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Personality disorders and perceived stress in Major Depressive Disorder

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Abstract

The investigation of comorbidity between major depressive disorder (MDD) and personality disorders (PDs) has attracted considerable interest. Whereas some studies found that the presence of PDs has adverse effects on the course and treatment of MDD, others have failed to demonstrate this link. These inconsistent findings suggest that specific PD comorbidity might affect the course of MDD by modulating factors that increase the overall risk of depression, including an elevated tendency to perceive stress. To investigate whether the presence of a specific PD cluster was associated with elevated levels of stress appraisal, we administered the Perceived Stress Scale (PSS) before and after treatment to 227 MDD outpatients enrolled in an 8-week open-label treatment with fluoxetine. Following treatment, multiple linear regression analyses revealed that the presence of Cluster A, but not Cluster B or C, was associated with higher levels of perceived stress, even after adjusting for baseline depression severity and PSS scores, as well as various sociodemographic variables. The presence of Cluster A PD comorbidity was uniquely associated with elevated stress appraisal after antidepressant treatment, raising the possibility that stress exacerbation might be an important factor linked to poor treatment outcome in MDD subjects with Cluster A pathology.

Keywords

Depression; Axis II pathology; Stress Appraisal; Diathesis-Stress Model; Fluoxetine

1. Introduction

Over the years, increasing attention has been devoted to investigating the comorbidity between major depressive disorder (MDD) and personality disorders (PDs). In general, the presence of PDs is assumed to have adverse effects on the course and treatment of MDD (for a recent review, see Newton-Jones et al., 2006). Consistent with this hypothesis, co-occurrence of MDD and PD has been associated with poorer response to treatment in most (Peselow et al., 1992; Sato et al., 1993) but not all (Fava et al., 1994, 1997) studies, and with higher risk of depressive

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recurrence (Ilardi et al., 1997; Hart et al., 2001). Moreover, compared to MDD subjects without PD, those with comorbid PD reported significantly greater impairments in social and emotional functioning and lower well-being (Skodol et al., 2005); higher levels of residual symptoms (Shea et al., 1990); slower recovery (Patience et al., 1995); higher levels of psychotropic utilization at a 1-year follow-up (Casey et al., 2004); and more frequent referral to psychiatric services (Moran et al., 2001).

On the other hand, others have failed to find a link between comorbid PD and poor treatment response (Fava et al., 1994, 1997, 2002; Russell et al., 2003; Mulder et al., 2003). Echoing these negative findings, a recent meta-analysis including findings from six randomized controlled trials with strict methodological criteria found that MDD subjects with comorbid PD had only a 3% lower remission rate compared to MDD subjects without PD, a difference that was not statistically significant (Kool et al., 2005). Taken together, these findings raise the possibility that comorbid personality pathology is not necessarily associated with poor treatment response, and that other intervening variables might be involved.

One possibility is that the three PD clusters based on the Diagnostic and Statistical Manual (DSM; American Psychiatric Association, 1987, 2000), Cluster A (paranoid, schizoid, schizotypal), Cluster B (borderline, histrionic, narcissistic, antisocial), and Cluster C (avoidant, dependent, obsessive-compulsive) may be differentially related to the course and outcome of depression. Sato et al., (1994), for example, found that only the presence of a Cluster A PD had a significant negative effect on short-term outcome in depression, while Fava et al., (1994) showed that the presence of Cluster B (but not Cluster A or C) PD in MDD was associated with a more favorable outcome following treatment with fluoxetine. Similarly, in a cohort of depressed patients undergoing a 6-month treatment, the presence of symptoms of avoidant, schizotypal, and schizoid, but no other, PD was associated with poorer outcome (Mulder et al., 2006).

A second, not mutually exclusive, possibility is that the presence of comorbid PD among MDD subjects is associated with higher occurrence of factors that increase the risk of depression, such as life stressors and poor social support (Pfohl et al., 1984). Consistent with this hypothesis, in a community sample, symptoms of Cluster A and B, but not Cluster C, disorders predicted interpersonal chronic stress and self-generated episodic stress over 2 years, which in turn increased the vulnerability for depressive symptoms (Daley et al., 1998). Thus, in the Daley et al.,'s study, life stress mediated the relationship between personality pathology and later depression, even when controlling for initial depressive severity.

