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Anxiety Impairs Depression Remission in Partial Responders During Extended Treatment in Late-Life

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Abstract

Objectives—More than half of older adults with major depressive disorder require extended treatment because of incomplete response during acute treatment. This study characterizes the effect of anxiety on remission during extended treatment for partial responders.

Methods—Following 6 weeks of escitalopram 10mg/day + Depression Care Management (DCM), 124 partial-responders (Hamilton Rating Scale for Depression (HRSD) scores of 11–14) were randomly assigned to receive extended treatment with escitalopram 20 mg/day + DCM with or without interpersonal psychotherapy (IPT) for 16 weekly sessions. Remission was defined as three consecutive weekly scores ≤ 7 on the HRSD. We assessed concurrent symptoms of anxiety using the Hamilton Rating Scale for Anxiety (HRSA) at pre-treatment and after 6 weeks. We conducted Cox regression analysis of time to remission and logistic modeling of rates of remission. We also explored whether anxiety severity altered any impact of IPT.

Results—Pre-treatment anxiety was not associated with time to or rates of remission during 16 weeks of extended treatment. In contrast, more severe psychological symptoms of anxiety after 6 weeks of treatment was associated with both longer time to and lower rates of remission. However, there was no evidence that IPT showed any differential effects as a function of anxiety.

Conclusions—In partial responders to six weeks of lower-dose escitalopram and DCM, planning for extended treatment should account for psychological symptoms of anxiety.

Keywords

Geriatric Psychiatry; Depression; Anxiety; Effect Modifiers; Survival Analysis; Antidepressive Agents

INTRODUCTION

While the goal of treatment of late-life depression is complete symptom remission and restoration of psychosocial and physical functioning, fewer than 50% of older adults ever achieve remission with first-line antidepressant pharmacotherapy [1,2]. Treatment response variability may be due to many factors, including psychiatric comorbidity such as anxiety [3–6].

These partial responders to antidepressant pharmacotherapy present clinicians with difficult treatment choices. Using decision-tree analysis, our group recently showed that partial response at four weeks is unlikely to convert to full response if the antidepressant dose is not increased [7]. In a separate study examining partial responders to escitalopram + Depression Care Management (DCM), we observed no benefit from the addition of a depression-specific psychotherapy (Interpersonal Psychotherapy [8]; IPT) relative to increasing the escitalopram dose alone [9]. Identifying predictors of treatment variability in partial responders may guide both the initial therapeutic decision-making as well as next-step interventions for these complex patients.

Multiple studies have shown pre-treatment anxiety to be both a covariate and a factor influencing whether treatment effects are observed in initial response, remission, and recurrence [3,4,10–12]. For example, more severe anxiety before starting antidepressant pharmacotherapy has been associated with both 1) lower rates of response and remission, and 2) increased time to response during treatment with both tricyclics and serotonin reuptake inhibitors in older adults [6,12,13]. In studies of maintenance antidepressant pharmacotherapy, anxiety symptoms both at baseline and during treatment have been associated with early recurrence [13]. The diagnosis of a co-morbid anxiety disorder according to DSM-IV criteria, on the other hand, has not been shown to predict antidepressant treatment variability [10]. A recent meta-analysis of eight randomized controlled trials evaluating only acute pharmacotherapies without dosage increases reported no difference in the response rates between older depressed patients with or without anxiety symptoms at baseline [14].

The present study is based on work from our group in which we observed that depressed older adults were less likely to respond to six weeks of acute pharmacotherapy with lower-dose escitalopram and DCM if they endorsed high levels of anxiety prior to acute treatment [15]. Our goal in the current analyses was to explore the influence of anxiety symptoms among partial responders who were subsequently randomized to extension treatment consisting of higher-dose escitalopram and DCM with or without IPT. We hypothesized that more severe anxiety symptoms at pre-treatment and after 6 weeks would predict both longer time to and lower rates of remission for both treatment conditions during the 16 weeks of extension treatment. In addition, based on our earlier findings [15], we hypothesized that pre-treatment anxiety severity would negatively affect any response to IPT (i.e., patients with more severe anxiety would show little benefit from IPT, even if IPT benefited less anxious patients). We hypothesized this negative interactive effect because high levels of anxiety have been shown to predict worse depression outcomes during treatment with interpersonal psychotherapy [16].

