CHAPTER 3

COMORBID DEPRESSION AND ANXIETY: SYMPTOM AND FUNCTIONAL SEVERITY IN THE CLINICAL SETTING

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Abstract

Background
Comorbidity between depression and anxiety disorders is widely understood to be associated with poorer outcome, increased symptom severity and more functional impairment. However, symptom severity and functional impairment in comorbidity have not been compared directly to those in pure depression and pure anxiety disorder in general psychiatric patient samples. The aim of this study is to determine in a large outpatient sample whether patients with comorbidity have increased symptom severity and greater functional impairment as compared to patients with only a depressive or an anxiety disorder.

Method
Analyses were performed on a large sample consisting of 2278 outpatients with a depression and/or an anxiety disorder from a general psychiatric setting. We studied the relation of diagnostic status with global severity, functional severity, depression severity and anxiety severity.

Results
Symptom severity (global severity, depression severity and anxiety severity) and functional impairment were increased in the comorbid group as compared to the pure groups. Depression severity in the comorbid group was higher than in the pure depression group and anxiety severity in the comorbid group was higher than in the pure anxiety group. The latter was also the case when analyses were repeated for specific DSM-IV anxiety disorders.

Conclusions
In a large general psychiatric outpatient sample comorbidity is associated with increased depressive and anxiety severity, and increased functional impairment.

3.1 Introduction

High rates of comorbidity between anxiety disorders and depression have been reported in the general population (Kessler et al., 1996), in primary care (Roca et al., 2009) and in secondary care (Brown et al., 2001). Comorbidity between depression and anxiety disorders is widely understood to be associated with increased severity, poorer outcome and more functional impairment. Researchers have argued that comorbidity of depression and anxiety disorders even warrants a separate diagnosis (e.g. Tyrer, 2001; Silverstone & Von Studnitz E., 2003). The appreciation of the importance of comorbidity is also reflected in the goals set for the next version of the Diagnostic and Statistical Manual (DSM)-5, as this version should enable clinicians and researchers to take the presence and effects of comorbidity into account (www.dsm5.org).

However, contrary to many studies on the prevalence of comorbidity or its effects on disease outcome (Emmanuel, Simmonds, & Tyrer, 1998), studies reporting on the severity of depressive and anxiety symptoms in comorbidity usually did not include the full spectrum of symptomatology. In these studies, only depression with and without comorbid anxiety disorders (e.g. Dalrymple & Zimmerman, 2007; Fava et al., 2004), or only anxiety disorders with and without comorbid depression (Kaufman & Charney, 2000), but never the three groups together, were examined. Furthermore, these studies have only been performed in the general population or in samples from specialized psychiatric care settings, or did assess only the severity of one type of symptoms (depressive or anxiety) or the impact of comorbidity of depression and anxiety on general distress and daily functioning (Pirkola et al., 2003; Wittchen, Carter, Pfister, Montgomery, & Kessler, 2000).

It is of relevance for routine clinical practice and for the ongoing research into the nature and consequences of comorbidity, to obtain more insight in the severity of depressive and anxiety symptoms and their effects on functioning in patients with comorbidity in routine general psychiatric practice settings. In this study, we examined the severity of depressive and anxiety symptoms and the related functional impairment of patients with comorbid and pure mood and anxiety disorders in a large naturalistic routine psychiatric outpatient sample. We hypothesized that patients with comorbidity of depression and anxiety disorders would have 1) a higher global symptom severity than patients with only one disorder, 2) more severe depressive symptoms than patients with a pure depression, 3) more severe anxiety symptoms than patients with a pure anxiety disorder and 4) a higher severity of functional impairment than patients with a pure depression or a pure anxiety disorder. Because one can expect different effects for different anxiety disorders, we also tested the third hypothesis for specific anxiety disorders.

