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# Relationships between major depressive disorder and comorbid anxiety and personality disorders☆

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**Abstract**

**Objective:** The aim of the study was to examine whether comorbid anxiety disorders influence depressed patients' likelihood of meeting criteria for a personality disorder (PD) and whether comorbid anxiety disorders influence the stability of the PDs in patients with remitted depression.

**Methods:** The initial sample consisted of 373 outpatients who met criteria for major depressive disorder (MDD) (by Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*—Patient Edition) and who were enrolled in the 8-week acute treatment phase of a study of fluoxetine for MDD. Sixty-four subjects who responded to fluoxetine treatment in the acute phase met criteria for remission throughout a 26-week continuation phase during which they remained on fluoxetine with or without cognitive behavioral therapy. Stability of PDs was defined as meeting criteria for a PD at both beginning and end point of the continuation treatment phase.

**Results:** Before fluoxetine treatment, anxious depressed patients (defined as meeting criteria for MDD as well as at least one comorbid anxiety disorder) were significantly more likely to meet criteria for any comorbid PD diagnosis compared with depressed patients without comorbid anxiety disorders. In particular, there was a significant relationship between the presence of Cluster A and C PDs and the presence of anxious depression at baseline before antidepressant treatment. After successful treatment of MDD, we found a significant relationship between anxious depression diagnosed at baseline and the stability of a Cluster C PD diagnosis.

**Conclusion:** Anxious depression may place patients at greater risk of having a PD diagnosis, especially one from Cluster A or C. Once the depression remits, patients who initially met criteria for anxious depression may be more likely to maintain a Cluster C PD diagnosis compared with patients initially diagnosed with MDD alone.



## 1. Introduction

Research suggests a complex relationship between major depressive disorder (MDD), anxiety disorders, and personality disorders (PDs). In some cases, meeting criteria for MDD as well as at least one comorbid anxiety disorder is referred to as anxious depression [1], which appears quite prevalent. For example, Fava and colleagues [2] found that 44.7% of 255 outpatients with MDD met criteria for a comorbid anxiety disorder, whereas Melartin and colleagues [3] found that 57% of 269 patients with MDD met criteria for a comorbid anxiety disorder. Some investigators have examined the impact of anxious depression on the treatment of MDD, with varied results. Most studies report a decreased likelihood of response to antidepressant treatment if a patient meets criteria for anxious depression [4-6], although not all studies support this view [7].

As part of the Harvard/Brown Anxiety Research Project, Dyck and colleagues [8] found that whereas generalized anxiety disorder, social phobia, and MDD were positively associated with the presence of one or more PDs, panic disorder with agoraphobia was not positively associated with the presence of PDs. Zlotnick and colleagues [9] examined the relationship between borderline personality disorder (BPD) and posttraumatic stress disorder. They found that women having both disorders were likely to have more general dysfunction and increased risk of hospitalization.

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There is limited research on the impact of anxious depression on personality pathology. Reich [10] proposed that personality pathology might emerge in part from stress related to comorbid anxiety and depression. By reviewing previously published studies, Reich [10] found an association between comorbid anxiety, depression, and PDs.

A few studies [11,12] have shown that different profiles of the Tri-dimensional Personality Questionnaire [13] emerged between patients with MDD alone compared with patients with anxious depression. For example, 2 studies showed that anxious depressed patients exhibit higher harm avoidance (HA) scores compared with those that have MDD alone [11,12]. In addition, Ongur and colleagues [14] found that patients who have MDD with comorbid social anxiety disorder or generalized anxiety disorder reported higher HA scores, whereas patients who have MDD with comorbid social anxiety, obsessive compulsive disorder, or panic disorder reported lower scores in novelty seeking. Melartin and colleagues [3] have also suggested that anxious depression is associated with specific personality clusters. These reports suggest that specific patterns of personality pathology may be significantly related to anxious depression.