METHODS

Details of the study protocol are described in detail elsewhere [9]. Briefly, subjects were 60 years of age and older with a diagnosis of a non-psychotic, non-bipolar major depressive episode per the Structured Clinical Interview for DSM-IV (SCID) [17]. Pre-treatment, subjects scored ≥ 15 on the Hamilton Rating Scale for Depression (HRSD; 17-item) [18]. Participants also scored at least 18 on the Folstein Mini-Mental State Examination (MMSE) [19] and had never received a diagnosis of dementia. We included this wide range of MMSE scores to increase the generalizability of the results to a broad geriatric population. Subjects with a range of medical comorbidities were included as long as they were clinically stable and could be managed as outpatients. Informed consent was obtained from all subjects after the nature of the procedures was explained.

In the initial phase of the study, 319 participants initiated 6 weeks of open-label treatment with 10 mg/day escitalopram and DCM. DCM was delivered by advanced-practice psychiatric nurses and masters and PhD-level psychologists who were supervised by faculty geriatric psychiatrists. DCM consisted of weekly face to face appointments, psychoeducation about the nature of depression, close monitoring of symptoms of depression, management of treatment-emergent side effects, and the monitoring and management of suicidal ideation. All antidepressants were stopped prior to treatment initiation. Participants who could not tolerate discontinuation of benzodiazepines were converted to an equivalent dose of lorazepam (usually 1 to 2 mg/day). By week six, 39 participants (12.2%) had exited the study prior to completion of acute treatment. At week 6, 94 responders (29.5%) (HRSD-17 < 10) and 62 non-responders (19.4%) (HRSD-17 score $\geq$ 15) also exited the study. One hundred twenty-four (38.9%) partial responders (defined by HRSD-17 scores of 11–14 at week six), the sample included in this analysis, had the escitalopram increased to 20 mg/day and were randomly assigned to extension treatment with continued DCM (n = 64) or DCM + IPT (n = 60) for up to 16 weeks. The same clinicians who had delivered the initial six weeks of depression care management with 10 mg of escitalopram daily also delivered extension treatment. We have adopted the term “extension” treatment (instead of “continuation” treatment) because the participants were all partial (as opposed to full) responders [20,21].

Assessments

Depression—We used the Hamilton Rating Scale for Depression [18] (HRSD, 17-item version) to assess depression severity at baseline and to detect change in depression severity during the course of treatment. Inter-rater reliability was maintained at an intraclass correlation coefficient (ICC) of 0.95.

Anxiety—Anxiety severity was measured with the Hamilton Rating Scale for Anxiety (HRSA) [22]. This instrument consists of 14 items scored on a 5 point scale ranging from 0 (not present) to 4 (very severe). The HRSA was further divided into psychic and somatic subscales. The psychic subscale consists of: anxious mood, tension, fears, insomnia, intellectual/cognitive components of anxiety, and clinician-observed behavior. The somatic subscale consists of symptoms from the following systems: muscular, sensory, cardiovascular, respiratory, gastrointestinal, genitourinary, and autonomic. In accordance with a recent report from our group, we recomputed the total anxiety score by removing the depression item (question 6) [15], and used this modified HRSA score for all analyses. Inter-rater reliability was high with an ICC for the HRSA of 0.95.

Statistical Analysis

We hypothesized that more severe anxiety symptoms both before and after 6 weeks of initial pharmacotherapy and depression care management would predict longer time to remission and lower remission rates during the 16 weeks of extended treatment for both arms of the study. In addition, we hypothesized that pre-treatment anxiety symptoms would negatively influence the response to IPT. Our primary categorical outcome measure was remission of major depression, defined by three consecutive weekly HRSD-17 scores of $\leq$ 7. The HRSA was analyzed as a continuous variable. As HRSD scores were obtained weekly throughout treatment, we were able to document trajectory and speed of symptom change. To examine time to remission, each predictor variable was entered into a Cox regression using intent to treat analysis (i.e., dropouts contributed data to the analyses until the point of censoring). Logistic models were used to compare rates of remission in completers to capture the full dose of the intervention. Both Cox regression and logistic model analyses provided Wald X^2 values for significance testing. The combined, or interactive, effect of IPT was explored by inserting an interaction term of treatment group by anxiety into the models. We controlled

for age and benzodiazepine use in all of the analyses to account for any differences between groups. An alpha of 0.05 for each analysis was used as the criterion of statistical significance.