Findings of a possible mediating role of stress on the relationships between PD and depression are intriguing, particularly since stress has been implicated in the etiology and maintenance of depression (Kendler et al., 1999; Brown and Harris, 1989; Hammen, 2005), and has been associated with poorer treatment outcome and more frequent relapse (Tennant, 2002). Of note, research has suggested that risk for depression increases when individuals perceive stress as uncontrollable, unpredictable, and severe, and deem coping resources as insufficient (Cohen and Williamson, 1988; Hammen, 2005; Lazarus and Folkman, 1984). In addition, compared to pre-treatment levels, perceived stress markedly diminishes following antidepressant treatment, and the degree of stress reduction tends to be highly related to the degree of depressive symptom reduction (Fava et al., 1992).

In the present study, we evaluated 384 MDD outpatients enrolled in an 8-week open-label treatment with fluoxetine for the presence of Cluster A, B, or C PD, as defined by the DSM-III-R (American Psychiatric Association, 1987). To investigate whether PD was associated with elevated stress perception, a subgroup of these participants ($n=227$) filled out before and after treatment the Perceived Stress Scale (PSS; Cohen et al., 1983), which assessed the degree

to which participants appraised their daily life as unpredictable, uncontrollable, and overwhelming. Specifically, our goal was to test whether the presence of a given DSM-III-R-based PD cluster predicted levels of stress after 8-week antidepressant treatment with fluoxetine. We hypothesized that the presence of Cluster A or Cluster B PD comorbidity would predict elevated levels of perceived stress in MDD outpatients.

2. Methods

2.1. Participants

Data from the current study were derived from a larger study conducted at the Depression Clinical and Research Program (DCRP) at Massachusetts General Hospital (Fava et al., 2002; Farabaugh et al., 2002). The main goal of the parent study, which included 384 outpatients between the ages of 18 and 65, was to evaluate the efficacy of fluoxetine in the treatment of MDD. In order to be enrolled in an 8-week open treatment of fluoxetine 20 mg/day, subjects were required to meet criteria for MDD, as assessed with the Structured Clinical Interview for DSM-III-R, Patient Edition (SCID-P; Spitzer et al., 1989), and have a score of ≥ 16 in the 17-item Hamilton Rating Scale for Depression (HAMD-17; Hamilton, 1960) at baseline (pretreatment). Exclusion criteria included: pregnancy, breast-feeding, lack of birth control, suicide risk, history of neurological illness, serious unstable medical illness, organic mental disorders, substance abuse during the last year, schizophrenia, delusional disorder, bipolar disorder, severe antisocial personality disorder, and mood-congruent or -incongruent psychotic features. History of multiple adverse drug reactions, allergy to the study drug, current use of other psychotropic drugs, and evidence of hypothyroidism also led to exclusion. Finally, subjects were excluded if they had previously shown non-response or intolerance to fluoxetine (60–80 mg/day) or if they had failed at least one adequate antidepressant treatment during their current major depressive episode. Anxiety comorbidity was allowed.¹

During the acute treatment, outpatients were seen biweekly for safety and efficacy assessments. At both baseline as well as at the end of the 8-week treatment, subjects were also administered the SCID-II (including its screening questionnaire) (First et al., 1997) to assess the presence of any personality disorder. All the clinical assessments (SCID-I, SCID-II, HAMD-17) were carried out by psychiatrists and clinicians at the DCRP, who were fully trained in their administration. Before entering the study, participants provided written informed consent to a protocol approved by the Institutional Review Board of the Massachusetts General Hospital.

