Regular Article

Psychotherapy and Psychosomatics

Psychother Psychosom 2012;81:153–160
DOI: 10.1159/000334909

Received: July 12, 2011
Accepted after revision: November 3, 2011
Published online: March 3, 2012

Outcomes of Acute Phase Cognitive Therapy in Outpatients with Anxious versus Nonanxious Depression

Jasper A.J. Smits[a] Abu Minhajuddin[b] Michael E. Thase[c–e] Robin B. Jarrett[b]

[a]Department of Psychology, Southern Methodist University, and [b]Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas, Dallas, Tex.; [c]University of Pennsylvania School of Medicine, and [d]Philadelphia Veterans Affairs Medical Center, Philadelphia, Pa.; [e]University of Pittsburgh Medical Center, Pittsburg, Pa., USA

Key Words
Cognitive therapy · Major depressive disorder · Anxious depression · Treatment outcome

Abstract
Objective: Compared to nonanxious depressed patients, anxious depressed patients respond less to pharmacotherapy, prompting consideration of alternate treatments. Based on the transdiagnostic principles of cognitive therapy (CT), we predicted that anxious depressed patients would respond as well to CT as nonanxious depressed patients. ***Method:*** Adults (n = 523) with recurrent major depressive disorder received 12–14 weeks of CT as part of the Continuation Phase Cognitive Therapy Relapse Prevention Trial. Anxious depressed patients (n = 264; 50.4%) were compared to nonanxious depressed patients (n = 259; 49.6%) on demographic variables, initial severity, attrition, and rates and patterns of response and remission. ***Results:*** Anxious depressed patients presented with greater illness severity and had significantly lower response (55.3 vs. 68.3%) and remission rates (26.9 vs. 40.2%) based on clinician-administered measures. By contrast, smaller between-group differences for attrition, and for response (59.1 vs. 64.9%) and remission (41.7 vs. 48.7%) rates on self-report measures were not significant. Further, anxious depressed patients had greater speed of improvement on self-reported anxiety symptom severity and clinician-rated depressive and anxiety symptom severity measures. ***Conclusion:*** Consistent with prior reports, anxious depressed patients presented with greater severity and, following CT, had lower response and remission rates on clinician-administered scales. However, anxious depressed patients improved more rapidly and response and remission rates on self-report measures were not significantly different from nonanxious depressed patients. Our findings suggest that anxious depressed patients may simply need additional time or more CT sessions to reach outcomes fully comparable to those of less anxious patients.

Introduction

Patients presenting with anxious depression do not fare as well with acute phase pharmacotherapy relative to those who present with nonanxious depression [1–5]. Distinct from the mixed anxiety and depressive disorder (i.e. the presence of subthreshold depressive and subthreshold anxiety symptoms) [6], anxious depression has been defined as either major depressive disorder (MDD) with high levels of anxiety symptoms (i.e. dimensional approach) or MDD with anxiety disorder comorbidity

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Jasper A.J. Smits, PhD
Department of Psychology, Southern Methodist University
Dedman College, PO Box 750442
Dallas, TX 75275 (USA)
Tel. +1 214 768 4125, E-Mail jsmits@smu.edu

(i.e. syndromal approach) [4, 6–8]. The dimensional approach is often regarded as having greater ecological validity [8], since many patients with MDD have debilitating anxiety symptoms that do not meet criteria for a specific disorder [4]. Defined this way, anxious depression is common among outpatients and inpatients alike with MDD. For example, 46% of outpatients participating in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial met criteria for anxious depression [7]. Similarly, 49% of inpatients who enrolled in the German Algorithm Project, phase 3 (GAP3), presented with anxious depression [4]. Moreover, those with anxious depression are more likely to report features of the atypical or melancholic depressive subtypes and evidence not only greater illness severity, but also more functional impairment than nonanxious depressed patients [2, 4, 7–9]. Although not yet recognized in the Diagnostic and Statistical Manual of Mental Disorders (DSM), such findings support the notion that anxious depression is a distinct subtype of MDD [4, 7, 8, 10].

