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Cognitive Therapy Alone and in Combination with Antidepressants for Anxious Depression: A STAR*D Report

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Abstract

Background—Anxious depression, defined as MDD with high levels of anxiety, has been associated with lower rates of antidepressant response and remission as well as greater chronicity, suicidality and antidepressant side-effect burden. The primary aim of this study was to assess the effectiveness of cognitive therapy (CT) alone or in combination with medications for anxious versus non-anxious depression.

Methods—We assessed the STAR*D study participants who were partial or non-responders to citalopram. Subjects were then either switched (n = 696) to a new antidepressant or to CT alone, or they were kept on citalopram and augmented (n = 577) with another antidepressant or CT. We compared response and remission rates of those who met criteria for anxious depression to those who did not across treatment conditions.

Results—Those with anxious depression had significantly lower remission rates based on the QIDS, whether assigned to switch or augmentation, compared to those with non-anxious depression. Those with anxious depression, compared to those without, had significantly lower response rates based on the QIDS only in the switch group. There was no significant interaction between anxious depression and treatment assignment.

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Contributors

Maurizio Fava, Jonathan Alpert, Michale W. Otto, John Rush, Madhukar Trivedi, Ed Friedman, and Stephen R. Wisniewski designed and implemented the original STAR*D study. Stephen R. Wisniewski, Roy Perlis and G.K. Balasubramani undertook the statistical analysis. Edward Friedman and Michael Thase oversaw the Cognitive Behavioral Therapy training. All authors were involved in manuscript preparation.

Limitations—Limitations include the use of citalopram as the only Level 1 pharmacotherapy and medication augmentation option, depression-focused CT rather than anxiety-focused CT, and focus on acute treatment outcomes.

Conclusions—Individuals with anxious depression appear to experience higher risk of poorer outcome following pharmacotherapy and/or CT after an initial course of SSRI, and continued efforts to target this challenging form of depression are needed.

Keywords

anxious depression; MDD; CT; psychosocial interventions; STAR*D

Introduction

Whether defined as Major Depressive Disorder (MDD) co-occurring with a syndromally defined anxiety disorder or as MDD with high levels of anxiety symptoms, anxious depression appears to be a common subtype of depression, accounting for somewhere between one-third and one-half of individuals with MDD (Kessler et al., 1998; Rush et al., 2005). Some studies have suggested that individuals with anxious depression compared with non-anxious depression may be characterized by distinctive clinical features including earlier age of depression onset, greater risk of suicidality, lower educational attainment, higher unemployment, and slower recovery (Belzer and Schneier, 2004; Kessler et al., 2005; Novick et al., 2005; Pollack, 2005; Wittchen et al., 2000). Some (Davidson et al., 2002; Fava et al., 1997), though not all (Hirschfeld et al., 2002; Tollefson et al., 1994), pharmacotherapy trials have indicated lower acute response and/or remission rates among individuals with anxious depression compared with those with non-anxious depression.

Among the 2,876 subjects receiving Level 1 treatment with citalopram in the STAR*D study, and the 1,292 subjects receiving Level 2 treatments with various pharmacological switch and augmentation strategies (not including the cognitive therapy (CT) switch/augmentation arm), acute treatment outcomes were significantly poorer among subjects with anxious compared with non-anxious depression when anxious depression was defined by a 17 item Hamilton Depression Rating Scale Anxiety/Somatization Score ≥ 7 (Fava et al., 2008). In addition, anxious depressed subjects had greater side effect frequency, intensity and overall burden, higher discontinuation rates due to treatment intolerance, and greater number of serious adverse events. Similarly, the presence of any DSM-IV anxiety disorder with the exception of social anxiety disorder predicted lower rates of antidepressant remission in STAR*D (odds ratios ranging from 0.65 to 0.80; Trivedi et al., 2006). Carried out in a large effectiveness sample in primary care and mental health outpatient settings, the STAR*D findings have generally underscored the challenges of pharmacotherapy in the treatment of MDD complicated by anxiety.

