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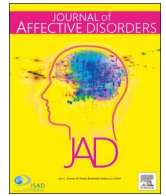
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Research paper

The influence of comorbid anxiety on the effectiveness of Cognitive Therapy and Interpersonal Psychotherapy for Major Depressive Disorder

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ABSTRACT

Background: Anxious depression is an important subtype of Major Depressive Disorder (MDD) defined by both syndromal (anxiety disorders) and dimensional (anxiety symptoms) criteria. A debated question is how anxiety affects MDD treatment. This study examined the impact of comorbid anxiety disorders and symptoms on the effectiveness of and dropout during Cognitive Therapy (CT) and Interpersonal Psychotherapy (IPT) for MDD.

Methods: Depressed individuals were randomized to CT ($n = 76$) or IPT ($n = 75$). Outcome was depression severity measured with the Beck Depression Inventory-II (BDI-II) at the start of each therapy session, post treatment, and monthly up to five months follow-up. Anxiety disorders were assessed with the Structured Clinical Interview for DSM-IV Axis I disorders, (phobic) anxiety symptoms were assessed with Brief Symptom Inventory subscales.

Results: Approximately one third of participants had a comorbid anxiety disorder. Comorbid anxiety disorders and anxiety symptoms were associated with less favorable depression change during IPT as compared to CT in the treatment phase, but not in the trial follow-up phase. Individuals with a comorbid anxiety disorder had significantly higher treatment dropout during both treatments.

Limitations: Not all therapists and participants were blind to the assessment of comorbid anxiety disorders and the assessments were performed by one rater.

Conclusions: A preference for CT over IPT for MDD is justifiable when comorbid anxiety is present, although long-term differences are not established and replication of this finding is needed. Clinicians should be aware of the risk of dropout for depressed individuals with an anxiety disorder.

1. Introduction

Given high comorbid anxiety in Major Depressive Disorder (MDD), anxious depression is considered to be an important subtype (American Psychiatric Association, 2013; Rao and Zisook, 2009; Ten Have et al., 2016). This subtype can be defined as MDD with a comorbid anxiety disorder (syndromal definition) or subthreshold comorbid anxiety symptoms (dimensional definition) (Ionescu et al., 2013; Rao and Zisook, 2009). For both definitions, anxious depression has been associated with a severe clinical picture including more severe depressive symptoms (Brown et al., 1996; Fava et al., 2004; Penninx et al., 2011; Smits et al., 2009), more functional impairment (Fava et al., 2004;

Smits et al., 2009) and intensified suicidal thoughts and behavior (Brown et al., 1996; Fava et al., 2004; Fawcett et al., 1990; Pfeiffer et al., 2009). With these profound clinical disadvantages, one could expect an adverse effect of comorbid anxiety on MDD treatment outcome and treatment continuation. However, findings regarding the impact of comorbid anxiety on MDD treatment outcome and dropout are inconsistent for both pharmacotherapy and psychotherapy, and there has been little agreement on tailored treatment recommendations.

Studies examining the effects of antidepressants found that individuals with comorbid anxiety disorders had less favorable outcomes (Howland et al., 2009; Lee et al., 2012) and higher dropout rates (Arnouk et al., 2007; Howland et al., 2009). In contrast to anxiety

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disorders, the impact of comorbid anxiety symptoms on MDD outcome varied from lower response and remission rates (Davidson et al., 2002; Fava et al., 2008; Flint and Rifat, 1997; Frank et al., 2011; Papakostas et al., 2008; Wiethoff et al., 2010) to no adverse effects (Forand and Derubeis, 2013; Fournier et al., 2009; Joffe et al., 1993; Nelson, 2010; Russell et al., 2001; Tollefson et al., 1994). In addition, anxiety symptoms were not associated with dropout in other antidepressant trials (Flint and Rifat, 1997; Fournier et al., 2009; Russell et al., 2001; Tollefson et al., 1994; Wiethoff et al., 2010).

In psychotherapy research, findings on the influence of comorbid anxiety on treatment outcome and continuation are even more inconclusive. Two effective and frequently applied psychotherapies for MDD are Cognitive Therapy (CT) and Interpersonal Psychotherapy (IPT). Most of the psychotherapy studies that examined the impact of comorbid anxiety on MDD outcome focused on CT. Overall, CT studies did not show an adverse effect of anxiety on MDD outcome. Several studies showed similar treatment outcomes for individuals with and without anxiety disorders or with and without anxiety symptoms (Brent et al., 1998; Forand and Derubeis, 2013; Fournier et al., 2009; McEvoy and Nathan, 2007; Persons et al., 2006; Smits et al., 2009). Surprisingly, other CT studies reported a more accelerated depressive symptom improvement when comorbid anxiety disorders or symptoms were present (de Azevedo Cardoso et al., 2014; Forand et al., 2011; Kashdan and Roberts, 2011; Rohde et al., 2001; Smits et al., 2012). With regard to treatment continuation, in the majority of CT studies, anxiety disorders (Forand et al., 2011; Kashdan and Roberts, 2011; Rohde et al., 2001; Schindler et al., 2013; Smits et al., 2009) and anxiety symptoms (Forand et al., 2011; Fournier et al., 2009; McEvoy and Nathan, 2007; Smits et al., 2012) did not affect treatment dropout, although one study reported higher dropout rates for individuals with a comorbid anxiety disorder (Arnouk et al., 2007). For IPT, fewer findings on the impact of comorbid anxiety on MDD treatment outcome and completion are available. In contrast to CT, findings of these studies suggest an adverse effect of (lifetime) anxiety disorders and anxiety symptoms on MDD outcome (Brown et al., 1996; Frank et al., 2011, 2000; Young et al., 2006). In addition, one study reported higher dropout rates for individuals with lifetime anxiety disorders as compared to individuals without lifetime anxiety disorders (Brown et al., 1996). To date, there are no head-to-head comparisons of CT and IPT focusing on anxious depression, although one study showed that axis I disorders *in general* did not predict (differential) MDD treatment outcomes for CT and IPT (Carter et al., 2011).

