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Comorbid Anxiety in Late-Life Depression: relationship with remission and suicidal ideation on venlafaxine treatment.

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Abstract

OBJECTIVE: The purpose of this study was to examine the influence of comorbid anxiety symptoms on antidepressant treatment remission in older adults with Major Depressive Disorder.

METHOD: In this multi-site clinical trial, 468 older adults aged 60 years or older with Major Depressive Disorder received open label protocolized treatment with venlafaxine ER titrated to a maximum of 300 mg daily. At baseline, anxiety was assessed with the Anxiety Sensitivity Index (ASI), the Brief Symptom Inventory (BSI) anxiety subscale and the Penn State Worry Questionnaire (PSWQ). To measure treatment response, depressive symptoms and suicidality were assessed every 1–2 weeks with the Montgomery–Asberg Depression Rating Scale and the 19-item Scale for Suicide Ideation; anxiety was assessed with the BSI. Logistic regression and survival analysis were used to evaluate whether anxiety symptoms predicted depression remission. We also examined the relationships between the anxiety scores and suicidality at baseline.

RESULTS: Baseline anxiety symptoms did not predict remission or time to remission of depressive symptoms. Depressive, worry, and panic symptoms decreased in parallel in patients with high anxiety. Anxiety symptoms were associated with severity of depression and with suicidality.

CONCLUSION: In older adults with Major Depressive Disorder, comorbid anxiety symptoms are associated with symptom severity but do not affect antidepressant remission or time to remission.

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Introduction

Anxiety symptoms and disorders are common in depressed individuals across the lifespan (Flint, 1994; Kessler et al., 1996; Lenze et al., 2000). Up to 65% of elderly patients with depression have co-occurring symptoms of anxiety (Alexopoulos, 1990; Lenze et al., 2000). Although neither a DSM-IV nor a DSM-5 diagnosis, the term “anxious depression” has been used to characterize presentations with features of both a depressive and an anxious syndrome (Lenze et al., 2001). It typically entails a major depressive disorder (MDD) with coexistent anxious distress or with a comorbid generalized anxiety disorder (Ionescu, Niciu, Henter &Zarate, 2013). The concept of anxious depression has long been of interest to clinicians as it may represent a distinct syndrome with implications for treatment. It is also thought to be associated with more severe anxiety and depression (Ionescu, Nicio, Mathews, Richards &Zarate, 2013; Schoevers, Beekman, Deeg, Jonker &van Tilburg, 2003). Thus, a dimensional approach to comorbid depression and anxiety may have implications for management and treatment options (Ionescu, Niciu, Henter &Zarate, 2013; Schoevers, Deeg, Van Tilburg & Beekman, 2005).

Anxiety disorders are subdivided into multiple categories in the DSM-5 that can be grouped in two main symptom categories: worry/distress disorders and fear disorders. Krueger (1999) described two of those three psychopathological variances as internalizing patterns of ‘anxious-misery’ and fear or phobic-based patterns. In worry disorders, exemplified by generalized anxiety disorder, the source of anxiety is more distal and rather marked by apprehension; symptoms are often chronic with periods of exacerbations. In contrast, fear disorders exemplified by panic disorder are characterized by a peri- and post- anxious state of acute intense hyperarousal. This distinction is important because of neuroimaging and genetic evidence that these two phenotypes are distinct (Martin et al., 2009). Moreover, despite the chronicity of both these disorders, there is some evidence that fear symptoms (e.g., panic) decline with aging, while worry symptoms may be more common in older depressed individuals (Schaakxs et al., 2017; Jeste et al., 2006, Wuthrich et al., 2015). Time and experience are thought to aid in the development of emotional regulation (Jarvik et al., 1979). Moreover, age-related atrophy of the locus coeruleus and other anxiety-associated brain regions as well as changes in peripheral physiology are thought to attenuate anxious arousal in older individuals (Flint, 1994; Flint et al., 2002). However, aging is associated with degeneration of other brain regions that promote adaption to anxiety, for instance the dorso-lateral prefrontal cortex. As well, the aging process is associated with new stressors such as health concerns for self or loved ones, disability, and financial stressors (Diefenbach et al., 2001). It is therefore important to better understand the role of comorbid anxiety symptoms, particularly worry, in depression outcomes in older patients.

