.3)
Age range	18-65
Level of education (years), mean (s.d.)	11.9 (3.3)
MASQ-D30 scales: median (Interquartile range)	
General distress	24 (18-32)
Anhedonic depression	40 (34-46)
Anxious arousal	17 (13-21)
Psychiatric Characteristics	
Only depressive disorder (MDD or dysthymia), n (%)	227 (22.9%)
Only anxiety disorder, n (%)*	400 (40.3%)
Panic Disorder, n (%)	170 (42.5%)
Social Anxiety, n (%)	187 (46.8%)
Generalized Anxiety Disorder, n (%)	78 (19.5%)
Agoraphobia (without panic)	65 (16.2%)
Comorbid MDD, dysthymia and anxiety disorders, n (%)	365 (36.8%)
Antidepressant use at baseline, n (%)	384 (38.7%)
Percentage of months with symptoms in past 4 years, mean (s.d.)	31.6 (20.1)
Age of onset of index episode, mean (s.d.)	20.9 (12.5)
Care setting, n (%)	
Primary care	443 (44.7%)
Specialized mental health care	458 (46.2%)
General population	91 (9.2%)

SD, standard deviation; MASQ-D30, Mood and Anxiety Symptoms Questionnaire Dutch short adaptation; IDS-SR, Inventory of Depressive Symptomatology Self Report; FQ, Fear Questionnaire.
*) 63 patient with single Social phobia, 46 with Panic disorder, 33 with Agoraphobia, 15 with GAD, 5 with Panic disorder + GAD, 18 with panic disorder + social phobia, 3 with GAD + Agoraphobia, 8 with GAD + Social phobia, 12 with Social phobia + Agoraphobia, 9 with >2 anxiety diagnoses.

GD is often described as a general indicator of depression and anxiety severity (Clark & Watson, 1991; Mineka et al., 1998). Thus, its general predictive value for course trajectories was in line with expectations. However, it also pointed out that depression or anxiety-specific symptoms had no overall prognostic value.

From a clinical perspective, the current findings indicate that within a group of patients with the same diagnosis, *dimensions* capture inter-individual differences in symptomatology, which account for differences in prognosis. For instance, varying levels of AA in a depressed group could reflect varying risk of future (comorbid) panic disorder and varying levels of AD in a panic disorder group could reflect varying risk of future (comorbid) depression. Eventually, symptom dimensions could become part of routine risk assessment, which may for instance be useful to judge the potential efficacy of therapy (Sotsky et al., 1991).

The present study had several strengths, including a large sample size, systematic course assessments and thorough statistical adjustment. However, there were also study-limitations. (1) Sample attrition may have caused selection and/or attrition bias. (2) Only three symptom dimensions were used, whereas much more dimensions may exist (Den Hollander-Gijsman et al., 2010; 2011). (3) Only prevalent cases were included at baseline, excluding incident cases during the follow-up period. (4) Not all anxiety disorders (e.g. post-traumatic stress disorder) were assessed at baseline. Future research could focus on a broader range of more specific sub-dimensions and multiple dimensional assessments over time.

Table 7.2: Associations of the tripartite dimensions at baseline with the 1-month diagnosis at follow-up and the 2-year course trajectories of depression and/or anxiety in 992 psychiatric outpatients.

MASQ-D30 Dimension & Model	Diagnosis at follow-up				Course-trajectory during follow-up		
	Healthy (n=438)	Depression (n=115) OR (95% CI)	Anxiety (n=211) OR (95% CI)	Depression and anxiety (n=177) OR (95% CI)	Early remission (n=252)	Late remission/ recurrence & remission (n=324) OR (95% CI)	Chronic Course (n=416) OR (95% CI)
GeneralDistress:							
Crude	Ref.	1.16 (0.99-1.35)	1.06 (0.93-1.20)	1.30 (1.13-1.50)***	Ref.	1.24 (1.08-1.43)**	1.29 (1.13-1.47)***
Model 1	Ref.	1.11 (0.94-1.30)	1.09 (0.95-1.24)	1.27 (1.09-1.47)**	Ref.	1.24 (1.08-1.43)**	1.27 (1.10-1.45)***
Model 2	Ref.	1.12 (0.94-1.33)	1.01 (0.88-1.17)	1.25 (1.07-1.45)**	Ref.	1.21 (1.05-1.41)**	1.21 (1.04-1.39)*
Anhedonic Depression:							
Crude	Ref.	1.36 (1.15-1.59)***	1.00 (0.89-1.12)	1.19 (1.03-1.38)*	Ref.	1.05 (0.93-1.18)	1.09 (0.97-1.22)
Model 1	Ref.	1.27 (1.08-1.50)**	1.05 (0.93-1.18)	1.18 (1.02-1.37)*	Ref.	1.05 (0.93-1.18)	1.10 (0.98-1.24)
Model 2	Ref.	1.24 (1.05-1.46)*	1.05 (0.92-1.19)	1.14 (0.98-1.33)	Ref.	1.06 (0.94-1.20)	1.10 (0.97-1.24)
AnxiousArousal:							
Crude	Ref.	0.99 (0.82-1.20)	1.35 (1.16-1.56)***	1.43 (1.22-1.67)***	Ref.	1.05 (0.89-1.21)	1.19 (1.02-1.39)**
Model 1	Ref.	0.97 (0.80-1.18)	1.28 (1.10-1.49)**	1.35 (1.15-1.59)***	Ref.	1.03 (0.88-1.21)	1.11 (0.95-1.29)
Model 2	Ref.	0.97 (0.80-1.19)	1.32 (1.12-1.55)**	1.37 (1.16-1.62)***	Ref.	1.02 (0.87-1.21)	1.13 (0.96-1.32)

Results of multinomial regression analyses: Odds Ratio's (OR) are given for 5-point increments on each dimension with 95% Confidence intervals (CI). MASQ-D30=Mood and Anxiety Symptoms Questionnaire Dutch 30-item adaptation.

Crude: dimensions adjusted for each other; Model 1: adjusted for DSM-IV diagnosis; Model 2: additionally adjusted for age, gender, years of education, duration of disorder at baseline, age of onset of the disorder at baseline.

*p<0.05, **p<0.01, ***p<0.001.