Evidence of poorer outcomes with pharmacotherapy for anxious, relative to nonanxious, depressed patients comes from two recent large-scale pharmacotherapy trials. Indeed, anxious depressed patients in the STAR*D and GAP3 trials evidenced lower response rates (STAR*D: 41.7 vs. 52.8%, $p = 0.001$; GAP3: 59.5 vs. 69.7%, $p = 0.023$), lower remission rates (STAR*D: 22.2 vs. 33.4%, $p = 0.002$; GAP3: 48.6 vs. 61.6%, $p = 0.018$), and took longer to achieve remission than nonanxious depressed patients ($p < 0.001$) [2, 4]. Collectively, these findings call for the need to identify symptoms of anxiety in patients who present for pharmacotherapy but also for the consideration of alternate interventional modalities or adjunctive treatments for this common MDD subtype.

One alternate modality is cognitive therapy (CT). Conceptually, CT is a logical intervention for patients with significant co-occurring anxiety due to its 'transdiagnostic' nature [11]. That is, CT for MDD targets distressing thoughts and behaviors; thus, the approach is flexible enough to target upsetting thoughts and behaviors linked to both depressed and anxious mood. For patients presenting with high levels of anxiety symptoms, cognitive restructuring and behavioral exercises may center on decreasing emotional response and behavioral avoidance to anxiogenic cues, thereby facilitating improvement in depressed mood and improving overall functioning. Indeed, evidence supports the idea that reducing anxiety with cognitive and behavioral strategies guides subsequent reductions in depression [12]. Moreover, CT approaches to MDD are associated with improvements in psychiatric comorbidities [13]. Accordingly, it is plausible that the outcome of CT for MDD does not vary as a function of the presence of high anxiety symptom levels. Initial support for this hypothesis comes from Smits et al. [14], who found that patients with MDD with comorbid social phobia showed comparable outcomes with acute phase CT to patients with MDD without comorbid social phobia.

The present study aimed to build upon extant work by investigating whether outpatients with anxious MDD differ significantly from their counterparts with nonanxious MDD with respect to their pattern of response and remission during acute phase CT. We compared the two subtypes on measures obtained at diagnostic evaluation and on the following acute phase CT outcomes: (1) attrition; (2) response and remission; (3) stable remission; (4) time to response and remission, and (5) rate of improvement in depressive and anxiety symptoms. We predicted that anxious depressed patients would evidence greater illness severity at presentation relative to nonanxious depressed patients. However, based on the therapeutic principles and procedures of CT, we predicted that the anxious depressed patients would not show significantly poorer treatment outcome relative to their nonanxious depressed counterparts. These predictions were tested using data collected within the open trial of acute phase CT of the Continuation Phase Cognitive Therapy Relapse Prevention (C-CT-RP) trial [15].

Method

Study Overview

Details of the C-CT-RP trial are given elsewhere [15]. The aim of the C-CT-RP trial was to examine the risk of relapse and recurrence following shorter and longer courses of CT. To this end, 523 adult outpatients with recurrent MDD were first enrolled in 12–14 weeks of acute phase CT. Acute phase responders were then stratified into higher- and lower-risk (for relapse/recurrence) groups. Higher-risk responders were subsequently enrolled in an 8-month randomized trial comparing the effects of C-CT versus blinded fluoxetine or pill placebo with respect to preventing relapse and/or recurrence during a 2-year follow-up period. Lower-risk responders completed follow-up evaluations but received no further interventions. Data were collected at the University of Texas Southwestern Medical Center at Dallas and the University of Pittsburgh Medical Center with the approval of their Institutional Review Boards. For the present secondary analysis we report only on data from the open trial of acute phase CT (before randomization).

Participants

The sample, recruited via advertisement and referral, comprised adults with recurrent MDD (n = 523) as determined by the Structured Clinical Interview for DSM-IV [16]. Inclusion criteria were: (1) evidence of recurrence defined as either remission be-

tween depressive episodes, at least 1 prior episode with complete inter-episode recovery, or antecedent dysthymic disorder; (2) Hamilton Rating Scale of Depression ($HRSD_{17}$) [17] score ≥14 at the initial and second interview, and (3) patients who were taking psychotropic medication were withdrawn from the medication and had to be without medication for at least 1 week prior to study entry. Exclusion criteria were: (1) severe or poorly controlled concurrent medical disorders that may cause depression; (2) presence of the following comorbid DSM-IV disorders: psychotic or organic mental disorder, bipolar disorder, active alcohol or drug dependence, primary obsessive-compulsive disorder or eating disorders; (3) insufficient command of the English language; (4) active suicide risk; (5) history of nonresponse to a trial of at least 8 weeks of CT conducted by a certified therapist; (6) history of nonresponse to at least 6 weeks of 40 mg of fluoxetine; (7) pregnancy or planned pregnancy during 11 months after intake. All potential participants provided written authorization from the Health Insurance Portability and Accountability Act of 1996 and informed consent for evaluation and treatment.