Depression with comorbid anxiety is of particular relevance to older adults because of its association with dysfunction, morbidity, and mortality. It is associated with more severe depressive symptoms (Coryell et al., 1992), more impairment of social functioning (Lenze et al., 2000), greater memory decline (DeLuca et al., 2005, Parmelee et al., 1993), and more somatic complaints, (Hegeman et al., 2012, Stordal et al., 2003) even when chronic medical illness is accounted for (Schaakxs et al., 2017). Although the effect of concurrent anxious and depressive symptoms in older people has shown inconsistent effects on all-cause

mortality (Herrmann et al., 2000, Van der Weele et al., 2009), there have been reports of increased risk of cardiac-related mortality in this population (Moser & Dracup, 1996). Moreover, older adults with anxious depression have increased suicidality and completed suicides compared to depressed older adults without anxiety (Allgulander & Lavori, 1993; Batterham et al., 2013; Bronisch & Wittchen, 1994; Conwell et al., 1996; Lenze et al., 2001; Jeste et al., 2006). For instance, Bartels et al (2002) reported that anxious depressed elderly were twice as likely to have suicidal ideation as non-anxious depressed individuals. Suicidality in the context of anxious depression may be a treatment-relevant subtype of this syndrome warranting more intensive management.

Several studies in depressed older adults have examined the effect of comorbid anxiety on antidepressant treatment response. Some studies have reported poor response of depression with comorbid anxiety treated with nortriptyline (Flint & Rifat, 1997) or SSRIs (Andreescu et al., 2009; Dew et al., 1997; Fava et al., 2008; Mulsant et al., 1996; Saghafi et al., 2007). One study that divided baseline anxiety symptoms into worry and fear found that worry symptoms, but not fear symptoms, predicted longer time to respond to treatment, and shorter time to relapse, in older adults receiving protocolized antidepressant treatment for depression (Andreescu et al., 2009). However, these findings have been contradicted by other reports in which comorbid anxiety did not predict likelihood or time to response in older depressed individuals (Nelson et al., 2009).

Overall, as reviewed by Whyte et al. (2004), it appears that comorbid anxiety is a predictor of poorer antidepressant outcome, but with the caveat that published reports were either small prospective studies or secondary retrospective analyses in which anxiety was assessed with single item or subscales of depression scale such as the Hamilton Depression Rating Scale (HDRS) or the Montgomery–Asberg Depression Rating Scale (MADRS). The validity and reliability of measuring anxiety symptoms this way have not been established and it is preferable to use scales specifically designed and validated to assess anxiety symptoms.

In order to test whether depression with comorbid anxiety symptoms is truly a treatment-relevant subtype in older adults, we carried out an analysis of data from the Incomplete Response in Late-Life Depression: Getting to Remission (IRL-GRey) study, a large prospective antidepressant trial. Our first goal was to examine the influence of comorbid anxiety symptoms on remission of the depressive symptoms and on the time to remission. We hypothesized that higher levels of baseline anxiety symptoms –particularly worry– would predict worse treatment outcomes. Our second goal was to examine the relationship between comorbid anxiety symptoms and suicidal ideation, both at baseline and over the course of treatment. Based on previous reports (Allgulander & Lavori, 1993; Bartels et al., 2002; Batterham et al., 2013; Bronisch & Wittchen, 1994; Conwell et al., 1996; Lenze et al., 2001; Jeste et al., 2006), we hypothesized that patients with higher levels of anxiety symptoms would be more likely to have suicidal ideation.

Methods

The IRL-GRey study (Lenze et al., 2015) was a multi-center, 2-phase clinical trial conducted in three academic centers (University of Pittsburgh, Pennsylvania, USA [coordinating site];

Centre for Addiction and Mental Health, Toronto, Canada; and Washington University, St. Louis, Missouri, USA). For this analysis we used data from the lead-in, open label venlafaxine treatment phase of the study. All participants provided written, informed consent. The study was approved by each site's institutional review board. The methods of the IRL-Grey study have been described in details elsewhere (Lenze et al., 2015); they are summarized briefly here. This was an NIMH funded study without pharma investment other than providing free medication.

Participants

Between July 2009 to January 2014. 468 older adults aged 60 years or older with MDD were enrolled and received open label treatment with venlafaxine ER. The inclusion criteria were: DSM-IV-TR criteria for a major depressive episode with symptoms of at least moderate severity, as defined by a MADRS score ≥ 15 (ranges 0–60; higher scores indicating a greater severity of depression) (Montgomery & Åsberg, 1979). Exclusion criteria were: current diagnoses of dementia, bipolar disorder, or schizophrenia; current psychotic symptoms; substance abuse or dependence within the past six months. Patients with co-morbid anxiety disorders were not excluded from the study. Remission was defined as a MADRS score ≤ 10 at both of the final two consecutive visits. After 12–14 weeks, participants who did not achieve remission with venlafaxine monotherapy were randomized to double-blinded augmentation with either aripiprazole or placebo, while continuing the venlafaxine ER dosage reached at the end of the open first phase. This analysis focuses exclusively on data obtained during the open first phase.