A possible explanation for these mixed results is the use of different definitions to classify anxious depression (Ionescu et al., 2013). This concern is illustrated by a recent study that showed that the syndromal and dimensional definitions of anxious depression classify two different groups of individuals under the same “anxious depression” label (van der Veen et al., 2014). This lack of overlap is not surprising; the syndromal definition refers to two distinct disorders, while the dimensional criteria define a certain subtype of depression. These different conceptualizations of anxious depression are however a major concern for integrating the outcomes of previous studies into broader knowledge and translating findings to clinical practice. In addition, mixed results could be explained by small study samples and the different measures of anxiety disorders and anxiety symptoms. Anxiety disorders diagnoses are measured both lifetime and current, with different types of instruments. Furthermore, diagnosing a distinct anxiety disorder from an acute phase depression can be challenging. For anxiety symptoms, some studies used specific anxiety oriented instruments while others used the Anxiety/Somatization Factor of the Hamilton Rating Scale for Depression (Fava et al., 2000).

The aim of this study was to examine the (differential) effect of comorbid anxiety on the effectiveness and treatment continuation of CT and IPT for MDD in a head-to-head comparison. In order to confirm the assumption that the syndromal definition of anxious depression is different from the dimensional one, the impact of anxiety disorders,

anxiety symptoms (i.e. generalized anxiety symptoms), and phobic anxiety symptoms (i.e. agoraphobic symptoms) was examined separately. Based on previous studies, we expected no adverse effect of comorbid anxiety on MDD treatment outcomes and completion for CT. Based on the limited research available for IPT, one could expect less favorable outcomes and higher dropout rates for individuals with comorbid anxiety disorders or symptoms treated with IPT.

2. Method

2.1. Study design

Data were collected in the context of a randomized controlled trial examining the effectiveness of CT and IPT for MDD. Individuals with a primary MDD diagnosis as confirmed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I, First et al., 1995) by trained clinicians were recruited from the mood disorders unit of the Maastricht Outpatient Mental Health Center (RIAGG Maastricht). Additional inclusion criteria were: internet access, an email address, and sufficient knowledge of the Dutch language. Exclusion criteria were a bipolar or chronic depression (current episode > 5 years), elevated acute suicide risk, concomitant pharmacological or psychological treatment, drugs and alcohol abuse/dependence, and mental retardation (IQ < 80). A total of 1562 individuals were screened for eligibility. Of these 1562 individuals, 1191 did not meet the inclusion criteria (main reasons were the use of antidepressant medication ($n = 362$) or MDD not being the primary diagnosis ($n = 434$), 78 patients met inclusion criteria but refused to participate, and 111 were excluded for other reasons. A total of 182 depressed outpatients were randomly allocated to CT ($n = 76$), IPT ($n = 75$), or a 2-month waiting-list control condition followed by treatment of choice ($n = 31$). For the current analyses, we limited the sample to data of individuals randomized to the active conditions CT and IPT ($n = 151$) in the acute phase of therapy (month 0–7) and a trial follow-up phase (month 7–12). The study was approved by the Medical Ethics Committee of Maastricht University Medical Center, written informed consent was obtained, and the study was registered at isrctn.com (identifier: ISRCTN 67561918). A detailed description about the study design and main outcomes are provided elsewhere (Lemmens et al., 2015, 2011).

2.2. Treatments and therapists

CT and IPT were carried out using the guidelines by Beck et al. (1979) for CT, and the guidelines by Klerman et al. (1984) for IPT. Participants received 16–20 sessions of 45 min (17 sessions on average, $SD = 2.9$) by ten experienced licensed psychologist, psychotherapists, and psychiatrists (9.1 years of clinical experience on average, $SD = 5.4$, range 4–21 years). Therapists were already trained in the treatment modality that they delivered in the study, but received additional training (2 × 8 h) by Steven Hollon (CT) and John Markowitz (IPT) prior to the start of the study, and delivered exclusively CT or IPT. Sessions were scheduled weekly and allowed to be less frequent planned towards the end of therapy. All sessions were videotaped and a random selection of 106 tapes were examined on treatment competence (i.e. quality of treatment) and adherence (i.e. therapy-specific behavior) by independent raters. Treatment competence was rated good to excellent using the Cognitive Therapy Scale for CT (Dobson et al., 1985, $M = 3.31$, $SD = 0.93$) and the short version of the IPT Adherence and Quality Scale for IPT (Stuart, 2011, $M = 3.50$, $SD = 0.70$). The Collaborative Study Psychotherapy Rating Scale version 6 (Hollon et al., 1984, 1988) indicated significant differences in therapy-specific behavior between CT and IPT with higher CT-specific behavior in CT as compared to IPT ($M = 80.80$, $SD = 25.64$ vs. $M = 52.42$, $SD = 13.00$ $t = 7.23$, $p < 0.001$), and higher IPT-specific behavior in IPT as compared to CT ($M = 85.75$, $SD = 23.22$ vs. $M = 44.57$, $SD = 15.06$, $t = 10.79$, $p < 0.001$) (Lemmens et al., 2015). Anxiety disorders,

phobic anxiety symptoms and anxiety symptoms did not change quality of treatment or therapy-specific behavior of the therapists (results not shown, all p -values > 0.3).