Assessment

A strict quality assurance protocol was followed to maintain high diagnostic reliability in clinician ratings [15].

Demographics. Patient demographics were collected at the diagnostic evaluation using a questionnaire [15].

Psychiatric Diagnosis. Experienced evaluators administered the Structured Clinical Interview for DSM-1 [16] at diagnostic evaluation and the current MDD section of the interview once during weeks 4, 8 and 12 of the acute phase and at the first blinded evaluation, which occurred within 1 week of the last session.

Symptom Severity. Depressive symptom severity was assessed using the following psychometrically sound measures: $HRSD_{17}$ [17], Inventory of Depressive Symptomatology – Self-Reported (IDS-SR) [18] and Beck Depression Inventory (BDI) [19]. Clinicians administered the $HRSD_{17}$ and patients completed the BDI and IDS-SR at diagnostic evaluation and weekly during CT. Independent evaluators administered the $HRSD_{17}$ one week following the last session. Similar to previous work [14, 20], we used the IDS-SR anxiety/arousal factor in addition to the $HRSD_{17}$ anxiety/somatization factor to assess anxiety symptom severity.

Definition of Anxious Depression

Following previous studies [2, 7, 8], we defined anxious depression as MDD with high levels of anxiety symptoms as indexed by an $HRSD_{17}$ anxiety/somatization factor score ≥7 at diagnostic evaluation [21].

Cognitive Therapy

Experienced cognitive therapists provided 16–20 individual sessions of CT as described by Beck et al. [22]. Consistent with this CT manual, therapists tailored treatment and homework assignments to the individual. Homework exercises were designed to prompt patients to gather disconfirmatory evidence for their negative thoughts and beliefs; therefore exposure to feared cues was possible. CT was delivered over 12–14 weeks. Sessions 1–8 occurred twice weekly, after which patients who experienced ≥40% reduction in the $HRSD_{17}$ score from diagnostic evaluation began weekly sessions, while all others continued twice-weekly sessions for 4 more weeks. Therapists received ongoing supervision and were monitored for competency using the CT Rating Scale [23].

Statistical Analyses

Attrition, Response and Remission. In this analysis, we defined acute phase CT response by either (1) $HRSD_{17}$ score ≤12 and absence of DSM-IV major depressive episode (MDE) at the last visit or (2) a diagnostic evaluation to the last assessment reduction of ≥50% in the Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR) score. We included the second criterion to remain consistent with definitions employed by Fava et al. [2]. The QIDS-SR score was derived from the IDS-SR score. Also consistent with Fava et al. [2], remission was defined as either (1) $HRSD_{17}$ score ≤7 or (2) QIDS-SR score ≤5 at the last visit. Lastly, stable remission was defined as the last 7 consecutive $HRSD_{17}$ scores <7. We included this latter index because it has been associated with a lower risk of relapse and recurrence during the 24 months following acute phase CT [24], thereby providing useful prognostic data. A hierarchical decision model was used to determine the $HRSD_{17}$-based response for patients who did not complete acute phase CT. Specifically, of the 523 patients who consented to acute phase CT, nonresponse of 395 (75.5%) was defined as described above. When patients failed to complete either the CT or the post-CT evaluation, then the available data closest to their exit date were imputed using the following hierarchy: (a) for patients who exited early and completed their independent evaluation within 4 weeks of their final CT session, this $HRSD_{17}$ and MDE were used to define the response (n = 11; 2.1%); (b) for those who did not complete an early-exit independent evaluation or did so >4 weeks from their last CT session, comparable data (i.e. $HRSD_{17}$ and MDE) were imputed from the final available CT session but were collected by the treating therapist (n = 42; 8.0%); (c) for those who had a therapist's diagnosis of MDE that was missing at the final CT session, 2 IDS-SR scores were used as a proxy for MDE and the final $HRSD_{17}$ from the therapist was also analyzed (n = 45; 8.6%); and (d) did not start CT or dropped out before session 6, data were imputed from the diagnostic evaluation (n = 30; 5.7%). Similarly, for patients who failed to complete either the CT or the post-CT evaluation, the available data closest to their exit date were imputed. Accordingly, in some cases remission as defined by the $HRSD_{17}$ scores was based on ratings by the treating therapist. We used χ^2 tests to compare anxious versus nonanxious depressed patients with respect to attrition, response, remission and stable remission rates. These tests included data from all patients (i.e. intent-to-treat analyses) and were followed by logistic regression analyses in order to adjust for initial depression severity. Consistent with Fava et al. [2], we adjusted for scores on the $HRSD_{17}$ without the anxiety/somatization factor at diagnostic evaluation in analyses of attrition and outcomes defined by changes on the $HRSD_{17}$, and adjusted for diagnostic evaluation QIDS-SR scores in analyses of response and remission defined by changes in the QIDS-SR.