There is a surprising paucity of published studies on the psychosocial treatment of anxious depression. Some psychotherapy studies focusing on treatment of anxiety disorders have included subjects with comorbid syndromal MDD or depressive symptoms. Generally these studies, particularly those involving cognitive behavior therapy (CBT), have suggested that the presence of depressive symptoms does not necessarily hinder treatment of anxiety disorders (for review Deveney and Otto, 2010). Indeed, CBT targeted to anxiety disorders often will significantly reduce comorbid depression (Joormann et al., 2005; Ost and Breitholtz, 2000; Rosa-Alcazar et al., 2008; Bryant et al., 2003; Tsao et al., 2005). Some studies have also suggested that improvement in anxiety mediates improvement in depression (Moscovitch et al., 2005). As such, CBT for anxiety disorders may be more resilient to the presence of depression, than depression focused treatment to the presence of anxiety (for review Deveney and Otto, 2010).

In a study of interpersonal psychotherapy (IPT), Brown and colleagues (1996) found that depressed individuals with a lifetime history of anxiety disorders, though showing improvement during treatment, were nevertheless less likely to complete treatment, showed overall less improvement, and took longer to recover than those with depression alone. Given the STAR*D findings suggesting poorer pharmacological outcomes in anxious versus non-anxious depression and the dearth of studies on psychosocial interventions for anxious depression, we decided to undertake the current ad hoc study which assesses the effectiveness of CT either alone or in combination with an antidepressant for the treatment of anxious depression. A secondary aim was to establish whether there is a differential effect of switching to CT versus augmenting with CT for individuals with anxious versus non-anxious depression.

Methods

We evaluated the sub-sample from the STAR*D study who received CT (see Fava et al., 2003 for a detailed description of the methods and inclusion/exclusion criteria for STAR*D; see Friedman et al., 2004 for a complete discussion of CT implementation in STAR*D). The STAR*D was approved by the institutional review board. Eligible subjects were outpatients, ages 18–75, seeking treatment in primary care or specialty mental health settings who met DSM-IV criteria for single or recurrent nonpsychotic MDD, had a score of ≥ 14 on the HAMD-17, and had not shown treatment resistance to an adequate trial of an antidepressant during the current depressive episode (MDE). In addition, patients with substance abuse were permitted to enroll unless they required detoxification. Exclusion criteria included a diagnosis of schizophrenia, schizoaffective disorder, anorexia, bulimia, or obsessive compulsive disorder as a primary diagnosis, active suicidality or active medical problems that precluded safe randomization to the treatments offered in STAR*D. All participants provided written informed consent prior to study participation. In STAR*D Level 1, all subjects received a flexible dose of citalopram for 12 weeks. Those subjects who failed to remit on citalopram were offered randomization to Level 2 treatment strategies including switching to another SSRI or other class of antidepressant, pharmacological augmentation, or switch to or augmentation with CT. The current study's sample consists of 577 individuals who were randomized to augmentation and 696 individuals who were switched at Level 2. In the augmentation group, 79 individuals received augmentation with CT and 498 received augmentation with another pharmacological agent. In the switch group, 57 individuals were switched to CT, while 639 were switched to another antidepressant. Tables 1 and 2 describe the demographics per treatment arm.

Anxious depression was defined as a HAMD-17 anxiety/somatization factor score ≥ 7 (Cleary and Guy, 1977). The anxiety/somatization factor score consists of six items: psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, hypochondriasis, and insight. Response was defined as a reduction of ≥ 50% in baseline QIDS-C (the 16-item Quick Inventory of Depression Symptomatology-Clinician Rating; Rush et al., 2003) score at endpoint. Remission was defined as a QIDS-C ≤ 5 at endpoint.

Statistical Analysis

Baseline characteristics were compared across treatment groups using a chi-square or Fisher's exact test for discrete baseline characteristics and either a parametric or nonparametric analysis of variance for continuous baseline characteristics. Logistic and linear regression models were used to assess the differential effect of CT on various outcomes. Models include main effects for treatment (CT versus medication), anxious depression, and the two-way interaction. Logistic regression models were also used to assess the effect of anxiety on remission and response within each treatment group. We used the QIDS-C, both response and remission, as our primary outcome measures. The HAMD-17

was not used as our primary outcome, as it was our grouping variable. We adjusted for significant demographic variables. However, we did not control for severity of depression at baseline of level 2, as higher levels of depression are inherent in the condition of anxious depression.

For the examination of differences between the anxious and the non-anxious cohorts, the treatment augmentation and the treatment switch conditions were considered as factors examined alone and in interaction with the presence of anxiety. Significant interaction terms would indicate the need to examine the simple effects of the presence of anxiety separately in the switch and the augmentation conditions. Likewise, we also included the type of switch as an additional stratification factor and again, the main effect of anxiety and the significance of the interaction term between the stratification factor and the presence of anxiety were of primary interest. Significant findings were subsequently examined in the context of multivariable regression models, entering the covariates (significant demographic factors associated with the presence of anxiety) prior to evaluating the significance of the presence of anxiety as a predictor.