RESULTS

As shown in Table 1, the mean age of IPT-randomized participants was 2.3 years younger than the non-IPT group. Pre-treatment, subjects randomized to receive IPT had worse anxiety symptoms than patients not receiving IPT. The anxiety severity scores, however, were equivalent after 6 weeks of treatment (e.g., at randomization). Diagnosis of a co-morbid anxiety disorder was only weakly correlated with baseline HRSA scores ($r=.12$, $p=.20$). Although the associations between the HRSD and modified HRSA scores at both baseline ($r=0.56$, $p<0.0001$) and randomization ($r=0.25$, $p=0.008$) were statistically significant, the measures were far from completely overlapping and thus each warrant consideration. During the randomized phase of the study, IPT subjects completed a mean (SD) of 11.8 (3.6) sessions. The DCM (non-IPT) subjects completed 12.6 (2.9) sessions. The average dose of escitalopram for the DCM+IPT and DCM groups was 17.7 (4.5) and 17.0 (4.6) mg/day, respectively, reflecting the fact that not all subjects could tolerate 20 mg/day.

Does Anxiety Severity Predict Remission?

Using intent to treat analysis and censoring dropouts, the pre-treatment HRSA was not associated with time to remission during extension treatment (Wald $X^2=2.96$, $df=1$, $p=0.09$, hazard ratio=0.94 [0.87,1.01]). Likewise, completer analysis showed no association between anxiety severity at baseline and rate of remission (Wald $X^2=3.29$, $df=1$, $p=0.07$, OR=0.88 [0.78,0.99]). We also examined the effect of anxiety severity at week 6 (at randomization) on time to and rates of remission. Using both intent to treat (ITT) and completer analyses, the HRSA scores at week 6 were associated with both time to remission ($X^2=7.84$, $df=1$, $p=0.005$, hazard ratio=0.90 [0.83, 0.99]) and final rates of remission ($X^2=12.07$, $df=1$, $p=0.001$, OR=0.78 [0.66,0.91]) respectively (the results were the same for both ITT and completer analyses). In contrast, the diagnosis of a co-morbid anxiety disorder (established pre-treatment using the Structured Clinical Interview for DSM-IV [17]) was not associated with either time to or rate of remission.

To further clarify the effects of anxiety on remission, we created prognostic survival curves from each Cox regression and logistic model at baseline and randomization (Table 2). Figure 1 represents the prognostic survival curve generated for the Cox regression model for anxiety severity at 6 weeks. From this model, curves were generated based on high and low anxiety severity using HRSA scores of 5 and 15 respectively. These cutoffs represent the 10th and 90th percentiles for anxiety severity for this population.

Given the association with the HRSA scores at week 6 and treatment outcome, we examined which symptoms of anxiety were associated with depression outcome. HRSA scores were divided into psychic and somatic subscales [15]. We analyzed both subscales for an association with time to remission using Cox regression models and rate of remission using logistic models. A higher score on the psychological subscale at randomization (i.e., 6 weeks) was associated with both: 1) prolonged time to remission ($p=0.005$, $X^2=7.99$), and 2) lower final remission rate ($p=0.001$, $X^2=10.72$). The somatic subscale was not a significant predictor of time to remission ($p=0.16$, $X^2=1.93$) or rates of remission ($p=0.05$, $X^2=3.72$).

Does Anxiety Alter Any Impact of IPT on Remission?

Our hypothesis that IPT would show differential effects as a function of pre-treatment anxiety severity was not supported by the data (i.e. there was no treatment by anxiety interaction) ($p=0.52$, $X^2=0.42$).