On a related note, Joyce and colleagues [15] suggested that a combination of risk factors (temperament, childhood experiences, and childhood/adolescent psychopathology) contributes to the presence of personality pathology, especially BPD and avoidant personality disorder. The authors suggested that although BPD may arise from a combination of childhood abuse and/or neglect, borderline temperament, and childhood/adolescent depression, avoidant personality disorder is more likely to arise from a combination of high HA, parental neglect, and childhood and adolescent anxiety disorders [15].

In regard to stability of PD diagnoses, we have previously shown that although a number of PD diagnoses are no longer present among depressed outpatients successfully treated with antidepressants [16], PD diagnoses are generally more stable among outpatients with remitted MDD [17]. Based on our literature review, no studies have examined the impact of anxious depression on the stability of PDs in remitted depressed outpatients.

Given the above findings, and the frequent co-occurrence of comorbid anxiety and comorbid personality pathology in MDD, we wanted to further clarify the relationship between comorbid anxiety disorders and the occurrence of PDs in patients with MDD and the relationship between anxious depression and the stability of PDs in patients with remitted MDD.

## 2. Methods

### 2.1. Population and procedures

This study examines data from a larger study conducted at the Depression Clinical and Research Program at Massachusetts General Hospital. The primary purpose of that study was to assess the efficacy of fluoxetine alone compared with fluoxetine plus cognitive behavioral therapy (CBT) in treating outpatients with remitted MDD. After the acute phase of treatment (8 weeks of fluoxetine 20 mg/d), all eligible patients who wanted to continue in the study entered the randomized continuation phase (26 weeks of fluoxetine 40 mg/d alone or fluoxetine 40 mg/d plus CBT). Before entering the study, subjects provided written consent to participate. The institutional review board of the Massachusetts General Hospital approved the consent form.

At baseline of the acute phase, outpatients were required to meet criteria for MDD diagnosed with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* (*DSM-III-R*)—Patient Edition (SCID-P) [18]. Patients were also required to have a 17-item Hamilton Rating Scale for Depression (HAMD-17) [19] score of 16 or higher at baseline. The Structured Clinical Interview for *DSM-III-R*—Axis II Disorders (SCID-II) [20] was also administered at baseline to assess for comorbid PDs. Additionally, another inclusion criteria was a history of chronic depression. Chronic depression was defined as having experienced at least three episodes of MDD, having current depressive symptoms last continuously for 36 months, or having a history of poor interepisode recovery from depression (defined as persistent residual symptoms of depression).

The following criteria were exclusionary: pregnancy, breast-feeding, use of a birth control pill, serious suicide risk, history of neurologic illness including seizure disorder, serious/unstable medical illness, organic mental disorders, substance use disorders active within the last year, schizophrenia, delusional disorder, bipolar disorder or antisocial PD, mood-congruent or mood-incongruent psychotic features, history of multiple adverse drug reactions or allergy to the study drugs, current use of other psychotropic drugs, and clinical or laboratory evidence of hypothyroidism.

Patients were excluded if they had a history of nonresponse to or intolerance of fluoxetine (60-80 mg/d) or to the combination of fluoxetine and desipramine, or fluoxetine and lithium, or if they had failed to respond during the course of their current major depressive episode to at least one adequate antidepressant trial ($\geq$6 weeks of treatment with either $\geq$150 mg of imipramine or its tricyclic equivalent, $\geq$60 mg of fluoxetine or its selective serotonin uptake inhibitor equivalent, or $\geq$60 mg of phenelzine or its monoamine oxidase inhibitor equivalent).

During the 8 weeks of treatment with fluoxetine 20 mg/d, patients were seen every 2 weeks for safety and efficacy assessments. At the end of the 8-week acute phase of treatment, patients were readministered the mood disorder module of the SCID-P, the SCID-II, and the HAMD-17. These instruments were administered either by the same or different rater. Every effort was made to minimize rater expectations by keeping the raters blind to the results of earlier assessments. The SCID-P, SCID-II, and HAMD-17