Time to First Response and Time to First Remission. Time to first response and time to first remission were operationalized as weeks passed from the first CT visit to the first visit during which the response criterion (reduction of ≥50% in the QIDS-SR score) or remission criterion ($HRSD_{17}$ score ≤7 or QIDS-SR score ≤5) was achieved. Because DSM-IV MDE was not assessed at each visit, we did not conduct time to response analysis using the $HRSD_{17}$ score ≤12 and absence of DSM-IV MDE criterion. We employed Kaplan-Meier analyses to estimate the median time to response/remission and a log-rank test to compare the two groups. These tests were followed by Cox proportional hazard regression analyses to adjust for depression severity at diagnostic evaluation.

Rate of Improvement in Depressive and Anxious Symptoms. In order to compare anxious versus nonanxious depressed patients on their pattern of change in depressive and anxiety symptoms during the course of treatment, we subjected weekly scores on the respective depressive symptom measures (BDI, $HRSD_{17}$, QIDS-SR) and anxiety symptom measures ($HRSD_{17}$ anxiety/somatization factor, IDS-SR anxiety/arousal factor) to multilevel linear regression analyses (i.e. 5 analyses). At level 1 of these analyses, an intercept and a slope were estimated for each patient. Here, the intercept reflects the score on the measure at the first session adjusting for depression severity at diagnostic evaluation, and the slope reflects the weekly decrease in this score during the course of acute phase CT. At level 2, these person-specific parameters were modeled as a function of anxious depression status (no/yes). Because these analyses include data from all persons, they are intent-to-treat analyses.

Results

Sample Characteristics

Sample characteristics are reported in table 1. Of 523 patients, 264 (50.4%) presented with anxious depression. Scores on measures of depressive and anxiety symptom severity were significantly elevated among anxious depressed versus nonanxious depressed patients. Relative to nonanxious depressed patients, anxious depressed patients also reported a greater number of MDD episodes, current comorbid anxiety disorders and current comorbid DSM-IV diagnoses, had completed significantly fewer years of education and were significantly more likely to be non-Caucasian. No significant differences were observed for age of onset, length of current episode or current double-depression rates.

Attrition, Response, Remission and Stable Remission

Results are presented in table 2. Compared to nonanxious depressed patients, anxious depressed patients had significantly lower response and remission rates using the $HRSD_{17}$-based definitions, even after controlling for initial depression severity ($HRSD_{17}$-defined response: $\chi^2 = 4.6$, $p < 0.031$, odds ratio = 0.666, 95% confidence interval, CI, = 0.461–0.964; $HRSD_{17}$-defined remission: $\chi^2 = 5.9$, $p < 0.015$, odds ratio = 0.627, 95% CI = 0.430–0.915). By contrast, anxious and nonanxious depressed patients did not differ with respect to attrition ($\chi^2 = 0.26$, $p < 0.609$), nor with respect to response ($\chi^2 = 2.29$, $p < 0.130$) and remission rates ($\chi^2 = 0.25$, $p < 0.620$) using QIDS-SR criteria. The groups likewise had similar rates of stable remission ($\chi^2 = 0.91$, $p < 0.341$).