Clinical Assessments

Participants were assessed at baseline (pre-treatment) and on a weekly or biweekly basis with the MADRS, the Brief Symptom Inventory anxiety subscale (BSI-anxiety; Derogatis & Melisaratos, 1983) and the 19-item Scale for Suicide Ideation (SSI; Beck et al., 1979). The Anxiety Sensitivity Index (ASI; Reiss et al., 1986) and the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990) were obtained at baseline only.

The ASI is a 16-item self-report instrument that investigates the construct of anxiety sensitivity. This construct underlies many fear based disorders such as panic disorder, and it assesses 'fear of fear' or an individual's sensitivity to anxiety symptoms that they are having. ASI total scores are predictive of the development of panic symptoms (Schmidt et al., 1997, 1999). Each item is scored on a Likert scale between 0 and 4; the total score (range: 0–64) has been shown to have good psychometric properties (Peterson & Reiss, 1987; Reiss et al., 1986), including in older adults (Mohlman & Zinbarg, 2000). It is correlated with fear and predictive of panic attacks (Reiss.,1991; Schmidt et al., 1997). The ASI has been frequently divided into three distinct factors measuring social concerns, mental incapacitation concerns, and physical concerns. The items used for each factor have been described elsewhere (Rodriguez et al., 2004; Mohlman & Zinbarg, 2000).

The BSI is a 6-item psychological self-assessment of anxiety symptoms (Derogatis & Melisaratos, 1983). Each of the 6 items is scored on a Likert scale between 0 and 4, with higher scores indicating higher anxiety. The BSI overall score (range 0–4) is the mean score

of the scores of the 6 items. Three items focus on general nervousness while the other three focus on fear or panic (Andreescu et al., 2009).

The PSWQ is a 16-item self-report instrument that assesses the symptoms and thought process of worry or anxiety. Each item is scored on a Likert scale between 1 and 5; the total score (range: 16–80) has been shown to have good validity, test re-test reliability, and internal consistency (Meyer et al., 1990).

Internal consistency (Cronbach's alpha) for these 3 measures was very good to excellent: ASI (0.90), BSI (0.86) and PSWQ (0.92).

Participants were also asked to complete the Scale for Suicide Ideation (Beck et al., 1979), a 19-item questionnaire evaluating the desire to live, the desire to die, and other suicidal intentions. It has high internal consistency and good correlations with other clinical assessments of self-harm and of suicidal risk. It includes a 5-item screener that assesses both passive and active suicidality; if suicidality is detected with this screener, then the entire 19-item scale is completed. All items are scored between 0 to 2.

Comorbid physical illness was evaluated with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992).

Venlafaxine ER Protocolized Treatment

As described elsewhere (Joel et al. 2013), participants were initially treated with venlafaxine ER at a starting dose of 37.5 mg/day, titrated (typically over 2–4 weeks) to 150 mg/day. After 6 weeks, in the absence of remission, venlafaxine ER was titrated up to 300 mg/day depending on MADRS score and tolerability.

No other pharmacologic or psychotherapeutic treatments were initiated during the study, yet participants were allowed to continue previously prescribed low-dose benzodiazepine. The benzodiazepines used were: alprazolam (n=28), chlordiazepoxide/clidinium (n=1), clonazepam (n=56), diazepam (n=4), lorazepam (n=196), oxazepam (n=1), and temazepam (n=9).

Analytic Strategy

Our analyses were initially performed using baseline anxiety scores of ASI, BSI and PSWQ as individual predictors. We also used ASI sub-scale factors (social concerns, mental incapacitation concerns and physical concerns) as individual predictors. We then repeated those initial analyses controlling for 7 baseline covariates: age, sex, race, Cumulative Illness Rating scale for Geriatrics (CIRSG), education, site and benzodiazepine use.

Differences in baseline characteristics between remitters and non-remitters were evaluated using a two-tailed t-test for continuous variables, and a chi-square test for categorical variables. Because the anxiety measures were correlated with MADRS, we did an analysis of covariance between the remitters and non-remitters, using a modified MADRS (rescored by removing the anxiety 'Inner Tension' component item) as a covariate. We also examined the relationships between the anxiety scores and suicidality at baseline.