2.3. Measures

2.3.1. Primary outcome

The primary outcome, depression severity was measured with the Beck Depression Inventory, second edition (Beck et al., 1996), a 21-item self-report instrument. The total score was obtained by summing up the items, ranging between 0 and 63, with a higher score indicated more severe depressive symptoms. The BDI-II has shown to be a strong screening measure for depression with high reliability and improved concurrent, content, and structural validity (Wang and Gorenstein, 2013). The BDI-II was repeatedly assessed across the treatment phase (BDI-II measures at the start of each therapy session), and the subsequent trial follow-up phase (BDI-II measures at 7, 8, 9, 10, 11 and 12 months).

2.3.2. Comorbid anxiety

Anxiety disorders were assessed at baseline using the results of the SCID-I (First et al., 1995). Prior to treatment, anxiety symptoms and phobic anxiety symptoms were measured with the Brief Symptom Inventory (BSI) anxiety subscale and the phobic anxiety subscale representing generalized anxiety symptoms and agoraphobic symptoms respectively. Higher scores indicated more severe symptoms (de Beurs, 2009; Derogatis and Melisaratos, 1983). The BSI is a 53-item self-report instrument that derived from the Symptom Checklist 90 Revised and has demonstrated to have good psychometric properties (De Beurs and Zitman, 2005; Derogatis and Melisaratos, 1983; Khalil et al., 2011). Therapists and participants were blind to the results of the BSI (anxiety symptoms), but not to the outcomes of the SCID-I assessment (anxiety disorders).

2.4. Statistical analysis

To examine pre-treatment characteristics, cutoffs for low and high (phobic) anxiety symptoms were used based on the Dutch outpatients population (de Beurs, 2009). Pre-treatment characteristics and (study and treatment¹) dropout rates of individuals with and without comorbid anxiety disorders, with low and high anxiety symptoms, and with low and high phobic anxiety symptoms were examined with t -tests and χ^2 -tests where appropriate. To examine the differential impact of anxiety disorders, anxiety symptoms, and phobic anxiety symptoms on study and treatment dropout for CT and IPT, logistic regression models were applied. To confirm that the syndromal definition of anxious depression differs from the dimensional one, anxiety symptoms (standardized continuous score of the BSI anxiety subscale) and phobic anxiety symptoms (standardized continuous score of the BSI phobic anxiety subscale) were compared between individuals with and without an anxiety disorder (t -test with Cohen's d). In addition, subgroups of individuals who met the criteria for the syndromal and dimensional definition were identified, and overlap between these groups was examined with a kappa statistics.¹¹

To analyze the impact of anxiety disorders, anxiety symptoms (standardized continuous score of the BSI anxiety subscale) and phobic

anxiety symptoms (standardized continuous score of the BSI phobic anxiety subscale) on BDI-II change across treatment (measured at the start of each therapy session) and follow-up (measured at 7, 8, 9, 10, 11 and 12 months), mixed-effects models were used (Diggle et al., 2002). Analyses were intention-to-treat, using all available data of the 151 study participants. Since sessions were allowed to be scheduled in a flexible manner, for some participants, there was a slight overlap between treatment and trial follow-up phase (1 or 2 sessions). Due to this overlap, BDI-II change was modeled separately for each phase. The following fixed effects were included in the models: standardized BDI-II baseline scores (to adjust for different BDI-II scores prior to treatment (Lemmens et al., 2015)), time (treatment phase model: number of sessions; trial follow-up phase model: time in months), treatment (centered at CT = -0.5 or IPT = 0.5), and a time-by-treatment interaction (difference between CT and IPT over time). Anxiety disorder diagnosis (centered at no diagnosis = -0.5 or one or more = 0.5), anxiety symptoms (standardized continuous score of the BSI anxiety subscale) and phobic anxiety symptoms (standardized continuous score of the BSI phobic anxiety subscale) were subsequently added to these models together with their interactions with treatment, time and treatment-by-time. Since previous studies showed that anxiety could affect different types of depression change (i.e. early rapid change instead of overall change) (Forand and Derubeis, 2013; Forand et al., 2011), different transformations of time (linear quadratic, loglinear) were assessed for each model with fit indices and visual inspection. For the acute phase model with anxiety disorder diagnosis as a predictor, a curvilinear parametrization of time (linear and quadratic slope) was considered the best fit. All other models had the best fit with only linear slopes. For these linear models, the endpoint of time was coded as zero (treatment phase model: session 20; trial follow-up phase model: month 12). To reduce multicollinearity between the linear and quadratic slopes, time was centered midway for the curvilinear model (treatment phase model: session 10) (Forand et al., 2011). For all models, intercepts and slopes were allowed to be correlated and vary randomly over individuals. An autoregressive covariance structure for the residuals was modeled, with a correction for the irregularly spaced time lags between the sessions (Jones, 1993). Backwards elimination was applied when the anxiety-by-treatment-by-time-interaction was not significant ($p > 0.05$).

For all models, we conducted a sensitivity analysis by subsequently adding the following variables measured at baseline to the models: therapist, demographics (age, gender, employment, level of education), clinical features (first or recurrent depression) and functionality (Work and Social Adjustment Scale (W&SAS), Mundt et al., 2002), the RAND-36 (van der Zee and Sanderman, 1993) and the EuroQol-6D (EQ-6D, EuroQol, 1990) for the EQ-5D).