2.2. Questionnaires

The Perceived Stress Scale (PSS; Cohen et al., 1983) was used to assess the degree to which participants appraised their daily life as unpredictable, uncontrollable, and overwhelming. The PSS was selected because it has been found to better predict stress-related psychological symptoms, physical symptoms, and health service utilization compared to commonly used life event scales (e.g., Cohen et al., 1983). This stress appraisal scale includes 14 items (e.g., “In the last week, how often have you felt that you were unable to control the important things in your life?”); each item is scored on a 5-point scale, ranging from 0 (never) to 4 (very often). The internal and short-term reliability (coefficient alpha reliability: 0.84; two-day test-retest reliability: 0.85; Cohen et al., 1983) have been found to be satisfactory. In the present sample, PSS scores at *both* the pre- and post-treatment assessment were available for 227 MDD subjects. With the exception of higher education ($t(382)=2.67, p<0.008$), these subjects did not

¹Note: Exploratory analyses were performed to assess whether the presence of anxiety comorbidity had an effects on stress appraisal. For each cluster separately, a 2 (PD comorbidity: yes vs. no) $\times$ 2 (Anxiety comorbidity: yes vs. no) analysis of variance (ANOVA) was performed on PSS scores using Time (pre- vs. post-treatment) as repeated measures. No significant effects involving Anxiety comorbidity emerged (all $F_s<2.48$, all $P_s>0.12$)

differ in any demographic or clinical variable compared to subjects without PSS data at both assessments.

2.3. Statistics

To evaluate the effects of the 8-week open fluoxetine treatment on depression severity and stress perception, two-tailed paired t-tests comparing pre- and post-treatment HAMD-17 ($n=384$) and pre- and post-treatment PSS scores ($n=227$), respectively, were performed in a first step.

Next, the effects of PD comorbidity on depression severity and stress perception were evaluated. Prior studies reported that a substantial proportion of MDD subjects no longer met DSM diagnosis of PD after antidepressant treatment (e.g., Joffe and Regan, 1988; Fava et al., 1994, 2002), raising the possibility that diagnosing PD in patients with active Axis I pathology may be confounded by the patient's state (Zimmerman, 1994). To avoid this issue, only MDD subjects meeting DSM-III-R criteria for Cluster A, B or C at *both* the pre- and post-treatment assessment were considered (hereafter, "stable PD"). These subjects were compared to MDD subjects who did not meet *any* PD criteria at either assessment. For both the pre- and post-treatment assessments, unpaired t-tests were used to compare the PSS and HAMD-17 scores of MDD subjects with a stable PD vs. those without any PD. A Bonferroni correction was applied to correct for the number of t-tests performed ($3 \text{ clusters} \times 2 \text{ scales} \times 2 \text{ assessments} = 12$; $p = 0.05/12 = 0.0042$).

Subsequently, for each DSM-III-R PD cluster separately, a multiple linear regression was performed to assess the relationship between presence/absence of a given PD cluster and post-treatment PSS score adjusting for pre-treatment depression severity (HAMD-17) and PSS scores as well as for various sociodemographic variables that have been previously found to affect PSS scores (Cohen and Williamson, 1988). All subjects with SCID-II and PSS data at both the pre- and post-treatment assessments were considered for these analyses. The post-treatment PSS score was the dependent variable and PD, the sociodemographic variables, and the baseline severity measures were the independent variables. The sociodemographic variables included age, gender, education (college degree, less than college degree), employment status (currently employed, unemployed), and marital status (currently married, not married). When considering Cluster A PD, 135 subjects (42 with stable Cluster A, 93 without any PD) were included in the regression analysis. For Cluster B, 133 subjects were evaluated (40 with stable Cluster B PD, 93 without any PD). Finally, for Cluster C, 213 subjects were considered (120 with stable Cluster C PD, 93 without any PD).