We then performed a logistic regression analysis to evaluate baseline anxiety symptoms as predictors of remission. We separately examined the 3 anxiety variables (ASI, BSI and PSWQ) before and after addition of covariates. Survival analysis using a Cox Proportional-Hazards Model was then used to investigate the predictive value of baseline anxiety scale scores on time to remission. For both the logistic regression and proportional hazards regression analyses, we excluded the 96 non-completers. Analyses were conducted using SAS v9.4. (SAS Institute Inc., Cary, NC).

Results

Participants' baseline characteristics are shown in Table 1. Average dose of venlafaxine at end point, in mg/day (SD), was of 228.4 (229.7) for non-remitters and of 165.2 (158.8) for remitters. As expected, non-remitters had higher baseline MADRS scores than remitters. Baseline anxiety scores (ASI, BSI and PSWQ) did not differ between remitters and non-remitters (see Table 2). To put into context with what is available in the literature: higher anxiety is usually associated with a BSI greater then 1.0, as previously described by Andreescu et al. (2007). An ASI score of 25 (Taylor et al., 1999) is suggested as a cut off of low versus high anxiety, a PSWQ score of 50 or greater generally defines clinically significant anxiety as seen in GAD (Stanley et al., 2003; Webb et al., 2008 Wuthrich et al., 2014).

Baseline anxiety and remission

Baseline anxiety scores did not predict the likelihood of remission of depressive symptoms. Using standardized data, the odds ratio of remission of depression on venlafaxine were the following: ASI, OR 0.85 (95% CI 0.69–1.04; p=0.11); BSI, 0.82 (95% CI 0.67–1.01; p=0.06); PSWQ, 0.90 (95% CI 0.73–1.10; p=0.31); the results remained similar when controlling for the covariates mentioned above: age, sex, race, Cumulative Illness Rating scale for Geriatrics (CIRSG), education, site and benzodiazepine use. They continued to remain similar when controlling for all of the prior covariates except benzodiazepine use. In addition, incorporating all three scale variables into one model produced similar results, including a non-significant omnibus test ($\chi^2(3) = 4.53$, $p = 0.21$). Moreover, when assessing the 3 distinct subcale factors of the ASI, the odds ratio of remisison of depression on venlafaxine were the following: Social Concerns, OR 0.89 (95% CI 0.72–1.09; p=0.26), Mental Incapacitation Concerns, 0.85 (95% CI 0.69–1.04, p=0.12) and Physical Concerns, 0.86 (95% CI 0.70–1.06, p=0.16).

Similarly, the baseline anxiety scores did not predict time to remission: ASI, HR 0.9 (95% CI 0.8–1.1; p=0.3); BSI, 0.9 (95% CI 0.8–1.03; p=0.1); PSWQ, 0.9 (95% CI 0.8–1.1; p=0.3). The results were similar when data were log-normalized or when controlling for the 7 covariates. They also remained similar when controlling for 6 covariates without controlling for benzodiazepine use. Additionally, no ASI subscale factor predicted time to remission: Social Concerns, HR 0.95 (95% CI 0.83–1.10, p=0.50), Mental Incapacitation Concerns, 0.94 (95% CI 0.81–1.09, p=0.38) and Physical Concerns, 0.93 (95% CI 0.80–1.07, p=0.28).

The trajectories of improvement in depressive symptoms were similar in participants with low anxiety (BSI scores ≤ 1) or high anxiety (BSI scores > 1) (see Figure 1). Similarly, the trajectories of improvement in depressive, worry, and panic symptoms were similar among participants with high anxiety (see Figure 2).

Baseline anxiety and suicidality

Suicidality at baseline (defined as present if the SSI total score ≥ 1) was associated with higher baseline MADRS, ASI, BSI and PSWQ scores (Table 3). The mean (SD) baseline SSI score was 1.8 (3.8) in remitters and 2.9 (5.1) in non-remitters.

Discussion

We examined the impact of comorbid anxiety symptoms on treatment response in a large prospective study of older adults with MDD receiving protocolized antidepressant treatment. Using validated anxiety scales, we had two main findings. First, baseline anxiety symptoms did not predict antidepressant treatment outcomes: remission of depression was just as likely in more and less anxious participants. Both worry and fear/panic symptoms improved as depressive symptoms improved. Second, the presence of suicidality at baseline was associated with more severe depression, worry, and fear/panic. Overall, these results suggest that, while anxiety symptoms in the setting of depression may be associated with more severe psychopathology, it does not negatively impact outcome to protocolized antidepressant treatment in older adults.