3. Results

3.1. Descriptive statistics

Pre-treatment characteristics are shown in Table 1. As described by Lemmens et al. (2015), the baseline EQ-5D and BDI-II were borderline significantly higher in CT as compared to IPT ($t = 2.00$, $df = 148$, $p = 0.05$ and $t = 1.90$, $df = 149$, $p = 0.06$) for the complete sample. There were no significant differences between the two conditions in treatment ($n = 36$, CT $n = 20$, IPT $n = 16$) and study ($n = 23$, CT $n = 20$, IPT $n = 16$) dropout.

3.1.1. Anxiety disorders

43 out of 151 individuals were diagnosed with one ($n = 35$; 23.2%; CT = 19, IPT = 16) or two ($n = 8$; 5.3%; CT = 5, IPT = 3) anxiety disorders. The number of individuals with anxiety disorders did not differ between the two conditions (CT = 24, IPT = 19, $\chi^2 = 0.72$, $df = 1$, $p = 0.40$). The most prevalent anxiety disorder was panic disorder ($n = 18$), followed by social phobia ($n = 16$), specific phobia ($n = 7$),

¹ Treatment dropout was defined as discontinuation of treatment; study dropout was defined as discontinuation of study participation.

¹¹ For the dimensional criteria (MDD plus subthreshold anxiety symptoms) the BSI anxiety subscale was used and not the BSI phobic anxiety subscale. We choose this subscale since these items overlapped most with the somatic and phobic anxiety subscales of the Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale that are often used to assess the dimensional criteria. Since guidelines for the appropriate thresholds of the BSI anxiety subscale for the dimensional definition were lacking, the analyses were repeated with different cutoffs based on a Dutch outpatient population (de Beurs, 2009).

Table 1
Pre-treatment comparisons of individuals without and with anxiety disorders, with low and high anxiety symptoms and, with low and high phobic anxiety symptoms (n = 151).

	Total sample		Anxiety disorders		Anxiety symptoms		Phobic anxiety symptoms	
	Cognitive Therapy (n = 76)	Interpersonal Psychotherapy (n = 75)	Individuals without anxiety disorders (n = 108)	Individuals with anxiety disorders (n = 43)	Individuals with low anxiety symptoms (n = 115)	Individuals with high anxiety symptoms (n = 36)	Individuals with low anxiety symptoms (n = 125)	Individuals with high anxiety symptoms (n = 26)
Demographics								
Age, years: mean (S.D.)	41.2 (12.4)	41.30 (11.8)	42.8 (12.0)**	37.3 (11.3)**	42.4 (11.7)*	37.4 (12.5)*	42.4 (11.9)*	35.8 (11.7)*
Female, n (%)	54 (71.1%)	46 (61.3%)	68 (63.0%)	32 (74.4%)	74 (64.3%)	26 (72.2%)	80 (64.0%)	20 (80%)
Partner, n (%)	43 (56.6%)	51 (68.0%)	72 (66.7%)	22 (51.2%)	45 (39.1%)	12 (33.3%)	80 (64.0%)	14 (56%)
Employed, n (%)	43 (56.6%)	47 (62.7%)	66 (61.1%)	25 (58.1%)	47 (40.9%)	12 (33.3%)	77 (61.6%)	14 (56%)
Education level, n (%)								
- Low, n (%)	16 (21.1%)	13 (17.3%)	18 (16.7%)	11 (25.6%)	21 (18.3%)	8 (22.2%)	22 (17.6%)	4 (16%)
- Intermediate, n (%)	48 (63.2%)	41 (54.7%)	64 (59.3%)	25 (58.1%)	65 (56.5%)	24 (66.7%)	72 (57.6%)	17 (68%)
- High, n (%)	12 (15.8%)	21 (28.0%)	26 (24.1%)	7 (16.3%)	29 (25.2%)	4 (11.1%)	31 (24.8%)	2 (0.08%)
Clinical features								
BDI-II baseline score, mean (S.D.)	28.4 (8.9)	31.2 (8.9)	28.9 (8.9)	31.9 (8.9)	27.5 (8.3)**	37.1 (7.1)**	28.5 (9.0)**	35.7 (6.5)**
Recurrent depression, n (%)	38 (50.0%)	36 (48.0%)	53 (49.1%)	21 (48.9%)	57 (49.6%)	17 (47.2%)	62 (49.6%)	12 (48%)
Functionality								
W&SAS, mean (S.D.)	23.2 (7.7)	22.4 (7.2)	22.6 (7.3)	23.2 (8.0)	22.6 (7.3)	23.4 (7.8)	22.4 (7.2)	24.7 (8.36)
EQ-5D, mean (S.D.)	0.6 (0.2)*	0.6 (0.3)	0.6 (0.3)	0.6 (0.2)	0.6 (0.2)**	0.5 (0.3)**	0.6 (0.2)*	0.5 (0.1)*
RAND-36, mean (S.D.)	15.5 (10.2)	13.8 (2.8)	14.8 (8.8)	14.0 (2.6)	14.9 (8.5)	13.6 (2.9)	14.8 (8.2)	13.6 (2.7)

Anxiety disorders, one or more anxiety disorder diagnosis on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I); high and low anxiety symptoms, a low or high score on the BSI anxiety subscale (cutoffs based on a Dutch outpatient population⁴⁹); high and low phobic anxiety symptoms, a low or high score on the BSI phobic anxiety subscale (cutoffs based on a Dutch outpatient population⁴⁹); S.D., Standard Deviation; BDI-II, Beck Depression Inventory Second Edition; BSI, Brief Symptom Inventory; W&SAS, Work and Social Adjustment Scale; EQ-5D, EuroQol 5D;

* p < 0.05;

** p < 0.01;

*** p < 0.001

post-traumatic stress disorder ($n = 6$), generalized anxiety disorder ($n = 2$), agoraphobia without panic disorder ($n = 1$), obsessive compulsive disorder ($n = 1$) and anxiety disorder not otherwise specified ($n = 1$). As shown in Table 1, individuals with a comorbid anxiety disorder were significantly younger compared to individuals without a comorbid anxiety disorder ($t = 2.62$, $df = 149$, $p = 0.0098$).