3. Results

Three hundred eighty-four subjects were enrolled in the 8-week open treatment of fluoxetine 20 mg/day (Fava et al., 2002). In this sample, 54.7% of the subjects were female ($n = 210$), 33.6% were married ($n = 129$), 56.5% completed at least a college degree ($n = 217$), and 62.5% were currently employed ($n = 240$). The mean age of this sample was 39.8 (S.D.: 10.5), and the mean baseline HAMD-17 score was 19.7 (S.D.: 3.5). The mean age of onset of the first MDD and the mean duration of the current MDD episode were 25.7 (S.D.: 12.9) and 3.3 years (S.D.: 5.9), respectively. Among the 384 subjects, 378 were administered the SCID-II at baseline; 243 (64.3%) met criteria for at least one PD before treatment. Among these 243 subjects, 87 (35.8%) had one comorbid PD, 61 (25.1%) had two comorbid PDs, and 95 (39.1%) had three or more comorbid PDs (Fava et al., 2002). When considering the DSM-based PD clusters, 42 (17.3%), 40 (16.5%), and 120 (49.4%) met criteria for Cluster A, Cluster B, and Cluster C, respectively, at both the pre- and post-treatment assessment. Ninety-three subjects did not meet criteria for *any* PD at either assessment.

Following treatment with fluoxetine, there was a significant reduction in depressive symptoms, as measured by the HAMD-17 (paired t-test: 19.72 ± 3.47 vs. 10.63 ± 7.17 ; $t(382) = -26.09$, $P < 0.0001$), and in levels of perceived stress, as measured by the PSS (paired t-test: 37.06 ± 6.83 vs. 25.90 ± 9.22 ; $t(226) = -17.50$, $P < 0.0001$).

3.1. Cluster A

Out of the 42 MDD subjects with a stable Cluster A PD, 29 (69.1%) were males compared to 33 of the 93 MDD subjects (35.5%) who did not meet criteria for any PD ($\chi(1) = 13.13$, $P < 0.005$). Eight of the 42 subjects (19.1%) with stable Cluster A, and 34 of the 93 (36.6%) of those never meeting criteria for any PD ($\chi(1) = 4.14$, $P < 0.05$) were currently married. Subjects with stable Cluster A and those without any PD comorbidity did not differ with respect to education ($\chi(1) = 0.38$, ns), employment status ($\chi(1) = 0.14$, ns), or age (40.29 ± 12.00 vs. 40.63 ± 9.84 ; $t(133) = 0.18$, ns).

Compared to MDD subjects without any PD comorbidity, those with stable Cluster A PD had significantly higher post-treatment PSS and HAMD-17 scores as well as higher pre-treatment HAMD-17 scores (Table 1). After Bonferroni correction, only the group difference in post-treatment PSS score remained. The multiple regression analysis indicated that the presence of stable Cluster A PD significantly predicted elevated post-treatment PSS scores even after adjusting for age, gender, education, employment status, marital status, pre-treatment PSS scores, and pre-treatment HAMD-17 scores (adjusted $R^2 = 0.18$; $t = 2.05$, $P < 0.05$). Pre-treatment PSS score was the only other variable predicting post-treatment PSS scores ($t = 2.59$, $P < 0.015$).

3.2. Cluster B

As for Cluster A, proportionally more males were represented in the MDD sample with Cluster B comorbidity (25/40 or 62.5% vs. 33/93 or 35.5%; $\chi(1) = 8.30$, $P < 0.005$). Subjects with Cluster B comorbidity versus those without any PD did not differ with respect to education ($\chi(1) = 0.01$, ns), employment status ($\chi(1) = 0.31$, ns), or marital status ($\chi(1) = 1.03$, ns). MDD subjects with Cluster B comorbidity were significantly younger than those without any PD (36.13 ± 10.62 vs. 40.63 ± 9.84 , $t(131) = -2.37$, $P < 0.02$).

Compared to MDD subjects without any PD, those with stable Cluster B PD had significantly higher pre- and post-treatment PSS scores as well as higher pre-treatment HAMD-17 scores ($P < 0.05$, corrected; Table 1). Contrary to the findings for Cluster A, the regression analysis indicated that the presence of a stable Cluster B PD was not a significant predictor of post-treatment PSS scores when adjusting for age, gender, education, employment status, marital status, pre-treatment PSS score, and HAMD-17 scores (adjusted $R^2 = 0.09$, $t = 0.65$, $P > 0.51$).