To our knowledge, no large study has prospectively examined response to treatment of late-life depression with comorbid anxiety symptoms using validated validated scales for each construct of anxiety. Our study used two anxiety measures, one focused on pathological worry and another focused on physiological sensations (including those associated with panic). Similarly, we used a validated scale to assess suicidality (Beck et al., 1979). Combined with protocolized treatment, the inclusion of these validated measures allowed us to carefully assess anxiety symptoms' impact on treatment response, to review its relation to suicidality, and to clearly distinguish between "true" treatment resistance and pseudoresistance. Pseudoresistance is the lack of antidepressant response in the context of inadequate treatment due to low antidepressant dosage, short trial duration, or failure to complete treatment (Cristancho et al., 2018).

These findings are important as they provide insights on the clinical impact of late-life anxious depression, an area of much disagreement and inconsistent evidence. To our knowledge, our study is the first and largest study of late-life depression to assess worry symptoms and anxiety sensitivity using validated scales for each construct of anxiety. It extends the findings of other studies, suggesting that anxiety symptoms may not be playing a significant role in late-life depression treatment response. Both a European naturalistic study (Dold et al., 2017) and a smaller study (Lenze et al, 2003) showed no significant difference in treatment response between older depressed patients with or without anxiety. Further, in a meta-analysis of eight placebo-controlled trials (Nelson et al., 2009) the odds ratio of treatment response of antidepressant versus placebo were similar in older depressed adults with or without anxiety. Our findings are not congruent with several other studies that had

shown a negative impact of comorbid anxiety on treatment outcome in older depressed patients (Andreescu et al., 2009; Flint et al., 1997; Mulsant et al., 1996; Dew et al., 1997; Saghafi et al., 2007; Fava et al., 2008; Schoevers, Deeg, Van Tilburg & Beekman, 2005). For instance, Flint et al. (1997) reported a significantly lower antidepressant response in the anxious depressed and found a higher drop out rate among the patients with worse anxiety. Similarly, Schoevers et. al (2005) reported that older patients with anxious depression had significantly lower remission rates than those subjects with exclusive depression or anxiety disorder. While the first study mentioned (Flint et al., 1997) was a clinical trial with a standardized and controlled treatment protocol, the study of Schoevers et al. (2005) was a naturalistic follow up study where comorbidity and treatment variability might have affected both treatment efficacy and outcome.

The discordance in the findings of various studies may be due to the different approaches to assess anxiety or differences in treatment (e.g., some antidepressants may be more efficacious in treating depression with comorbid anxiety symptoms). This is important because, compared to younger adults, older adults may be more likely to have worry symptoms, but less likely to have fear/panic symptoms (Lenze & Wetherell, 2011; Wuthrich et al., 2015) Still, our findings contradict a prior study by our group in depressed elderly patients (>70 years old) (Andreescu et al, 2009) in which response to treatment with paroxetine was lower among patients with high worry symptoms.

It is possible that venlafaxine affected symptoms of depression and anxiety simultaneously. This is supported by the similar trajectories of changes in anxiety scores and modified MADRS scores. Whyte et al. (2004) have proposed that intensive antidepressant treatment of patients with both depressive and anxious symptoms should lead to the concomitant improvement of both, mitigating the potential negative effect of anxiety on antidepressant treatment response. The IRL-Grey trial used an intensive approach to treatment, with frequent in-person follow-ups, measurement-based care, and rapid titration of venlafaxine up to a maximum of 300mg/day. Thus our results support the following clinical recommendation: the presence of comorbid anxiety should prompt an intensive course of treatment, including frequent follow-up visits and maximizing the antidepressant dosage before declaring non-response. We also speculate that the use of a dual-reuptake inhibitor may be preferable in depression with comorbid anxiety symptoms, as several studies using single-mechanism antidepressants (e.g., SSRIs) found a delay in the response of older patients with anxious depression (Dew et al., 1997; Mulsant et al., 1996; Saghafi et al., 2007), whereas our data did not show an association between baseline anxiety and time to remission. Our conclusions are limited by the lack of a comparison arm with an antidepressant from a different class.