3.1.2. Anxiety symptoms and phobic anxiety symptoms

36 of 151 individuals scored above the ‘high anxiety symptoms cutoff’ (de Beurs, 2009) on the BSI anxiety subscale and the number of individuals with high anxiety symptoms did not significantly differ between CT and IPT (CT = 17, IPT = 19, $\chi^2 = 0.18$, $df = 1$, $p = 0.67$). For the BSI phobic anxiety subscale, 26 of 151 individuals scored above the ‘high phobic anxiety symptoms cutoff’ (de Beurs, 2009) and appeared to be equally divided between CT and IPT as well (CT = 13, IPT = 13, $\chi^2 = 0.0014$, $df = 1$, $p = 0.970$). As presented in Table 1, participants with high anxiety symptoms and high phobic anxiety symptoms were significantly younger ($t = 2.30$, $df = 149$, $p = 0.03$ and $t = 2.59$, $df = 149$, $p = 0.01$), had higher baseline depression severity ($t = -6.23$, $df = 149$, $p < 0.001$ and $t = -3.88$, $df = 149$, $p = 0.002$), and lower quality of life measured with the EQ-5D ($t = 3.17$, $df = 148$, $p = 0.002$ and $t = 2.19$, $df = 148$, $p = 0.03$) as compared to individuals with low anxiety symptoms and low phobic anxiety symptoms respectively.

3.2. Comparing the syndromal and dimensional definition of anxious depression

Individuals with an anxiety disorder scored significantly higher on the BSI anxiety subscale as compared to individuals without an anxiety disorder ($M = 1.58$, $SD = 0.81$ vs. $M = 1.29$, $SD = 0.79$, $t = -2.0$, $df = 149$, $p = 0.05$, Cohen's $d = -0.36$). In addition, scores on the BSI phobic anxiety subscale were higher for individuals with an anxiety disorder compared to individuals without an anxiety disorder ($M = 1.36$, $SD = 0.81$ vs. $M = 0.81$, $SD = 0.71$, $t = -4.13$, $df = 149$, $p = 0.0001$, Cohen's $d = -0.74$). However, when dividing the sample into subgroups of syndromal and dimensional defined anxious depression and non-anxious depression, little agreement was found between the syndromal and dimensional subgroups with kappa statistics ranging between -0.003 and 0.16 .

Table 2

Results of mixed-effect models estimating the impact of baseline anxiety disorder(s) on repeated Beck Depression Inventory-II measurements for CT and IPT during treatment and trial follow-up phase.

	Treatment phase (BDI-II measurements at the start of each therapy session)*					Trial follow-up phase (BDI-II measurements at 7, 8, 9, 10, 11 and 12 months)**				
	Fixed effect			Random effect		Fixed effect			Random effect	
	β	S.E.	p	Var.	SE	β	S.E.	p	Var.	SE
Intercept	19.72	0.84	< 0.001	72.00	9.56	15.02	1.21	< 0.001	124.72	18.23
BDI-II baseline	7.33	0.52	< 0.001			5.27	0.94	< 0.001		
Condition	3.31	1.69	0.051			2.33	2.44	0.340		
Time	-0.83	0.08	< 0.001	0.43	0.09	-0.02	0.16	0.913	0.12	0.10
Time \times condition	0.44	0.16	0.006			0.13	0.31	0.670		
Time ²	0.001	0.001	0.838							
Time ² \times condition	0.01	0.01	0.435							
Anxiety Disorder (AD)	-0.19	1.69	0.912			-1.18	2.45	0.629		
AD \times condition	3.93	3.37	0.243			1.60	4.85	0.741		
AD \times time	-0.10	0.16	0.518			-0.07	0.31	0.831		
AD \times condition \times time	0.51	0.32	0.113			-0.76	0.62	0.221		
AD \times time ²	0.001	0.01	0.935							
AD \times condition \times time ²	0.09	0.03	0.001							

SE, Standard Error; Var., variance; BDI-II, Beck Depression Inventory second edition; AD, Anxiety Disorder; BDI-II baseline, standardized BDI-II score at baseline; time, linear slope; time², quadratic slope.

* model with a linear and a quadratic slope (best fit). Time is centered midway (at session 10).

** model with only a linear slope (best fit). The endpoint of time was coded as zero (at month 12).

3.3. The impact of anxiety disorders on BDI-II change and dropout

Table 2 provides the estimates of the mixed-effect models examining the impact of anxiety disorders on BDI-II change for the treatment phase (0–7 months) and the trial follow-up phase (7–12 months). For the treatment phase model, there was a significant three way interaction between anxiety disorder status, condition and the quadratic time slope, indicating higher BDI-II scores for individuals with an anxiety disorder receiving IPT as compared to CT. This effect is illustrated by Fig. 1, where the raw means of the BDI-II scores are plotted and show a curvilinear unfavorable course for IPT as compared to the CT group. This differential effect was not found in the trial follow-up phase. Sensitivity analyses did not change these results.