3.2 Method

Routine Outcome Monitoring

This study was conducted on data collected through Routine Outcome Monitoring (ROM, (De Beurs et al., 2011)). ROM is an ongoing monitoring system for patient care, implemented in the outpatient clinics of Rivierduinen (a large organization for the provision of mental health care in the province of Zuid-Holland, the Netherlands) and the Department of Psychiatry of the Leiden University Medical Center (LUMC). All patients referred to these clinics for treatment of a mood-, anxiety- or somatoform disorder, have assessment sessions with a psychiatric research nurse at the start, during, and at the end of the treatment (De Beurs et al., 2011). For this study, the baseline ROM-assessments were used. During these baseline assessments, a standardized diagnostic interview is administered and interviewer and self-reported ratings are completed. ROM data are primarily used for diagnosis and to inform clinicians and patients about treatment progress. The use of anonymous data of these patients for research purposes has been approved by the Medical Ethical Committee of the Leiden University Medical Center.

Sample

The initial group consisted of 3798 outpatients admitted consecutively between January 2004 and December 2006. For the present study, three diagnostic groups of patients were selected (total n=2278): (1) patients with one or more anxiety disorders and no depression (n=729), (2) patients with a depression and no anxiety disorders (n=860) and (3) patients with comorbid an anxiety disorder and a depression (n=689). The diagnosis 'depression' includes both Major Depressive Disorder (MDD) and dysthymia (respectively 62,6% and 5.4% of the total sample (n=2278)), but not bipolar disorder. The majority of the patients that were not included in this study had a single or comorbid somatoform disorder.

Instruments

Mini International Neuropsychiatric Interview (M.I.N.I.) - Plus 5.0.0.-R

To establish the presence of current and life-time Axis-I disorders according to the DSM-IV diagnostic criteria, The Dutch translation of the M.I.N.I.-Plus 5.0.0-R (Van Vliet, Leroy, & van Megen, 2000) was used (Sheehan et al., 1998). The M.I.N.I.-Plus is an extended version of the original M.I.N.I. Lecrubier and colleagues (Lecrubier et al., 1997) report sufficient reliability of the M.I.N.I (k=0.88-1.00; test-retest reliability= 0.76-0.93). Validity was demonstrated by sufficient concordance with the Composite International Diagnostic Interview (CIDI, WHO). Interviews were performed by extensively trained and supervised psychiatric research nurses. All diagnoses reported in this study were current at the time of assessment. In the M.I.N.I.-Plus some hierarchical exclusion rules

apply: in case of a current depression diagnosis, concurrent dysthymia is ruled out. Depression, and generalized anxiety disorder (GAD) can only be diagnosed concurrently if both disorders have a different time of onset.

Brief Symptom Inventory
The Brief Symptom Inventory (BSI) (Derogatis & Melisaratos, 1983; De Beurs, 2005) is a shortened version of the Symptom Checklist (SCL-90) (Derogatis, Lipman, & Covi, 1973) , and is used to measure psychological complaints or symptoms. The BSI consists of 53 items, rated on a five-point Likert scale, ranging from 0 (not at all) to 4 (very much). The items are subdivided into nine subdimensions: 1) somatic complaints; 2) cognitive problems; 3) interpersonal sensitivity; 4) depression; 5) anxiety; 6) hostility; 7) phobic fear; 8) paranoid ideation, and 9) psychoticism. The average score of all 53 items is the BSI-Global Severity Index (BSI-GSI), which is an overall measure of psychopathology severity. In the current study the BSI-GSI and the anxiety and depression subscale (BSI-ANX and BSI-DEP) were used.

Rating scales for symptom severity of depression and anxiety
Research nurses rated the symptom severity of depression on the 10-item Montgomery Åsberg Depression Rating Scale (MADRS; (Montgomery & Åsberg, 1979)) and anxiety on the 10-item Brief Anxiety Scale (BAS; (Tyrer, Owen, & Cicchetti, 1984)). Items on both scales (e.g., "pessimistic thoughts", "worries about minor issues") are rated on a 7-point scale anchored at 4 points (1, 3, 5, and 7).