Our other main finding was that both worry and fear/panic symptoms were associated with suicidal ideation. This is congruent with previous studies (Bartels et al., 2002; Batterham et al., 2013; Cristancho et al., 2017; Jeste et al., 2006). The literature has long reported increased levels of suicidality in depressed elderly with an anxiety component (Bartels et al., 2002; Batterham et al., 2013; Lenze et al., 2002; Jeste et al., 2006). In our study, all anxiety scales were associated with suicidal ideation. Suicidality itself has been noted in some studies as a predictor of poor short-term treatment response (Lopez-Castroman et al., 2016;

Szanto et al., 2003). For instance, Szanto et al. (2003) showed that older depressed patients with high levels of suicidality both had a longer time to response and were less likely to fully respond to treatment The association between comorbid anxiety and suicidality warrants a particular attention when dealing with older patients with anxious depression (Conwell et al., 1996). Comorbid depression and anxiety symptomatology has been associated with an increased risk of both attempted and completed suicide (Bronisch & Wittchen, 1994; Cougle et al., 2009; Jeste et al., 2006). In summary, it appears that anxiety symptoms (both worry and panic) and suicidal ideation may be markers of more severe depression, rather than representing a distinct phenotype ("anxious depression").

Our study had some limitations: it was an open-label study, with no placebo or comparison treatment arm. Also, anxiety was based on clinical questionnaires that may be subject to reporting biases and underreporting of anxiety in older adults (Lenze et al., 2009; Wuthrich et al., 2015). Additionally, we chose to measure panic/fear symptoms with a measure of anxiety sensitivity. Although some theoretical models highlight the importance of anxiety sensitivity in maintaining panic, justifying the use of this measure, it is possible that a more pure measure of fear may have produced different results. Finally, while patients were not started on any new pharmacotherapy during the study, they were allowed to continue with a prior low dose benzodiazepine prescription. It is possible that these low dose benzodiazepines masked anxiety symptoms. Notwithstanding these limitations, our study is the largest prospective assessment of anxiety symptoms as predictors of antidepressant response in older patients, and the only study that has assessed anxiety symptoms using several validated, anxiety-specific measures.

In conclusion, our findings and other evidence show that, with appropriate treatment, comorbid anxiety symptoms should not be interpreted as a predictor of treatment resistance in late-life depression. Intensive protocolized treatment with venlafaxine is beneficial for depression with comorbid anxiety symptoms in older adults.

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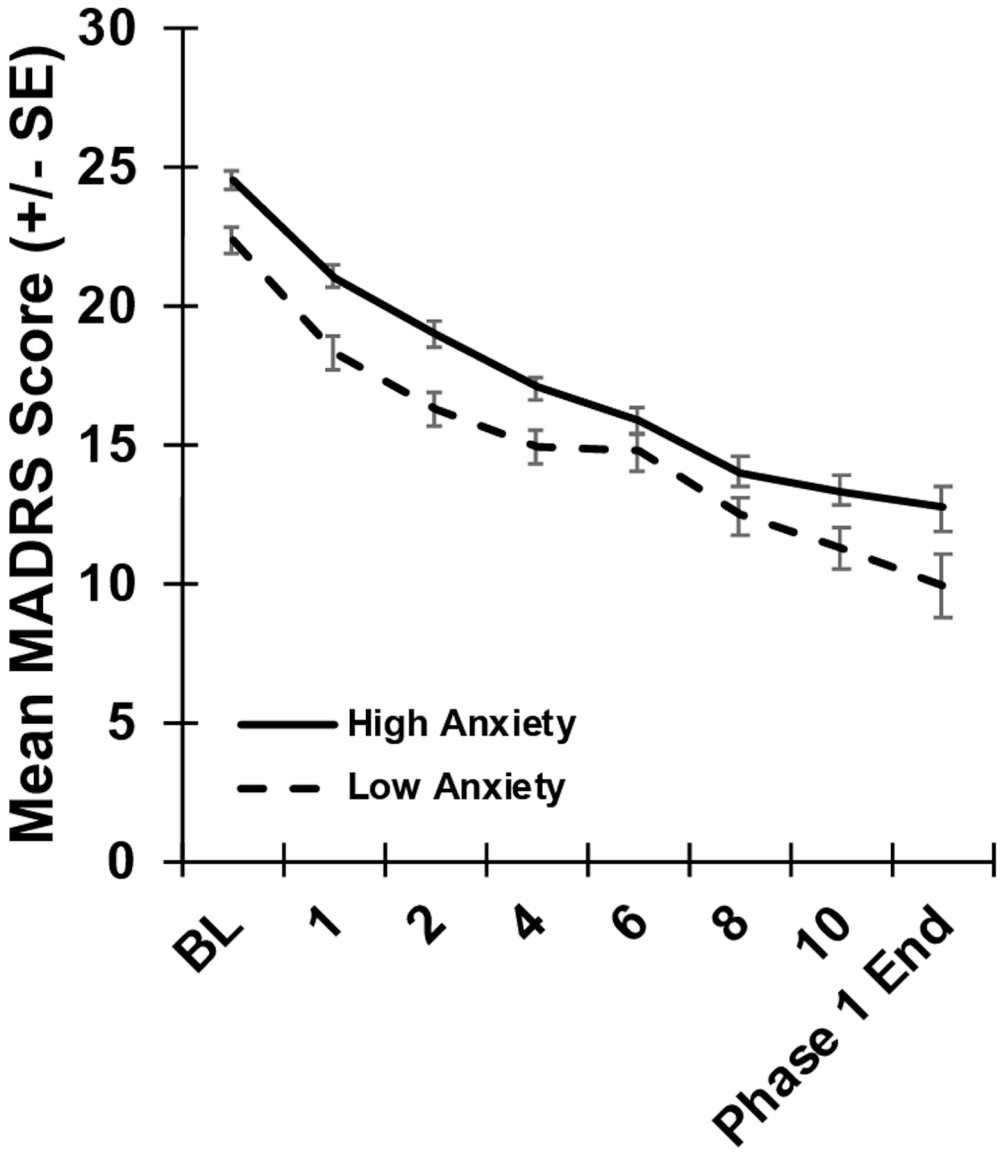