For individuals with a comorbid anxiety disorder the proportion of treatment dropouts was significantly higher ($n = 17$, 39.5%) as compared to individuals without a comorbid anxiety disorder ($n = 19$, 17.6%, $\chi^2 = 8.16$, $df = 1$, $p = 0.004$), although this difference was not found for study dropouts ($\chi^2 = 1.51$, $df = 1$, $p = 0.219$). As indicated by the non-significant treatment by anxiety disorder interactions in the logistic regression models, no differential effects between CT and IPT were found for both treatment ($\beta = 0.67$, $p = 0.409$) and study ($\beta = -0.23$, $p = 0.807$) dropout.

3.4. The impact of anxiety symptoms and phobic anxiety symptoms on BDI-II change and dropout

Table 3 summarizes the effects of anxiety symptoms (standardized continuous score of the BSI anxiety subscale) and phobic anxiety symptoms (standardized continuous score of the BSI phobic anxiety subscale) on BDI-II change as estimated with separate linear mixed-effects models. Initially, there was no (differential) effect of anxiety symptoms on BDI-II change in both conditions during treatment and trial follow-up phase. However, after eliminating the anxiety symptoms \times time \times condition interaction from the treatment phase model, a significant anxiety symptoms \times condition interaction appeared, indicating overall higher BDI-II scores for IPT compared to CT. Fig. 2 illustrates this lower order effect with mean BDI-II scores during the treatment phase. This effect was not found in the trial follow-up phase. Phobic anxiety did not affect BDI-II change and backwards elimination did not alter the lower order effects significantly. Sensitivity analyses did not

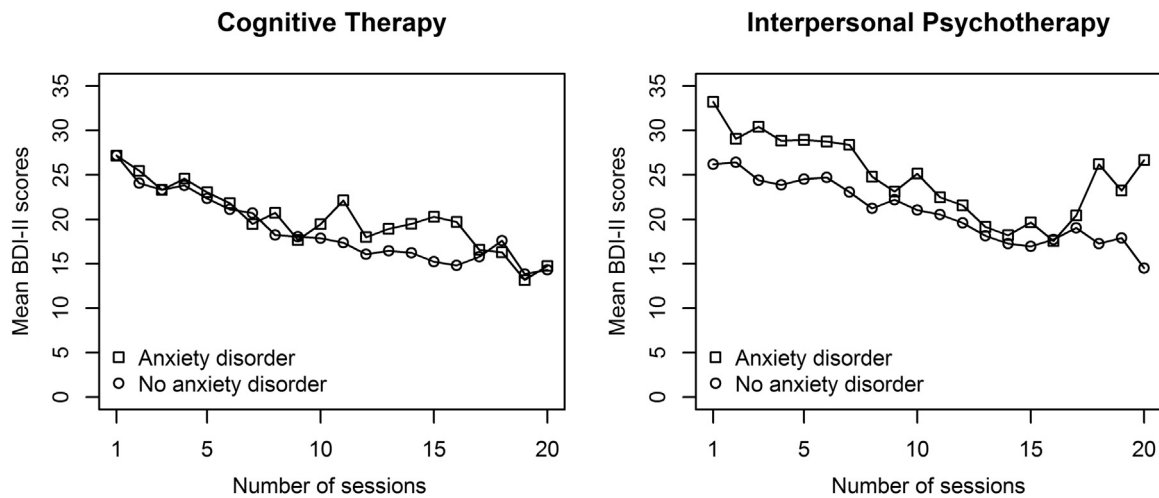


Fig. 1. Mean Beck Depression Inventory -II (BDI-II) scores for individuals with and without an anxiety disorder for Cognitive Therapy and Interpersonal Psychotherapy during the treatment phase. Data were available for 149, 142, 124, 89 and 25 individuals at session 1, 5, 10, 15 and 20 respectively (partly due to treatment termination).

change the results. *Treatment* dropout rates did not differ between individuals with low and high anxiety symptoms ($\chi^2 = 0.04$, $df = 1$, $p = 0.852$). However, there were significantly higher *study* dropout rates for individuals with high anxiety symptoms (27.8%) as compared to low anxiety symptoms (11.3%, $\chi^2 = 5.76$, $df = 1$, $p = 0.02$). No differences in treatment and study dropout rates were found between individuals with low and high phobic anxiety symptoms ($\chi^2 = 2.01$, $df = 1$, $p = 0.16$ and $\chi^2 = 1.50$, $df = 1$, $p = 0.22$). As indicated by the non-significant treatment by anxiety symptoms interactions in the logistic regression models, no differential effects between CT and IPT were found for both treatment ($\beta = 0.06$, $p = 0.474$) and study ($\beta = 0.02$, $p = 0.798$) dropout. For phobic anxiety symptoms, non-significant interactions for treatment ($\beta = 0.02$, $p = 0.837$) and study ($\beta = -0.07$, $p = 0.549$) dropout were found as well.

4. Discussion

The main goal of the current study was to determine the influence of comorbid anxiety on the effectiveness and treatment completion of CT and IPT for MDD. Our most important findings were that, in the treatment phase, anxiety disorders and anxiety symptoms were associated with better depression change in CT as compared to IPT, and that individuals with anxiety disorders (but not anxiety symptoms) were more likely to dropout during both treatments.

The finding that anxiety disorders and anxiety symptoms had a less favorable impact on depression change for IPT as compared to CT in the treatment phase, was not completely unexpected. Although no previous head-to-head comparisons were available, comorbid anxiety have been found to negatively impact MDD outcome for IPT (Brown et al., 1996; Frank et al., 2011, 2000; Young et al., 2006), in contrast to the absence

Table 3

Results of mixed-effect models estimating the impact of baseline anxiety symptoms and phobic anxiety symptoms on repeated Beck Depression Inventory-II (BDI-II) measurements for CT and IPT during treatment and trial follow-up phase.