3.3. Cluster C

Subjects with stable Cluster C PD comorbidity did not differ from those without any PD with respect to education ($\chi(1) = 0.01$, ns), employment status ($\chi(1) = 1.56$, ns), marital status ($\chi(1) = 0.13$, ns), or age (39.97 ± 10.80 vs. 40.63 ± 9.84 ; $t = -0.47$, ns). As for the other clusters, more males were represented in the MDD sample with Cluster C comorbidity (62/120 or 51.7% vs. 33/93 or 35.5%; $\chi(1) = 5.55$, $P < 0.05$).

Compared to MDD outpatients without PD, those with Cluster C PD had higher pre- and post-treatment PSS scores and HAMD-17 scores. When applying a Bonferroni correction, groups differed only in their pre-treatment HAMD-17 scores and post-treatment PSS scores ($P < 0.05$ corrected; Table 1). As for Cluster B, the regression analysis indicated that the presence of stable Cluster C PD failed to predict post-treatment PSS scores when adjusting for age, gender, education, employment status, marital status, pre-treatment PSS score, and HAMD-17 scores (adjusted $R^2 = 0.12$, $t = 1.33$, $P > 0.18$).

4. Discussion

Stress and major life events have been implicated in the etiology and maintenance of depression (Kendler et al., 1999; Brown and Harris, 1989; Hammen, 2005). Consistent with this hypothesis, prior studies have found that higher daily life stressors and perceived stress were associated with poorer outcome in major depressive disorder (Tennant, 2002). The main goal of this study was to investigate whether the presence of a stable PD comorbidity, specifically a DSM-III-R-based Cluster A, B or C PD, predicted the degree of perceived stress following an 8-week open-label treatment with fluoxetine in MDD outpatients. Based on prior findings in the literature (e.g., Daley et al., 1998; Sato et al., 1994), we hypothesized that the presence of enduring Cluster A or Cluster B PD comorbidity would be associated with elevated levels of pre- and post-treatment perceived stress.

Compared to MDD outpatients without any PD, those with a stable PD generally showed elevated levels of stress appraisal and depression severity both before and after the treatment. When appropriate statistical corrections were applied, MDD subjects with stable Cluster A, B, or C PD reported significantly higher PSS scores *after* antidepressant treatment. In addition, stable Cluster B comorbidity was associated with significantly elevated depression severity and stress perception before the treatment as well, whereas MDD outpatients with stable Cluster C comorbidity were also significantly more depressed before the treatment compared to MDD subjects without any PD. Interestingly, in the regression analyses, only the presence of a Cluster A PD predicted post-treatment PSS scores after controlling for initial depression severity and PSS scores as well as various demographic variables (age, gender, education, employment status, marital status). Accordingly, the enduring presence of Cluster A comorbidity explained unique variance in stress appraisal after antidepressant treatment, above and beyond initial depression severity and perceived stress, confirming our *a priori* hypothesis. For Cluster B, the expected relationship did not emerge after the proper adjustments.

The present finding highlighting a specific link between stable Cluster A comorbidity and elevated stress appraisal post-treatment is intriguing. Various factors might explain this link. First, in both community (e.g., Camisa et al., 2005; Costa and McCrae, 1990) and clinical (Blais, 1997; Gurrera et al., 2005) samples, Cluster A symptomatology has been associated with increased neuroticism. Neuroticism is a personality trait characterized by increased stress vulnerability and propensity to experience negative affect, and has been considered a potential trait marker and risk factor for depression (Kendler et al., 2004). Consistent with this assumption, recent findings indicate that individuals with high levels of neuroticism are more sensitive to the adverse effects of stress (Kendler et al., 2004). Of primary importance for the present findings, Daley et al., (1998) found in a prospective study that Cluster A and B (but not Cluster C) symptoms were associated with increased episodic stress and interpersonal chronic stress, which in turn were linked to subsequent depression. Thus, in the Daley et al., (1998)'s study, the effect of Cluster A pathology on subsequent depression was mediated by stress. Our findings indicate that enduring Cluster A comorbidity predicts elevated perceived stress following antidepressant treatment and is in line with this prior study, raising the possibility that among subjects with depressive symptomatology, comorbid Cluster A pathology may result in poorer outcome through stress exacerbation. Future studies should directly test whether elevated neuroticism in MDD subjects with Cluster A comorbidity might predispose them to experience more life stressors and/or react more poorly to them.