Figure 1.

Depressive symptoms in patients with high versus low anxiety †.

† High anxiety was defined as Brief Symptom Inventory score >1.

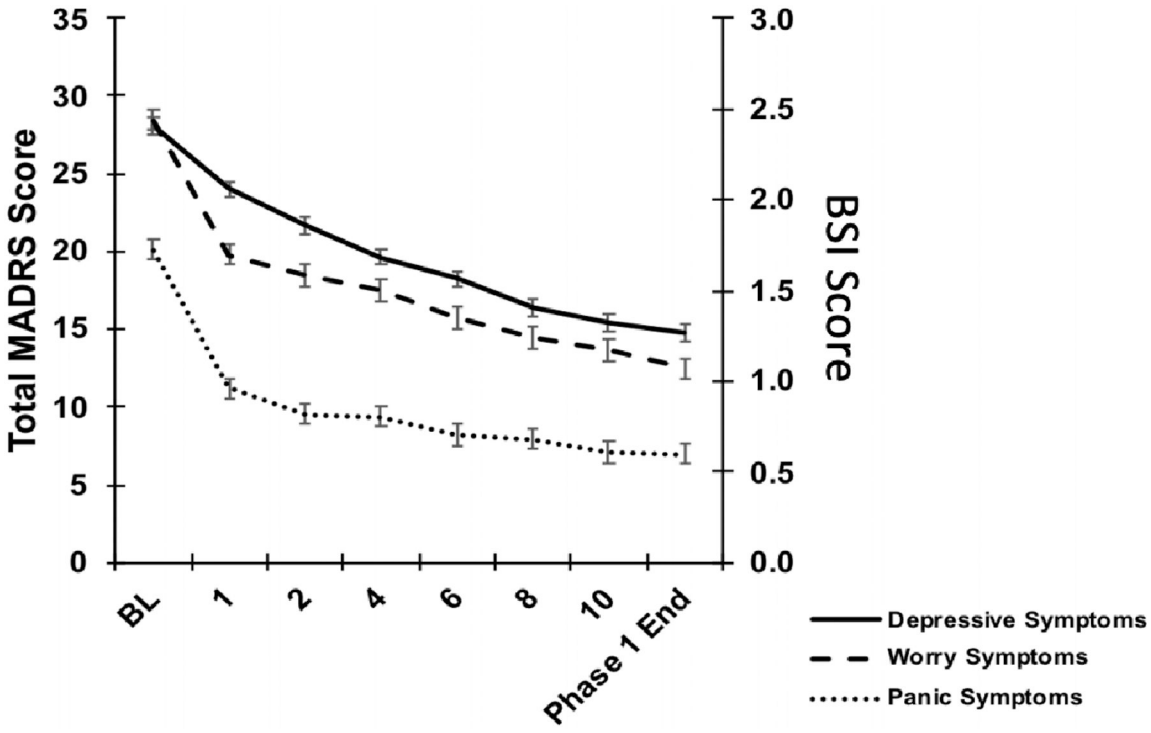

Figure 2.
Depressive, worry and panic symptoms in high anxiety patients(BSI>1).