SF-36 Health Survey
Functional status was measured with the SF-36 Health Survey (Aaronson et al., 1998; Ware, Jr. & Sherbourne, 1992). The SF-36 is composed of 36 questions and standardized response choices, organized into eight multi-item scales: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and general mental health (MH). All raw scale scores are linearly converted to a 0 to 100 scale, with higher scores indicating higher levels of functioning or well-being.

Demographic characteristics
Ethnic background, education, housing situation and employment status were assessed with a self-report questionnaire. A Dutch ethnic background was assumed when the patient and both parents were born in The Netherlands.

Statistical analyses

To investigate differences between the three diagnostic groups on socio-demographic variables, chi-square tests were used on categorical variables and analyses of variance (ANOVA) on continuous variables. To test our hypotheses, we performed several ANOVAs with the severity measures as dependent variables and with diagnostic group as independent variable with 3 levels (1: pure anxiety, 2: pure depression, 3: comorbid depression and anxiety).

Subsequently, we performed separate analyses for several specific anxiety disorders: obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), agoraphobia (AGO), panic disorder (PD) and panic disorder combined with agoraphobia (PD-AGO). For these analyses, we selected patients with singular anxiety disorders. To investigate differences between patients with- and without a comorbid depression in each of these anxiety disorders, we used t-tests with BSI-ANX as dependent variable and the presence of comorbidity as independent variable with two levels (1: only anxiety 2: anxiety and depression).

To investigate the role of age as a possible confounder, all analyses were rerun with Age as covariate. All analyses were conducted using SPSS 17. Casewise deletion was used, which resulted in different numbers for the analyses on different outcome measures.

3.3 Results

Sample characteristics

The demographic characteristics of the subjects arranged by diagnostic group are shown in Table 3.1. In the total sample (n=2278) mean age was 38.4 (SD=13.0) and 64.4% were women. A complete survey of demographic variables was available for 1919 (84%) patients in our sample. The percentage of patients with a completed survey did not differ significantly between the three diagnostic groups (resp. 85%, 85% and 83%).

No differences between the three diagnostic groups were found for gender and housing situation. The mean age did differ significantly between the three groups; the highest mean age was found in patients with a pure depression (mean age=41.0; SD=13.8). Other significant differences were found for ethnic background, educational status and employment status. Within the group 'pure anxiety' the number of patients with a Dutch ethnic background was higher than in the other two groups. Patients with comorbidity revealed a slightly lower percentage of patients with college education and a higher percentage of patients unable to work due to their sickness of disability.

	Total	Pure Anxiety	Pure Depression	Anxiety and depression	p-value
n	2278	729	860	689	
Gender (% female)	64.4	63.1	64.1	66.2	.47
Mean age (sd)	38.8 (13.0)	35.8 (12.4)$_a$	41.0 (13.8)$_b$	38.0 (12.0)$_c$	<0.001
n	1919	617	733	569	
Ethnic background (%)					.03
- Dutch	80.6	84.1	79.1	78.6	
- Other ethnicity	19.4	15.9	20.9	21.4	
Housing situation (%)					.53
- Living alone	25.7	24.5	27.6	24.6	
- Living with partner	49.9	51.1	49.4	49.2	
- Living with family	24.4	24.5	23.1	26.2	
Educational status (%)					<.001
- Lower education	10.4	7.0	11.1	13.4	
- High school (lower)	33.8	32.1	34.2	35.0	
- High school (higher)	38.4	41.8	35.5	38.3	
- College/university	17.5	19.1	19.2	13.4	
Employment status (%)					<.001
- Employed - part time	21.6	26.3	21.8	16.2	
- Employed - full time	22.0	29.3	20.3	16.2	
- Unemployed/retired	28.9	25.6	30.6	30.2	
- Unable to work due to sickness or disability	27.6	18.8	27.3	37.4	

Note. Means having a different subscript are significantly different at $p < .05$ in the Tukey difference comparison.

Table 3.1 Characteristics by diagnostic groups: gender and age and demographic variables.