DISCUSSION

In partial responders to six weeks of escitalopram (10 mg/day) and DCM, greater levels of anxiety symptoms at week 6 predicted both a longer time to remission and a lower rate of remission during 16 weeks of extension therapy with either 20 mg/day escitalopram with DCM or 20 mg/day escitalopram with DCM+IPT. In contrast, pre-treatment anxiety did not predict time to remission. Additionally, response to IPT was not differentially influenced by severity of pre-treatment anxiety. In agreement with previous studies, the categorical diagnosis of a comorbid anxiety disorder, as distinct from the dimensional measure of anxiety severity, did not predict remission [10,23].

To our knowledge, this is the first report analyzing the effects of anxiety on time to and rates of remission of depression in partial responders to acute therapy. Previous studies have observed various effects of pre-treatment anxiety on response to therapy [3,5,6,10], but not of anxiety severity after 6 weeks of treatment on subsequent outcome. Our results indicate that the psychic subscale of the HRSA after 6 weeks of treatment accounts for the effect of anxiety on remission. This is consistent with recent work by Andreescu et al [24] who reported that high worry components of the Brief Symptom Inventory [25] (BSI) anxiety scale predicted slower response and faster recurrence of depressive symptoms. Both their findings and ours suggest that the psychological symptoms of anxiety, both before and after initial treatment, may be better predictors of response to antidepressant therapy than the somatic symptoms of anxiety. In addition, the predictive nature of these symptoms may evolve during the course of treatment. For example, while our earlier report and that of Andreescu et al. showed that higher pre-treatment anxiety predicted non-response to acute therapy [15], in the current study we observed that more severe anxiety at week 6 is predictive of less favorable depression treatment outcomes during extension treatment. Because extension treatment differed from initial treatment in this study, it is not surprising that anxiety severity at the start of extension treatment provided a more accurate predictor of evolving treatment response.

These results may be consistent with current descriptions of aberrant activation of the prefrontal cortex in disorders involving anxious apprehension [26,27]. The predictive role of prefrontal dysfunction in treatment response in late-life depression is well-established [28,29], and may be relevant to understanding treatment response in mixed anxiety and depression in old age [30]. Alternatively, the tripartite model [31], in which the anxiety-depression comorbidity is explained almost exclusively by the presence of increased negative affect in both conditions [32–34], suggests that subjects with anxiety and residual symptoms of depression at week 6 may be characterized by increased levels of neuroticism, a feature frequently reported in the literature as predictive of poor treatment response [35]. Future investigation will address the personality characteristics of these subjects.

Contrary to our hypothesis and previous findings [36], we did not observe diminished response to IPT during the extension phase based upon severity of pre-treatment anxiety. Other studies have observed reductions in anxiety during treatment with IPT for social phobia [37] and post traumatic stress disorder [38]. Our data suggest that partially-responding patients who require extension treatment will not be at a clinical disadvantage if IPT is added during this phase. Although it appears that IPT is neither more nor less effective as a function of anxiety severity, these partial responders with high symptoms of

anxiety pose a therapeutic challenge. This is represented by Figure 1; more severe anxiety predicts lower likelihood of remission. These findings suggest that clinicians may need to pursue more aggressive treatment than just increasing the dose of antidepressant or adding a depression-specific psychotherapy such as IPT. While speculative, prescribing a depression-specific treatment that also is specific for the psychological symptoms of anxiety (e.g., worry, rumination, catastrophizing), such as cognitive behavioral therapy [39], may be required to achieve a robust response.

This study has several limitations. Patients who were randomized to IPT had higher anxiety levels at initial study enrollment. However, by six weeks of treatment (and before randomization), this difference had disappeared. While extension therapy for the partial responders was randomized, it was not placebo-controlled. Depression care management incorporates more components than usual care in a typical primary care encounter that is focused on depression. This was supported by our observation that remission in the DCM group was greater than reported in usual care [40]. Finally, results of the analysis examining differential effects of IPT as a function of anxiety severity must be interpreted cautiously, as the parent study was not powered to test interaction effects between treatment assignment and other variables. While exploratory, we hope these preliminary analyses will generate hypotheses and ideas for future research to improve the treatment options for these therapeutically challenging patients.