A second, not mutually exclusive, factor explaining a specific link between Cluster A comorbidity and increased stress appraisal might be related to the pervasive interpersonal impairments characteristic of subjects with Cluster A pathology. According to the DSM-IV-TR (American Psychiatric Association, 2000), individuals with schizoid PD are characterized by a persistent pattern of detachment from social relationships resulting in emotional coldness,

detachment, or flattened affectivity in interpersonal situation, a tendency to prefer solitary activities, and a lack of close friends or confidants. In a similar vein, individuals with schizotypal PD prototypically feature a pervasive pattern of social and interpersonal deficits characterized by discomfort with close relationships, and also often lack close friends or confidants. Finally, the enduring distrust and suspiciousness of others, and the reluctance to confide in others characteristic of Paranoid PD also point to considerable impairments in interpersonal situations. Interestingly, in the present study, MDD subjects with enduring Cluster A comorbidity, but not those with Cluster B or C comorbidity, had a significantly lower percentage of married individuals, a pattern that might reflect interpersonal impairments in Cluster A.

When considered in a larger context, these interpersonal impairments may lead to diminished (or absent) social support in periods of distress, which in turn might have deleterious consequences. In fact, social support has been associated with decreased stress responsiveness, including reduced cortisol levels after a psychosocial stressor (Heinrichs et al., 2003) and lower psychological distress after negative life events (Ystgaard et al., 1999). Likewise, in MDD subjects, low levels of social support have been associated with the onset of depressive symptoms (Wade et al., 2000), greater depressive symptoms (Romanov et al., 2003), delayed recovery after a MDE (Zuroff and Blatt, 2002), and depression chronicity (Lynch et al., 1999). Clearly, future studies will be required to test the hypothesis that increased levels of perceived stress in MDD subjects with Cluster A comorbidity may be partially mediated by the lack of social support. Moreover, in light of the observation that *most* PD are characterized by elevated neuroticism (e.g., Morey et al., 2002; Trull and Durrett, 2005), it is possible that the interaction of high neuroticism and low social support characterizing Cluster A PD may provide a diathesis for higher stress levels, and, perhaps, poor outcome and future relapse.

Based on prior findings indicating that stress mediated the link between Cluster B PD and depression (Daley et al., 1998), we hypothesized that Cluster B pathology in the present study would be associated with increased stress appraisal after treatment. This hypothesis was not confirmed by our regression analysis approach, in which several demographic variables and indices of initial illness severity were controlled for. Although the reasons for this null finding are not completely clear, it is interesting to note that in Cluster B low levels of neuroticism and high level of agreeableness were associated with favorable outcome in a recent 10-year follow-up study (Zanarini et al., 2006). As suggested by these authors, patients with this profile might have a more affiliative and agreeable personality, which in turn might increase the likelihood of receiving emotional and social support. Accordingly, although patients with Cluster B pathology are often characterized by unstable and stormy relationships, it is likely that they will nevertheless receive some form of social support, which might mitigate their stress appraisal.