	Treatment phase (BDI-II measurements at the start of each therapy session)					Trial follow-up phase (BDI-II measurements at 7, 8, 9, 10, 11 and 12 months)				
	Fixed effect			Random effect		Fixed effect			Random effect	
	β	S.E.	p	Var.	SE	β	S.E.	p	Var.	SE
Anxiety Symptoms (AS)	0.89	1.38	0.519			1.37	1.28	0.164		
Intercept	11.54	1.30	< 0.001	205.13	31.42	15.25	1.06	< 0.001	123.18	18.00
BDI-II baseline	6.45	0.65	< 0.001			3.86	1.16	0.001		
Time	-0.81	0.07	< 0.001	0.44	0.09	-0.003	0.13	0.998	0.12	0.09
Condition	5.41	2.63	0.039			2.10	2.12	0.323		
Time \times condition	0.34	0.14	0.013			0.36	0.27	0.179		
AS \times time	-0.027	0.07	0.691			-0.19	0.14	0.164		
AS \times condition*	2.30	1.04	0.028			0.12	1.84	0.946		
Phobic Anxiety Symptoms (PAS)	0.60	1.38	0.664			-0.10	1.21	0.934		
Intercept	11.62	1.32	< 0.001	210.19	31.96	15.21	1.06	< 0.001	124.77	18.07
BDI-II baseline	7.33	0.60	< 0.001			4.45	1.07	< 0.001		
Time	-0.81	0.07	< 0.001	0.44	0.09	-0.004	0.13	0.973	0.12	0.09
Condition	5.32	2.64	0.044			2.17	2.13	0.309		
Time \times condition	0.33	0.14	0.016			0.30	0.27	0.252		
PAS \times time	0.03	0.07	0.721			-0.37	0.14	0.007		
PAS \times condition	-0.45	2.71	0.868			-2.23	2.17	0.303		
PAS \times condition \times time	-0.12	0.14	0.406			-0.42	0.27	0.121		

SE, Standard Error; Var., variance, BDI-II, Beck Depression Inventory second edition; BDI-II baseline, standardized BDI-II score at baseline; AS, Anxiety Symptoms, standardized Anxiety Subscale score of the Brief Symptom Inventory; PAS, Phobic Anxiety Symptoms, standardized Phobic Anxiety Subscale score of the Brief Symptom Inventory. The endpoint of time was coded as zero (session 20 for the treatment phase model and month 12 for the trial follow-up phase model).

* Model with elimination of the anxiety-by-treatment-by-time-interaction: lower order effects appeared to be significant.

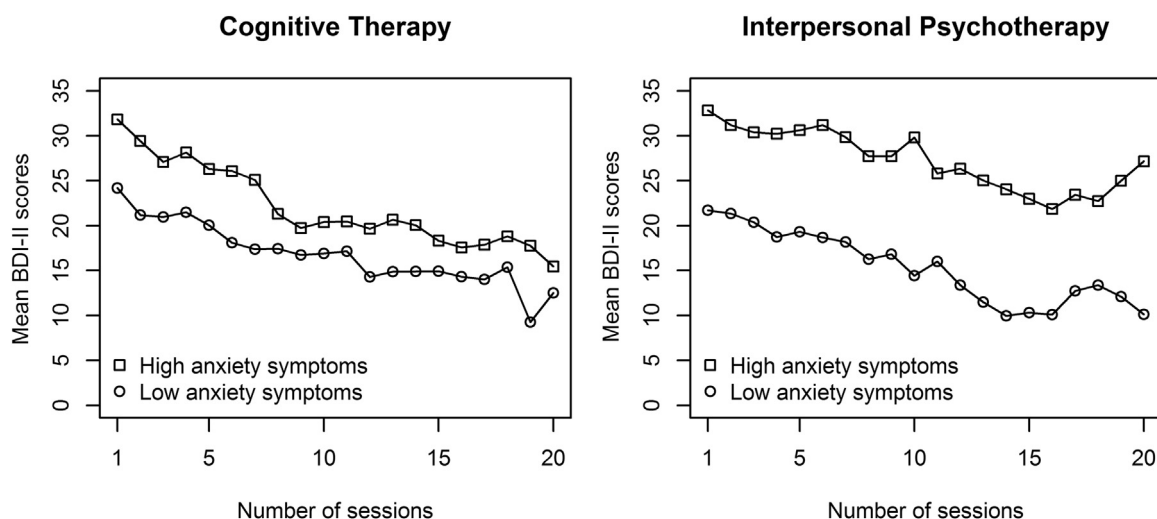


Fig. 2. Mean Beck Depression Inventory -II (BDI-II) scores for individuals with low and high anxiety symptoms for Cognitive Therapy and Interpersonal Psychotherapy during the treatment phase. Data were available for 149, 142, 124, 89 and 25 individuals at session 1, 5, 10, 15 and 20 respectively (partly due to treatment termination).

of adverse effects of anxiety for CT (Brent et al., 1998; de Azevedo Cardoso et al., 2014; Forand and Derubeis, 2013; Forand et al., 2011; Fournier et al., 2009; Kashdan and Roberts, 2011; McEvoy and Nathan, 2007; Persons et al., 2006; Rohde et al., 2001; Smits et al., 2009). In addition, there is evidence that CT outperformed IPT in the treatment of panic disorder (Vos et al., 2012) and social anxiety disorder (Stangier et al., 2011). A possible explanation for these differences is the focus on exposure in CT through “in vivo” homework assignments. The moderating effect of anxiety however was not found across five months follow-up indicating no differential effects in the long term. A possible interpretation of these follow-up findings could be that the impact of IPT took longer to manifest as compared to CT, but is equally effective for anxious depression at the longer term. Similar temporal patterns and differences between CT and IPT were also found in two randomized controlled trials on bulimia nervosa. In these trials, CT appeared to be more effective than IPT in reducing symptoms at the end of therapy. However, these differences were not found during follow-up (Agras et al., 2000; Fairburn et al., 1993). Possibly, these temporal differences could reflect specific mechanisms of change of CT and IPT. To better understand the discrepancies between our treatment and follow-up phase outcomes, further CT versus IPT comparisons on anxious depression are needed with longer follow-up durations and the inclusion of possible mediating variables that could explain different mechanism of change.