Time to First Response and Time to First Remission

As defined by a reduction of ≥50% in the QIDS-SR score, 87.1% of anxious versus 94.7% of nonanxious depressed patients achieved response; this small difference was statistically significant on the survival analysis (log-rank $\chi^2 = 6.1$, d.f. = 1, $p \leq 0.013$). The median time to achieve response was significantly greater for anxious (6.4 weeks) versus nonanxious (5.0 weeks) depressed patients, even after controlling for initial depression severity ($\chi^2 = 6.3$, d.f. = 1, $p \leq 0.012$, hazard ratio = 1.297, 95% CI = 1.058–1.588; online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000334909).

With respect to achieving remission, anxious depressed patients were less likely than nonanxious depressed patients to reach a $HRSD_{17}$ score ≤7 (74.2 vs. 81.5%; log-rank $\chi^2 = 13.8$, d.f. = 1, $p \leq 0.0002$) or a QIDS-SR score ≤5 (70.4 vs. 77.8%; log-rank $\chi^2 = 9.4$, d.f. = 1, $p \leq 0.002$). The median time to achieve $HRSD_{17}$-defined remission was significantly longer among anxious depressed (10.7 weeks) versus nonanxious depressed patients (8.0 weeks), even after controlling for initial depression severity ($\chi^2 = 5.84$, d.f. = 1, $p \leq 0.016$, hazard ratio = 1.327, 95% CI = 1.055–1.670; online suppl. fig. 1). However, the difference in the median time to QIDS-SR-defined remission (9.9 vs. 7.1 weeks) was not significant after adjusting for initial depression severity ($\chi^2 = 1.881$, d.f. = 1, $p \leq 0.170$, hazard ratio = 1.174, 95% CI = 0.933–1.478; online suppl. fig. 1).

Rate of Improvement in Depressive and Anxious Symptoms

Results are presented in the online supplementary figures 2 and 3. No between-group slope differences were observed for the BDI or the QIDS-SR ($p > 0.31$). Relative to nonanxious depressed patients, anxious depressed patients showed a significantly greater rate of improvement on the $HRSD_{17}$ [b = –0.917 vs. b = –0.811, F(1, 510) = 4.8, $p > 0.029$], the $HRSD_{17}$ anxiety/somatization factor [b = –0.289 vs. b = –0.213, F(1, 554) = 19.7, $p > 0.001$] and the IDS-SR anxiety/arousal factor [b = –0.666 vs. b = –0.583, F(1, 486) = 4.2, $p > 0.042$].

Discussion

The present investigation was prompted by research indicating that anxious and nonanxious depressed patients show significantly different response and remission rates and patterns with established pharmacotherapies [1–5], thereby providing support for the view that