In summary, we have shown that in partial responders to six weeks of lower-dose escitalopram and DCM, higher levels of anxiety following initial treatment predict longer time to remission and lower rates of remission. Since anxiety did not show any influence on response to IPT, other variables that may lead to differential treatment effects should be explored to further personalize the treatment of depressed older adults who partially respond to first line antidepressant care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Clinical Measures (mean $\pm$ SD)

Measure	IPT N=60	Depression Care Management N=64	X ² or t	Df	p
Pre-Treatment					
Age	71.1 (7.1)	73.4 (7.7)	1.69	122	0.09
% Female	73%	64%	1.23	1	0.27
% Benzodiazepine Use	32%	34%	0.10	1	0.75
Pre-intervention Clinical Measures					
% Recurrent Major Depressive Disorder	50%	52%	0.30	1	0.86
Duration of Illness (years)	16.2 (18.9)	15.1 (16.7)	0.34	122	0.73
Duration of current episode in weeks ⁺	129 (209)	133 (153)	0.58	122	0.57
Hamilton Rating Scale for Depression (HRSD)	19.0 (3.5)	18.0 (2.5)	1.90	122	0.06
Hamilton Rating Scale for Anxiety (HRSA)	16.3 (4.9)	14.3 (3.7)	2.61	121	0.01
Modified HRSA ++	16.3 (4.9)	14.4 (3.6)	2.54	121	0.01
% Anxiety Disorder Diagnosis [#] Subtypes, N (more than 100%)	38%	45%	0.62	1	0.43
Generalized Anxiety Disorder	18	23			
Panic Disorder	9	9			
Anxiety Disorder Not Otherwise Specified	0	3			
Social Phobia	5	5			
Obsessive Compulsive Disorder	0	1			
Randomization at 6 weeks					
HRSD	12.5 (1.0)	12.5 (1.1)	0.17	122	0.86
HRSA	12.4 (3.1)	13.2 (3.6)	1.36	120	0.18

Measure	IPT N=60	Depression Care Management N=64	X ² or t	Df	p
Modified HRSA	11.6 (3.5)	10.8 (3.0)	1.36	120	0.18

⁺ Natural log transformation prior to statistical comparison

⁺⁺ Modified Hamilton Rating Scale for Anxiety (HRSA) is the HRSA with the depression item removed.

[#] Includes Generalized Anxiety Disorder, Panic Disorder, Anxiety Disorder Not Otherwise Specified, Social phobia, and Obsessive Compulsive Disorder

Table 2

Multivariate Models for Remission

Measure	Cox regression Model 1 Baseline HRSA	Cox regression Model 2 Week 6 HRSA	Logistic regression Model 3 Baseline HRSA	Logistic Regression Model 4 Week 6 HRSA
Age	0.99 [0.96,1.03]	0.99 [0.96,1.03]	0.97 [0.91,1.02]	0.96 [0.91,1.03]
Female	0.99 [0.58,1.73]	0.91 [0.52,1.60]	0.79 [0.32,1.93]	0.78 [0.30,2.04]
Benzodiazepine Use	1.05 [0.62,1.81]	1.14 [0.66,1.97]	1.08 [0.43,2.74]	1.27 [0.48,3.37]
Depression Severity	1.02 [0.92,1.13]	0.76 [0.59,0.98]	1.08 [0.92,1.26]	0.65 [0.42,1.01]
Assignment to IPT	1.70 [0.99,2.89]	1.41 [0.85,2.37]	2.08 [0.88,4.88]	1.53 [0.63,3.74]
Anxiety Severity	0.94 [0.87,1.01]	0.90 [0.83,0.99]	0.88 [0.78,0.99]	0.78 [0.66,0.91]

Model 1 and 2 are hazard ratio results of Cox model for all subjects using intent to treat analysis

Model 3 and 4 are odd ratio results of logistic model in completed subjects

After controlling for other variables, anxiety remains significant in Cox model 2 (6 weeks) and both logistic models.