Results

There were statistically significant differences between anxious and non-anxious depressed patients in the Level 2 switch arm with regard to race, employment status, education category, medical insurance, monthly income, and Level 2 baseline depression scores on both depression rating scales (see Table 1). In the Level 2 augmentation arm, there were significant between group differences for gender, ethnicity, employment, medical insurance, education category, monthly income, Level 2 baseline depression scores on both depression rating scales (see Table 2).

The anxious depressed patients compared with non-anxious depressed patients showed worse outcomes across the different forms of treatment, including lower rates of response to switch (QIDS Response: $p<.01$; OR = .44), lower rates of remission to switch (QIDS Remit: $p<.01$; OR = .34), and lower rates of remission to augmentation (QIDS Remit: $p<.05$; OR = .21) following initial treatment with citalopram (see Tables 3, 4, & 5). There were no significant treatment by anxiety group interactions (all p's >.30).

Discussion

Previously, Fava and colleagues (2008) reported poor pharmacological outcomes among those with anxious depression in STAR*D. Our current report extends these findings to those with anxious depression assigned to a psychosocial intervention alone or combined with an antidepressant in STAR*D Level 2. Our results indicate that anxious depression is a clinically important risk factor for non-remission as well as non-response to both pharmacological and psychosocial treatments. In fact, according to our findings, patients with anxious depression are 21–66% less likely to respond or remit to second line interventions, including both switch and augmentation strategies, compared to those with depression alone. Our results are also consistent with others (Fava et al., 2004) who have noted that anxious depression is correlated with specific demographic and clinical variables.

Our findings are specific to depression-focused CT, and do not address the value of psychotherapy directed at anxiety symptoms rather than depressive symptoms. In reviews of the CBT treatment outcome literature on comorbid anxiety and depression, Otto and associates have argued that depression may be less impairing to anxiety-focused treatment than anxiety is to depression-focused treatment (Deveney and Otto, 2010; Otto et al., 2008). That is, many anxiety patients are responsive to treatment despite the presence of depression

(Erwin et al., 2002; Mennin and Heimberg, 2000) and depression often improves with CBT for anxiety (Moscovitch et al., 2005). As such, retargeting CBT to anxiety may offer depressed patients a differential opportunity to improve. Also, cognitive-behavioral interventions targeted at behavioral activation strategies may be useful for overcoming avoidance patterns associated with anxiety (Hopko et al., 2004). Finally, recognizing the possibility of elevated risk for suicidality among patients with anxious depression compared with non-anxious depression, the opportunity to provide an enhanced focus on suicide prevention strategies is likely to be an important aspect of psychosocial approaches for this patient population.

There are several limitations of this study. As STAR*D subjects were enrolled at Level 1 based on the suitability and acceptability of pharmacotherapy, the study population may not have included individuals specifically interested in psychosocial interventions. The relatively low rate of subjects opting for psychotherapy in Level 2 tends to support this hypothesis with only 136 of 1273 subjects in STAR*D Level 2 receiving CT. We cannot determine, therefore, whether our results are generalizable to subjects initially interested in a psychosocial intervention over pharmacotherapy. Also, anxious depression was defined in terms of the HAMD-17 anxiety/somatization factor symptoms (score ≥ 7). As shown by Trivedi and associates (2006), predictability of non-response may differ between a general measure of somatic anxiety and the use of specific diagnostic groups to define anxious depression. Accordingly, our results are specific to the former method of defining anxious depression. In addition, the small numbers of subjects with anxious depression in the CT switch and augmentation groups limits conclusions that can be drawn from this post-hoc study regarding the comparative efficacy of these two strategies, as well as regarding the efficacy of CT versus medication alone strategies for anxious depression. Furthermore, CT in STAR*D was primarily depression-focused and perhaps those participants with anxious depression would have benefited from an anxiety-focused therapy component, as is common in general practice. In addition, citalopram was the only pharmacotherapy option in Level 1 and CT plus citalopram was the only medication augmentation option. Thus it is not possible to determine whether CT as monotherapy following discontinuation of or as augmentation of other antidepressants, such as serotonin-norepinephrine reuptake inhibitors, would yield similar results. Finally, we focused on acute treatment outcomes in this study. We cannot determine from these data whether CT alone or combined with an SSRI had a subsequent impact on rates of MDD relapse or recurrence.