The higher treatment dropout rates for individuals with comorbid anxiety disorders have been found in some (Arnou et al., 2007; Brown et al., 1996; Howland et al., 2009), but not all (Forand et al., 2011; Kashdan and Roberts, 2011; Rohde et al., 2001; Schindler et al., 2013; Smits et al., 2009) previous studies. One could explain these higher dropout rates as a form of avoidance behavior, a key feature of anxiety disorders (American Psychiatric Association, 2013). In contrast to our hypothesis, no differential effects of anxiety symptoms on dropout rates were found between CT and IPT.

In our study, we also found that the two different (syndromal and dimensional) definitions for anxious depression define two different groups of individuals. This is line with the results of a previous study (van der Veen et al., 2014) and further supported by the differences we found for pre-treatment depression severity and quality of life with a more severe clinical picture for individuals with the dimensional definition of anxious depression. As mentioned before, a plausible explanation for these differences is that the syndromal criteria identify two distinct disorders (MDD and anxiety disorder), while the dimensional criteria identify a more severe (anxious) subtype of MDD. Logically, one of the exclusion criteria for a DSM anxiety disorder is “not

better accounted for by another mental disorder”, so the anxiety cannot be part of the depression symptomatology. With the central position of anxiety symptoms in MDD (Ten Have et al., 2016), one could argue that anxious depression should only be defined with dimensional criteria (Ionescu et al., 2013; Silverstone and von Studnitz, 2003), which is also in accordance to the newly proposed DSM-5 ‘anxious distress specifier’ for the diagnosis of MDD (American Psychiatric Association, 2013).

To our knowledge this is the first study that examined anxious depression determined by both syndromal and dimensional criteria in a head-to-head comparison of CT and IPT. Other strengths of our study are the random allocation, the relative large sample size, and the multiple assessments of depressive symptoms that were analyzed with state of the art mixed models (Lemmens et al., 2015). The current study also has some limitations. First, no inter-reliability data for the SCID-I was collected and patients and therapist were not blind for the results of the SCID-I. Therapists were blind for the results of the BSI anxiety subscale and phobic anxiety subscale. Although therapists were not instructed to adapt treatments if comorbid anxiety was present, this knowledge could have altered treatment strategies. However, our competence and adherence check revealed no impact of comorbid anxiety on quality of treatment or therapy specific behavior. Second, our treatment and the trial follow-up phase models slightly overlap since a few participants had one or two therapy session during the trial follow-up phase. Third, although the overall dropout rates of the current study were low, individuals with anxiety disorders had relatively high dropout rates. Due to the use of mixed models, this is unlikely to affect our findings drastically. However, we think that larger sample sizes of individuals with comorbid anxiety disorders are warranted. In addition, the presence of these high dropout rates is an informative and clinically relevant finding.

The findings of this study have significant clinical implications. Most importantly, the presence of anxiety disorders and anxiety symptoms should be considered when selecting an effective psychotherapy for a depressed individual. Based on these results, a preference to CT over IPT is justifiable. Selecting the best treatment option for a given individual, is in line with the “personalized medicine” movement in health care research and practice today (Simon and Perlis, 2010). If IPT is the first choice of treatment for other reasons, clinicians could also consider to use a modified version of IPT that includes cognitive-behavioral strategies to target symptoms of panic, anxiety and avoidance that interfere with interpersonal problem solving (Cyranowski et al., 2005). Another important clinical implication is that the patient’s adherence to therapy should be carefully monitored when a comorbid anxiety disorder is diagnosed. With the assessment of other

predictors of treatment drop-out (e.g. ethnic minority status, younger age, lower income, low motivation for change, poor therapeutic alliance, low treatment credibility and failure to improve early in treatment (Arnow et al., 2007; Cooper and Conklin, 2015; Schindler et al., 2013; Taylor et al., 2012)), individual risks for dropout should be estimated, and specific interventions to prevent dropout can be considered, for example motivational interviewing techniques (Miller and Rollnick, 2002). Another issue is that based on our finding that anxiety symptoms are associated with more severe depressive symptomatology and lower quality of life prior to treatment, a clinician can be confronted with significant levels of distress when anxiety symptoms are present. To deal with this more severe clinical picture, combination therapy (psychotherapy and pharmacotherapy) can be considered, since it has been formulated as the treatment of choice for severe depression (NICE, 2009). Finally, when depression and anxiety co-occur, transdiagnostic approaches for both CT and IPT focussing both on depressive and anxiety symptoms show promising results (Newby et al., 2015; Wright et al., 2014).

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Contributors

AA, MH, FP designed the study and wrote the protocol. Author SB managed the literature searches and analyses. Author SB undertook the statistical analysis, and author SB wrote the first draft of the manuscript. All authors (AA, MH, FP, LL, SB) contributed to and have approved the final manuscript

Conflict of interest

All authors declare that they have no competing interests.

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