Table 1. Sample characteristics as a function of anxious depression

Characteristics	Anxious depressed		Statistics	
	no (n = 259)	yes (n = 264)		
Demographic variables				
Sex (female)	169 (65.3)	184 (69.7)	$\chi^2 = 1.2$	$p \leq 0.278$[a]
Race (non-Hispanic white)	223 (86.1)	200 (75.8)	$\chi^2 = 9.0$	$p \leq 0.003$[a]
Mean age ± SD, years	42.8 ± 12.6	41.9 ± 11.6	$t_{521} = 0.88$	$p \leq 0.377$[b]
Marital status			$\chi^2 = 0.0$	$p \leq 0.936$[a]
Single	151 (58.3)	153 (58.0)		
Partnered	108 (41.7)	111 (42.0)		
Mean education ± SD, years	15.5 ± 2.9	14.6 ± 2.9	$t_{521} = 3.54$	$p \leq 0.000$[b]
Employment			$\chi^2 = 8.6$	$p \leq 0.196$[a]
Full time	124 (47.9)	104 (39.4)		
Part time	29 (11.2)	34 (12.9)		
Homemaker/caregiver	10 (3.9)	21 (8.0)		
Student	11 (4.2)	13 (4.9)		
Retired	7 (2.7)	9 (3.4)		
Other	17 (6.6)	11 (4.2)		
Unemployed	61 (23.5)	72 (27.3)		
Mean depression severity scores ± SD				
$HRSD_{17}$	18.1 ± 2.8	22.7 ± 3.7	$t_{521} = -16.1$	$p \leq 0.000$[b]
BDI	27.4 ± 8.5	30.5 ± 9.1	$t_{521} = -4.0$	$p \leq 0.000$[b]
QIDS-SR	14.7 ± 4.0	16.2 ± 4.2	$t_{521} = -4.2$	$p \leq 0.000$[b]
Mean age at onset ± SD, years	20.9 ± 11.1	21.5 ± 10.5	$\chi^2 = 0.81$	$p \leq 0.368$[c]
Median	19.0	18.0		
Mean length of current episode ± SD, years	27.7 ± 52.1	22.3 ± 37.0	$\chi^2 = 0.42$	$p \leq 0.518$[c]
Median	9.0	10.0		
Mean length of illness ± SD, years	21.5 ± 12.6	20.0 ± 11.0	$\chi^2 = 1.22$	$p \leq 0.269$[c]
Median	19.0	19.0		
Median number of episodes	3.0	4.0	$\chi^2 = 5.65$	$p \leq 0.017$[c]
Current double depression	14 (5.4)	13 (4.9)	$\chi^2 = 0.1$	$p \leq 0.804$[a]
Current comorbid anxiety disorders				
Panic disorder without agoraphobia	10 (3.9)	23 (8.7)	$\chi^2 = 5.20$	$p \leq 0.023$[a]
Panic disorder with agoraphobia	2 (0.8)	10 (3.8)		$p \leq 0.037$[d]
Agoraphobia without panic disorder	2 (0.8)	4 (1.5)		$p \leq 0.686$[d]
Social anxiety disorder	31 (12.0)	55 (20.8)	$\chi^2 = 7.48$	$p \leq 0.006$[a]
Generalized anxiety disorder	7 (2.7)	23 (8.7)	$\chi^2 = 8.73$	$p \leq 0.003$[a]
Posttraumatic stress disorder	12 (4.6)	11 (4.2)	$\chi^2 = 0.07$	$p \leq 0.795$[a]
Specific phobia	9 (3.5)	29 (11.0)	$\chi^2 = 10.94$	$p \leq 0.001$[a]
Comorbid DSM-IV diagnoses				
Current	96 (37.1)	133 (50.4)	$\chi^2 = 9.4$	$p \leq 0.002$[a]
Lifetime	193 (74.5)	207 (78.4)	$\chi^2 = 1.1$	$p \leq 0.294$[a]

Figures in parentheses indicate percentages.
[a] χ^2 statistics for contingency tables. [b] t statistics are from t tests for independent samples. [c] χ^2 statistics are from Kruskal-Wallis test for medians. [d] p value from Fisher's exact test.

anxious depression may be a meaningful subtype of MDD [2] that may benefit from either additional or different therapeutic tactics. Based on the transdiagnostic nature of CT we predicted that, while anxious depressed patients would present with greater illness severity, they would not evidence significantly poorer outcomes with CT for MDD relative to their nonanxious depressed counterparts.

We tested our predictions using data from a large trial of CT for recurrent MDD (n = 523) and employed defini-

Table 2. Attrition, response and remission rates as a function of anxious depression

Outcome	Anxious depression		Unadjusted p	Adjusted odds ratio	Adjusted p
	no (n = 259)	yes (n = 264)			
Attrition	56 (21.6)	57 (21.6)	0.993	0.893	0.609[a]
Response					
$HRSD_{17}$ score ≤12 + absence of MDE at the last visit	177 (68.3)	146 (55.3)	0.002	0.666	0.031[a]
≥50% in QIDS-SR score[c]	168 (64.9)	156 (59.1)	0.174	0.757	0.130[b]
Remission					
$HRSD_{17}$ score ≤7 at last visit	104 (40.2)	71 (26.9)	0.001	0.627	0.015[a]
QIDS-SR score ≤5 at last visit	126 (48.7)	110 (41.7)	0.109	0.912	0.620[b]
Stable remission					
Last 7 consecutive $HRSD_{17}$ scores <7[d]	32 (20.1)	18 (13.5)	0.136	0.730	0.341[a]

Figures in parentheses indicate percentages.