In conclusion, anxious depression is a prevalent form of depression that has been associated with poorer outcome following pharmacotherapy, greater chronicity and elevated risk of suicidality compared with non-anxious depression. This study of STAR*D participants who failed to remit on citalopram and were randomized to receive CT alone or in addition to an SSRI demonstrates poorer response and remission rates for patients with anxious depression following the psychosocial intervention. Further study of the sequential use of pharmacotherapy and psychotherapy in MDD (Guidi et al., 2011) will provide an important opportunity for developing optimal therapeutic strategies for this clinical population presenting with a common and often treatment refractory form of depression.

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Table 1

Level 2 Demographics by Switch

			Anxious Depression				Non-Anxious Depression				
	All (N=696)		Meds (n=284)		CT (n=14)		Meds (n=355)		CT (n=43)		
	n	%	n	%	n	%	n	%	n	%	*p*
OUTCOME											
Clinical Setting											0.16
-Primary	268	38.5	123	43.3	6	42.9	123	34.6	16	37.2	
-Specialty	428	61.5	161	56.7	8	57.1	232	65.4	27	62.8	
Gender											0.30
-Male	284	40.8	110	38.7	3	21.4	154	43.4	17	39.5	
-Female	412	59.2	174	61.3	11	78.6	201	56.6	26	60.5	
Race											<.01
-White	524	75.3	193	68.0	8	57.1	290	81.7	33	76.7	
-Black	122	17.5	71	25.0	4	28.6	44	12.4	3	7.0	
-Other	50	7.2	20	7.0	2	14.3	21	5.9	7	16.3	
Ethnicity											0.41
Caucasian	617	88.6	248	87.3	14	100	318	89.6	37	86.0	
Non-Caucasian	79	11.4	36	12.7	0	0.0	37	10.4	6	14.0	
Employment Status											<.01
-Employed	369	53.1	120	42.3	6	42.9	217	61.3	26	60.5	
-Unemployed	285	41.0	151	53.2	8	57.1	114	32.2	12	27.9	
-Retired	41	5.9	13	4.6	0	0.0	23	6.5	5	11.6	
Medical Insurance											<.01
-Private	310	45.7	104	38.1	4	30.8	176	50.3	26	60.5	
-Public	100	14.7	52	19.0	3	23.1	40	11.4	5	11.6	
-None	269	39.6	117	42.9	6	46.2	134	38.3	12	27.9	
Education Category											<.01
-High School (HS)	80	11.5	44	15.5	0	0.0	34	9.6	2	4.7	
-HS to College Grad	560	80.5	226	79.6	14	100	287	80.8	33	76.7	

			Anxious Depression				Non-Anxious Depression				
	All (N=696)		Meds (n=284)		CT (n=14)		Meds (n=355)		CT (n=43)		
	n	%	n	%	n	%	n	%	n	%	*p*
-College grad+	56	8.0	14	4.9	0	0.0	34	9.6	8	18.6	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	
Age at Baseline	41.9	12.9	43.3	12.8	38.3	13.1	40.9	12.8	43.0	13.9	0.07
Monthly Income	2021	2252	1544	1766	621	641	2434	2585	2135	1669	<.01
L2-Base HRSD Score	18.7	7.3	24.3	5.0	23.4	4.3	14.5	5.7	13.5	5.7	<.01
L2-Base IDS-C30	33.6	13.0	42.5	9.8	39.9	9.2	27.2	11.1	25.3	10.1	<.01