Subscale mean (sd)	Pure Anxiety (n=705)	Pure Depression (n=833)	Anxiety and depression (n=663)	F (df: 2, 2198)	p-value
BSI-GSI	1.06 (0.61)$_a$	1.35 (0.66)$_b$	1.74 (0.73)$_c$	180.00	<.001
Symptoms of depression					
- BSI-DEP	1.12 (0.85)$_a$	2.00 (0.92)$_b$	2.23 (0.96)$_c$	291.32	<.001
- MADRS	13.77 (8.02)$_a$	23.30 (7.91)$_b$	25.49 (8.16)$_c$	429.39	<.001
Symptoms of anxiety					
- BSI-ANX	1.45 (0.91)$_a$	1.34 (0.87)$_a$	1.96 (0.97)$_b$	92.86	<.001
- BAS	14.32 (6.47)$_a$	14.71 (5.70)$_a$	19.05 (6.66)$_b$	123.81	<.001

Note. MADRS = Montgomery - Åsberg Depression Rating Scale; BAS = Brief Anxiety Scale; BSI = Brief Symptom Inventory. BSI-GSI = global severity index. BSI-DEP = depression subscale. BSI-ANX = anxiety subscale.
Means having a different subscript are significantly different at $p < .05$ in the Tukey difference comparison.

Table 3.2 Global symptom severity and symptoms of depression and anxiety by diagnostic group in 2201 outpatients.

Diagnostic groups

Global Severity Index

The ANOVA with the BSI-GSI as dependent variable showed a significant overall-effect of diagnostic group ($p<0.001$). The pure anxiety group had a lower mean BSI-GSI than the pure depression group; the comorbid group had a higher mean BSI-GSI than both pure disorder groups (See Table 3.2).

Depression severity

The ANOVAs with measures of depression severity (BSI-DEP and MADRS) as dependent variable showed a significant overall-effect of diagnosis ($p<0.001$). The pure anxiety group had lower mean BSI-DEP and MADRS scores than the pure depression; the comorbid group had higher mean scores than both pure disorder groups (See Table 3.2).

Anxiety severity

The ANOVAs with the two measures of anxiety severity (BSI-ANX and BAS) as dependent variable showed a significant overall-effect of diagnostic group ($p<0.001$). The comorbid group had higher mean BSI-ANX and BAS scores than

both pure disorder groups; the scores did not differ between the pure groups (See Table 3.2).

Functional severity
The ANOVAs with each of the subscales of the SF-36 as dependent variable showed an overall effect of diagnostic group on all scales ($p<0.001$). The pure anxiety group had a higher mean score than the pure depression group on all subscales (i.e. a less severe functional impairment). The comorbid group had lower mean scores (i.e. higher functional impairment) than each of the pure groups (See Table 3.3). Only on the subscale 'Role limitations due to emotional problems (RE)', the comorbid group did not have a significant lower score than the pure depression group.

Because four of the eight subscales of the SF-36 had a skewed distribution, these variables were log-transformed (PF, BP) or dichotomized (RP, RE). Subsequently, to evaluate the impact of the skewness on the results, we repeated the analyses with the transformed variables: ANOVAs with the continuous outcome variables (PF, BP) and chi-square tests in with the dichotomous outcome variables (RP, RE). The results for the transformed SF-36 scales were highly similar to the results for the untransformed scales (See Table 3.3): all group differences were significant for all subscales except for RE, and in the same direction.

Specific anxiety disorders
The mean scores on BSI-ANX were compared between specific anxiety disorders with and without comorbid depression; mean BSI-ANX scores for the different groups are shown in Figure 3.1. T-tests revealed that in all but one of the specific anxiety disorder groups, the score on the BSI-ANX was significantly higher in patients with a comorbid depression compared to patients with only an anxiety disorder. Only for patients with GAD, mean scores on the BSI-ANX did not differ between the pure GAD group and the group with GAD and depression.

Adjustment for age
When the analyses were adjusted for age, only the difference in BSI-ANX between patients with a panic disorder and agoraphobia with and without a comorbid depression was no longer significant. All other effects remained unchanged.