[a] Adjusted for severity of depression at diagnostic evaluation as measured by $HSRD_{17}$ without the anxiety/somatization factor. [b] Adjusted for severity of depression as measured by QIDS-SR at diagnostic evaluation. [c] Eight patients had missing QIDS-SR data at diagnostic evaluation and their data were imputed for this analysis using the formula QIDS-SR = 0.33 + 0.84 × $HRSD_{17}$ [30]. [d] Stable remission could only be defined for 292 patients due to missing data: 159 anxious depressed patients and 133 nonanxious depressed patients.

tions of anxious depression and treatment outcome comparable to that in extant work [2]. Anxious depressed patients constituted approximately one half of our sample (50.4%) and, consistent with previous findings, a number of indices of pretreatment illness severity were more evident among anxious depressed than nonanxious depressed patients [4, 7]. As expected, we observed large improvements in measures tapping both depressive and anxiety symptoms in both subtypes, providing support for the hypothesis that CT for MDD is flexible enough to address both depressive and anxiety symptoms simultaneously. Interestingly, the rate of improvement in anxiety symptoms was greater in anxious depressed than nonanxious depressed patients. This finding may simply reflect that there is more room for improvement among anxious depressed patients, but may also suggest that strategies such as restructuring faulty threat appraisals and reducing avoidance are an important focus of CT in this group of depressed patients. Examination of session content is required to address this hypothesis.

Consistent with previous reports relating anxious depression to poorer pharmacotherapy outcomes [2, 4, 7], anxious depressed patients were less likely to achieve response and remission status as determined by clinician $HRSD_{17}$ ratings. However, other findings suggested that these between-group differences do not indicate that CT should be viewed as an ineffective treatment for anxious depressed patients. Specifically, it appears that because the anxious depression subgroup presented with more severe symptomatology ($HRSD_{17}$ mean ± SD: 22.7 ± 3.7 vs. 18.1 ± 2.8), it was simply more difficult to reach the cutoff scores for response ($HRSD_{17}$ = 12 plus absence of DSM-IV MDE) and especially remission ($HRSD_{17}$ = 7) within a 12- to 14-week protocol. Indeed, a comparison between the two subtypes regarding their speed of improvement in depressive symptoms as determined by clinicians (i.e. $HRSD_{17}$) suggested that the anxious depressed patients actually experienced a greater rate of improvement on the $HRSD_{17}$ than nonanxious depressed patients. Also important to note here is that anxious and nonanxious depressed patients showed comparable attrition rates, suggesting that, unlike what Fava et al. [2] documented for pharmacotherapy, the ability of patients to 'tolerate' a full course of CT may not vary as a function of severity of anxiety symptoms.

Corroboration of the hypothesis that anxious depressed patients do not evidence significantly poorer CT outcomes than nonanxious depressed patients also comes from self-report data. Specifically, although anxious depressed patients required more time than nonanxious depressed patients to achieve the QIDS-SR response cutoff, the subtypes did not evidence significantly different response and remission rates using QIDS-SR definitions, nor did they show a differential rate of improvement on the QIDS-SR and BDI. Interestingly, the two subtypes did not significantly differ with respect to stable remission rates either. Because stable remission has been associated with decreased risk of relapse and recurrence [24–26], this

finding may imply that anxious depressed patients treated with CT are not at an increased risk of poorer long-term outcomes. It will be possible to test this hypothesis when the follow-up phase of this study is complete.

Several study limitations deserve mention. First, we investigated potential group differences in the context of a standardized 'open' trial of CT. The absence of a credible treatment comparator or placebo makes it difficult to ascertain that response and remission patterns are due to the specific components of CT rather than nonspecific factors associated with clinical care and ongoing assessment. Thus, the present findings may not be specific to CT, but representative of therapeutic change occurring with care in general. Second, because we excluded patients with comorbid substance dependency or primary obsessive-compulsive disorder and patients unable to discontinue antidepressants or benzodiazepines, we may have inadvertently excluded persons with the highest levels of anxiety symptoms. Third, the omission of measures that tap anxiety psychopathology more broadly (i.e. cognitive, somatic and behavioral avoidance features) also limits us with respect to making inferences regarding improvements in anxiety psychopathology that occur with CT of MDD. Fourth, since anxious depressed patients presented with greater illness severity, more episodes, more anxiety disorders, less education, and were more likely to be non-Caucasian, it is possible that one or more of these characteristics did, in part or in combination, influence differences in outcomes where they were observed in this sample. Last, the study did not include a combined CT plus pharmacotherapy strategy, which is often used in clinical practice; thus, the data do not allow comment on this strategy.