Table 2

Level 2 Demographics by Augment

			Anxious Depression				Non-Anxious Depression				
	All (N=696)		Meds (n=284)		CT (n=14)		Meds (n=355)		CT (n=43)		
	n	%	n	%	n	%	n	%	n	%	*p*
OUTCOME											
Clinical Setting											0.14
-Primary	190	32.9	57	39.6	12	41.4	105	29.7	16	32.0	
-Specialty	387	67.1	87	60.4	17	58.6	249	70.3	34	68.0	
Gender											0.04
-Male	228	39.5	45	31.3	8	27.6	152	42.9	23	46.0	
-Female	349	60.5	99	68.8	21	72.4	202	57.1	27	54.0	
Race											0.92
-White	452	78.3	113	78.5	23	79.3	274	77.4	42	84.0	
-Black	93	16.1	24	16.7	5	17.2	59	16.7	5	10.0	
-Other	32	5.5	7	4.9	1	3.4	21	5.9	3	6.0	
Ethnicity											<.01
Caucasian	500	86.7	112	77.8	26	89.7	315	89.0	47	94.0	
Non-Caucasian	77	13.3	32	22.2	3	10.3	39	11.0	3	6.0	
Employment Status											0.02
-Employed	316	54.8	65	45.1	14	48.3	208	58.8	29	58.0	
-Unemployed	234	40.6	74	51.4	11	37.9	131	37.0	18	36.0	
-Retired	27	4.7	5	3.5	4	13.8	15	4.2	3	6.0	
Medical Insurance											0.01
-Private	289	51.9	60	42.9	15	55.6	187	55.0	27	54.0	
-Public	68	12.2	30	21.4	3	11.1	30	8.8	5	10.0	
-None	200	35.9	50	35.7	9	33.3	123	36.2	18	36.0	
Education Category											<.01
-High School (HS)	75	13.0	32	22.2	4	13.8	39	11.0	0	0.0	
-HS to College Grad	455	78.9	107	74.3	21	72.4	285	80.5	42	84.0	

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		All (N=696)		Anxious Depression				Non-Anxious Depression				
				Meds (n=284)		CT (n=14)		Meds (n=355)		CT (n=43)		
		n	%	n	%	n	%	n	%	n	%	*p*
-College grad+		47	8.1	5	3.5	4	13.8	30	8.5	8	16.0	
		M	SD	M	SD	M	SD	M	SD	M	SD	
Age at Baseline		41.1	12.6	43.3	12.3	40.3	14.2	40.2	12.7	41.3	11.2	0.10
Monthly Income		2198	2801	1395	1430	2053	2231	2530	3263	2364	2184	<.01
L2-Base HRSD Score		16.0	6.9	23.3	5.6	21.6	4.8	12.7	5.0	14.7	4.7	<.01
L2-Base IDS-C30		28.8	12.3	41.1	9.6	37.7	9.3	23.3	9.7	26.7	8.6	<.01

Table 3

Response and Remission Percentages for Switch and Augment

		Anxious Depression		Non-Anxious Depression	
		Meds	**CT**	**Meds**	**CT**
	QIDS-C L2	**% (n)**	**% (n)**	**% (n)**	**% (n)**
Switch (n=696)	Remit	15% (41)	21% (3)	36% (127)	51% (22)
	Response	18% (50)	14% (2)	36% (125)	36% (15)
Augmet (n=577)	Remit	21% (30)	14% (4)	43% (150)	38% (19)
	Response	28% (40)	31% (9)	31% (108)	38 % (19)

Table 4

Level 2 Clinical Outcome by Switch with Anxiety Adjusted for Significant Demographic Variables

Outcome	CT/Meds*		Anxious depression (yes/no)**		INTERACTION	
	OR (CI)	p value	OR (CI)	p value	OR (CI)	p value
L2-QIDS-C Remit	1.63 (0.85–3.15)	0.14	0.33 (0.22–.51)	**<.01**	1.13 (0.25–5.09)	0.88
L2-QIDS-C Response	0.88 (0.44–1.74)	0.70	0.44 (0.30–0.66)	**<.01**	0.93 (0.17–5.15)	0.94

Adjusted for Race, employment status, medical insurance, and education.

CT= Cognitive Therapy; Meds = Medications; OR = odds ratio; CI = 95% confidence interval

*Reference Group = Meds

**Reference Group = non-anxious depression

Table 5

Level 2 Clinical Outcome by Augment with Anxiety Adjusted for Significant Demographic Variables

Outcome	CT/ Meds*		Anxious depression (yes/no)**		INTERACTION	
	OR (CI)	p value	OR (CI)	p value	OR (CI)	p value
L2-QIDS-C Remit	0.87 (0.47–1.62)	0.66	0.39 (0.24–0.62)	**<.01**	0.54 (0.13–2.23)	0.40
L2-QIDS-C Response	1.42 (0.76–2.65)	0.28	0.90 (0.57–1.41)	0.64	0.73 (0.24–2.21)	0.58

Adjusted for gender, ethnicity, employment status, medical insurance, and education.

CT= Cognitive Therapy; Meds = Medications; OR = odds ratio; CI = 95% confidence interval

*Reference Group = Meds

**Reference Group = non-anxious depression