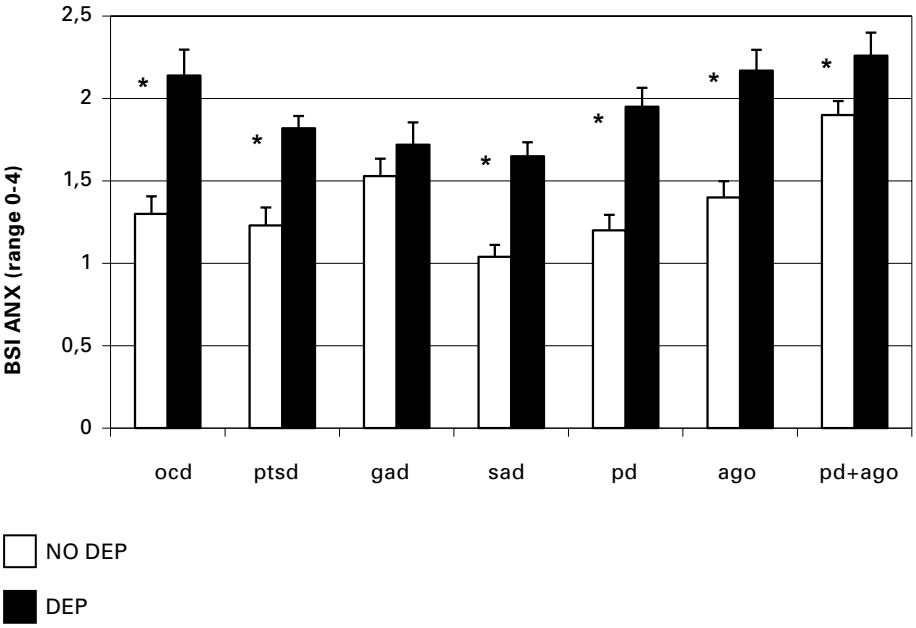
3.4 Discussion
We examined the severity of depressive and anxiety symptoms as well as functional impairment in patients with comorbid depression and anxiety disorders compared to those in pure disorders in a large general psychiatric

SF-36 subscale mean (sd)	Pure Anxiety (n=696)	Pure Depression (n=815)	Anxiety and depression (n=641)	F (df: 2, 2150)	p-value
Physical functioning (PF)	82.9 (20.5)a	73.6 (24.0)b	70.5 (24.4)c	54.06	<.001
Social functioning (SF)	55.8 (25.7)a	41.4 (25.3)b	34.8 (22.7)c	128.7	<.001
Role limitations due to physical health problems (RP)	54.5 (41.9)a	36.4 (38.7)b	30.4 (37.5)c	69.8	<.001
Role limitations due to emotional problems (RE)	41.5 (40.3)a	22.6 (32.0)b	19.3 (29.7)b	84.66	<.001
General mental health (MH)	50.3 (16.5)a	35.8 (16.0)b	31.9 (14.2)c	264.3	<.001
Vitality (VT)	45.2 (17.4)a	29.9 (15.6)b	27.5 (14.9)c	250.3	<.001
Bodily pain (BP)	75.8 (24.2)a	66.2 (27.1)b	61.5 (28.6)c	50.8	<.001
General health perception (GH)	58.9 (20.8)a	51.6 (21.1)b	47.5 (19.8)c	53.23	<.001

Note. SF-36 denotes Short Form 36 (RAND 36). Scores are on a 100 point-scale. A higher score corresponds to better functioning / health status. Means having a different subscript are significantly different at $p < .05$ in the Tukey difference comparison.