Taken together, our findings provide only limited support for the hypothesis that anxious depressed patients constitute a group resistant to established treatments. We note that the clinician ratings, in particular, provide some support for this hypothesis. Overall, our findings suggest that, at least with CT, in spite of presenting with greater illness severity, patients with anxious depression report decreases in symptoms that are not significantly poorer than that observed in their nonanxious counterparts. Instead, they may simply need additional time and/or sessions to achieve remission during acute phase treatment. We believe this is an important hypothesis that warrants further testing, calling for studies that manipulate the dose of acute phase CT. Indeed, findings consistent with this hypothesis would support an emphasis on training therapists to personalize CT to the patient's presenting symptoms – an idea at the very essence of what the first-generation CT therapists called a 'functional analysis' [27] as well as contemporary conceptualizations of the sequential model of treatment for depression [28] – instead of developing complex modular variants of basic CT for MDD. An additional important avenue of future research is testing whether anxious depression is a moderator of between-group differences in randomized controlled trials comparing CT to antidepressant medications or their combination. A recent report further suggests that it may be important to measure and include in the analyses patient preferences for treatment, because receiving the preferred treatment has been associated with improved outcomes both for CT and pharmacotherapy [29]. Results of such efforts can ultimately best guide recommendations for appropriate treatment modalities for anxious depressed patients.

Acknowledgments

This report was supported by Grants No. K24MH001571, R01MH058397 and R01MH069619 (to Robin B. Jarrett, PhD) and R01MH058356 and R01MH069618 (to Michael E. Thase, MD) from the National Institute of Mental Health (NIMH). We appreciate the support of the NIMH.

We wish to acknowledge the unrestricted support of Eli Lilly & Co., who provided the fluoxetine and matched pill placebo for use in the continuation phase of this research until 2006. Thereafter, study materials were purchased and prepared to appear identical for both sites by the pharmacy at the University of Texas Southwestern Medical Center at Dallas.

We are grateful to our patients who made this trial possible.

We appreciate the dedication and long-standing commitment of our research teams and our many colleagues at the University of Texas Southwestern Medical Center at Dallas, the University of Pittsburgh (where Dr. Thase was located during patient accrual), and the University of Pennsylvania.

We also appreciate the diligence of the members of the Data Safety and Monitoring Board.

Disclosure Statement

The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the NIMH or the National Institutes of Health. The C-CT-RP trial is registered at ClinicalTrials.gov (NCT00118404, NCT00183664, and NCT00218764).

Dr. Smits is currently supported by the National Institutes of Health Grants No. R01MH075889 and R01DA027533 and receives royalties from Oxford University Press. During the past 3 years, he has received grant support from Organon/Schering-Plough (now Merck).

Dr. Minhajuddin reports no financial relationships with commercial interests.

Dr. Thase has served as a consultant to and was a member of various advisory boards for Eli Lilly & Co. and received honoraria for talks sponsored by this company. In addition to Eli Lilly & Co.,

during the past 3 years Dr. Thase has consulted with, served on advisory boards for or received honoraria for talks from: Aldolor, Alkermes, AstraZeneca, Bristol-Myers Squibb, Dey, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Lundbeck, MedAvante Inc., Merck, Neuronetics Inc., Otsuka, PamLab, Pfizer Pharmaceuticals, PGx (now Forest), PharmaNeuroboost, Rexahn, Schering-Plough, Shire US Inc., Supernus Pharmaceuticals, Transcept Pharmaceuticals, and Wyeth Pharmaceuticals (now Pfizer). During the past 2 years, he has received grant support from Eli Lilly & Co., Forest, GlaxoSmithKline, Otsuka, and Rexahn, in addition to funding from the National Institutes of Mental Health and the Agency for Healthcare Research and Quality. He has equity holdings in MedAvante Inc. and has received royalties from American Psychiatric Publishing Inc., Guilford Publications, Herald House, and W.W. Norton & Co. Inc. One book currently promoted by American Psychiatric Publishing Inc. specifically pertains to CT. Dr. Thase also discloses that his spouse is an employee of Embryon Inc. (formerly Advogent and Cardinal Health), which does business with several pharmaceutical companies that market medications used to treat depression.

Dr. Jarrett's medical center receives fees from the CT she provides to patients. Dr. Jarrett is a paid consultant to the NIMH.

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