Table 1.

Baseline demographic and clinical characteristics

	Non-Remitters and Remitters (N = 372)	Non-Remitters (n = 181)	Remitters (n = 191)	Statistical Test	p-value
Age, mean (SD)	68.59 (6.97)	67.37 (6.10)	69.74 (7.53)	t(370) = −3.33	0.001
Gender, n (%)				$\chi^2(1) = 9.59$	0.002
Male	131 (35.22)	78 (43.09)	53 (27.75)		
Female	241 (64.78)	103 (56.91)	138 (72.25)		
Race, n (%)					
Caucasian	329 (88.40)	159 (87.80)	170 (89.00)	$\chi^2(1) = 0.12$	0.73
African American	36 (9.70)	17 (9.40)	19 (9.90)		
Other	7 (1.90)	5 (2.80)	2 (1.00)		
Education (years), mean (SD)	14.44 (2.85)	14.17 (2.81)	14.70 (2.86)	t(370) = −1.82	0.07
CIRS-G Score, mean (SD)	9.57 (4.33)	9.66 (4.43)	9.48 (4.24)	t(370) = 0.39	0.70
MADRS[a]	26.69 (SD 5.63)	28.44 (SD 5.47)	25.04 (SD 5.28)	t(370) = 6.09	< 0.001
Duration of Current Episode (weeks), mean (SD)	316.63 (661.65)	412.23 (764.30)	227.04 (535.04)	t(368) = 2.71	0.007
Site, n (%)				$\chi^2(2) = 9.06$	0.01
Pittsburgh	152 (40.86)	60 (33.15)	92 (48.17)		
Toronto	106 (28.49)	56 (30.94)	50(26.18)		
Washington University	114 (30.65)	65 (35.91)	49 (25.65)		
Early Non-Adherence, n (%)				$\chi^2(1) = 0.48$	0.49
Non-Adherent	24 (6.45)	10 (5.52)	14 (7.33)		
Adherent	347 (93.28)	170 (93.92)	177 (92.67)		
Early Side Effects, n (%)				$\chi^2(1) = 0.13$	0.72
No Side Effects	147 (39.52)	73 (40.33)	74 (38.74)		
Side Effects	224 (60.22)	107 (59.12)	117 (61.26)		
Benzodiazepine Use, n (%)				$\chi^2(1) = 0.92$	0.34
No	219 (58.87)	102 (56.35)	117 (61.26)		
Yes	153 (41.13)	79 (43.65)	74 (38.74)		

* MADRS: Montgomery–Asberg Depression Rating Scale; ASI: Anxiety Sensitivity Index; BSI: Brief Symptom Inventory; PSWQ: Penn State Worry Questionnaire.

Table 2.

Baseline anxiety scores in remitters vs. non-remitters to venlafaxine ER for depression

Baseline Clinical Assessment, mean (SD)	Non-remitters (n = 181)	Remitters (n = 191)	Statistical Test
ASI	26.52 (13.08)	24.44 (12.04)	t(368) = 1.59, p=0.11
BSI	1.55 (0.94)	1.37 (0.88)	t(368) = 1.92, p = 0.06
PSWQ	60.23 (13.36)	58.85 (12.91)	t(368) = 1.02, p = 0.31
MADRS	28.44 (5.47)	25.04 (5.28)	t(370) = 6.09, p < 0.001

MADRS: Montgomery–Asberg Depression Rating Scale; ASI: Anxiety Sensitivity Index; BSI: Brief Symptom Inventory; PSWQ: Penn State Worry Questionnaire.

Table 3.

Baseline anxiety scores and suicidality

	Suicidality: Yes (n = 186)	Suicidality: No (n = 282)	Statistical Test
Baseline Scores, mean (SD)			
ASI	27.11 (13.09)	24.69 (12.43)	t(460) = −2.01, p = 0.05
BSI	1.65 (1.03)	1.40 (0.84)	t (460) = −2.89, p = 0.004
PSWQ	61.28 (13.13)	58.20 (12.98)	t(460) = −2.49, p = 0.01
MADRS	28.04 (6.03)	25.77 (5.37)	t(466) = −4.26, p < 0.001

MADRS: Montgomery–Asberg Depression Rating Scale; ASI: Anxiety Sensitivity Index; BSI: Brief Symptom Inventory; PSWQ: Penn State Worry Questionnaire.