Table 3.3 Functional severity (SF-36 subscales) by diagnostic group in 2153 outpatients.

outpatient sample. The results confirmed our hypotheses and showed that in routine clinical practice, patients with comorbidity have a higher global and specific symptom severity and suffer more from severe functional impairment than patients with a pure depressive or anxiety disorder. Our main finding is that depression severity in the comorbid group was higher than that in the pure depression group, and anxiety severity in the comorbid group was higher than that of the pure anxiety group. Apparently, having an anxiety disorder in addition to a depression does not only increase the severity of anxiety symptoms, but also the severity of depressive symptoms. Similarly, having a depression in addition to an anxiety disorder does not only increase the



BSI ANX = anxiety subscale. NO DEP = no concurrent depression, DEP = concurrent depression. OCD = obsessive compulsive disorder, PTSD = posttraumatic stress disorder, GAD = generalized anxiety disorder, SAD = social anxiety disorder, PD = panic disorder, AGO = agoraphobia, PD+AGO = Panic disorder combined with agoraphobia.
*= p-value < 0.05 (t-test).

Figure 3.1 Mean (std error) scores on BSI anxiety scale for specific anxiety disorders without and with comorbidity with depression.

severity of depressive symptoms, but also the severity of anxiety symptoms. The latter was also the case when analyses were repeated for specific DSM-IV anxiety disorders.

Our findings are in line with the extended literature on comorbidity. Several studies found within a group of patients with MDD, that those with many anxiety symptoms were more severely depressed (e.g. Fava et al., 2004; Joffe, Bagby, & Levitt, 1993). Other studies focused on a specific anxiety disorder and reported higher anxiety severity or functional impairment (e.g. Wittchen et al., 2000; Cassin, Richter, Zhang, & Rector, 2009) in patients with comorbidity. We replicated these findings in a sample of patients with pure depression, pure

anxiety disorders and patients with comorbidity of depression and anxiety. With this study design, the symptom severity of the pure disorders could also be taken into account. Our data show that many patients with a 'pure' DSM IV depression also have anxiety symptoms, and patients with a 'pure' DSM IV anxiety disorder also have depressive symptoms. Moreover, we found that the mean scores on the anxiety measures (BSI-anx & BAS) did not differ significantly between patients with a pure depression and patients with a pure anxiety disorder.

Our findings are limited by the fact that we had no control group of subjects derived from the general population. This would have enabled us to determine whether the effect of diagnostic group on severity is cumulative or interactive, i.e. whether the increased symptom severity in comorbid patients equals the sum of the severity scores of the separate diagnoses or whether severity is exponentially increased when more than one diagnosis is present.

The finding that patients with comorbidity have increased anxiety severity compared to patients with a pure anxiety disorder was replicated for subgroups of patients with OCD, PTSS, PD, SAD, and Agoraphobia in our study. However, there was no difference in severity of anxiety symptoms for patients with comorbid depression in the subgroup of patients with GAD. Also, GAD revealed the highest score on depressive symptoms compared to the other anxiety disorders. This finding is in line with previous studies on the structure of DSM-IV anxiety and depression diagnoses that have shown that GAD is best grouped together with depression in a cluster of distress disorders, whereas all other anxiety disorders are grouped together in another class of fear disorders (Krueger, 1999; Watson, 2005). Our results provide further evidence that GAD might be more closely linked to depression than to other anxiety disorders.

An important strength of the current study is the large size and representativeness of the used sample. Also, the included patients were all well characterized and the sample comprised both a broad range of pure disorders and different forms of comorbidity, which enabled us to investigate the influence of comorbid depression in patients with different specific anxiety disorders. Moreover, we examined functional impairment in addition to symptom severity.

We believe that our findings give further support to the claims that depression and anxiety disorders should not be investigated in isolation (e.g. Beuke, Fischer, & McDowall, 2003). Moreover, the findings are in line with the idea that 'the use of categorical diagnostic approaches and dimensional rating scale in tandem will facilitate identification of meaningful phenotypes for future genetic, biochemical, neuroimaging, and treatment studies' (pag.73, Kaufman & Charney, 2000). This is not only relevant for research, but also for clinical practice. When using both a diagnostic interview and several severity measures at intake, a large amount of additional relevant information becomes

available to the clinician. This information can help to decide which treatment is most suitable for the patient at hand, and at follow-up, what effect the treatment has on different sorts of symptoms. Ultimately, large sets of these naturalistic data could be used to find an optimal treatment approach for patients with comorbid depression and anxiety.