Several limitations of the present study should be acknowledged. First, although the investigation of the effects of specific PD cluster on post-treatment stress appraisal is novel, data for the present study were derived from a larger study conducted by our group (Fava et al., 2002; Farabaugh et al., 2002). Second, stress appraisal was assessed using a single measure, the Perceived Stress Scale (Cohen et al., 1983). Although this scale has been found to reliably predict stress-related psychological symptoms, physical symptoms, and health service utilization (Cohen et al., 1983), we did not assess independently the types and severity of potential stressors. Third, a categorical approach based on the DSM was used to diagnose PD, and recent evidence suggests that a dimensional approach that considers personality as varying along a continuum might be more appropriate (Trull and Durrett, 2005). Fourth, the presence of stable Cluster A PD explained a relatively low amount of variance of post-treatment PSS scores (18%), and future studies should investigate the unique contribution of other factors (e.g., individual differences in cognitive vulnerability). Finally, the treatment plan did not

involve a placebo arm, preventing us to assess whether some of the present findings were in fact due to non-specific, placebo effects. Although the specificity of the main findings linking Cluster A and elevated post-treatment PSS scores speaks against the possibility of a large role of placebo effects, future studies should incorporate a placebo arm.

These limitations notwithstanding, the present findings indicate that enduring Cluster A comorbidity in a well-characterized MDD outpatient sample predicted elevated perceived stress following an 8-week open-label treatment with fluoxetine. MDD patients with Cluster A comorbidity might therefore benefit from treatment approaches involving a stress management program (e.g., Fava et al., 1991). The putative mediating role of elevated neuroticism and reduced social support on elevated stress appraisal in Cluster A comorbidity also warrants future scrutiny.

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References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM III-R). Washington, DC: American Psychiatric Press; 1987.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Text Revision. Washington, DC: American Psychiatric Press; 2000.
- Blais MA. Clinician ratings of the five-factor model of personality and the DSM-IV personality disorders. *The Journal of Nervous and Mental Disease* 1997;185:388–393. [PubMed: 9205425]
- Brown, G.; Harris, TO. *Life Events and Illness*. New York: Guilford Press; 1989.
- Camisa KM, Bockbrader MA, Lysaker P, Rae LL, Brenner CA, O'Donnell BF. Personality traits in schizophrenia and related personality disorders. *Psychiatry Research* 2005;133:23–33. [PubMed: 15698674]
- Casey P, Birbeck G, McDonagh C, Horgan A, Dowrick C, Dalgard O, Lethinen V, Ayuso-Mateos JL, Dunn G, Page H, Wilkinson C, Wilkinson G, Vazquez-Barquero JL. Personality disorder, depression and functioning: results from the ODIN study. *Journal of Affective Disorders* 2004;82:277–283. [PubMed: 15488258]
- Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *Journal of Health and Social Behavior* 1983;24:385–396. [PubMed: 6668417]
- Cohen, S.; Williamson, G. Perceived stress in a probability sample of the United States. In: Spacapan, S.; Oskamp, S., editors. *The Social Psychology of Health: Claremont Symposium on Applied Social Psychology*. Newbury Park: Sage; 1988. p. 31-67.
- Costa PT, McCrae RR. Personality disorders and the five-factor model of personality. *Journal of Personality Disorders* 1990;4:362–371.
- Daley SE, Hammen C, Davila J, Burge D. Axis II symptomatology, depression, life stress during the transition from adolescence to adulthood. *Journal of Consulting and Clinical Psychology* 1998;66:595–603. [PubMed: 9735575]
- Farabaugh A, Mischoulon D, Yeung A, Alpert J, Matthews J, Pava J, Fava M. Predictors of stable personality disorder diagnoses in outpatients with remitted depression. *The Journal of Nervous and Mental Disease* 2002;190:248–256. [PubMed: 11960086]

- Fava M, Littman A, Halperin P, Pratt E, Drews FR, Oleshansky M, Knapik J, Thompson C, Bielenda C. Psychological and behavioral benefits of a stress/type A behavior reduction program for healthy middle-aged army officers. *Psychosomatics* 1991;32:337–342. [PubMed: 1882025]
- Fava M, Rosenbaum JF, McCarthy M. Correlations between perceived stress and depressive symptoms among depressive outpatients. *Stress Medicine* 1992;8:73–76.
- Fava M, Bouffides E, Pava JA, McCarthy MK, Steingard RJ, Rosenbaum JF. Personality disorder comorbidity with major depression and response to fluoxetine treatment. *Psychotherapy and Psychosomatics* 1994;62:160–167. [PubMed: 7846259]
- Fava M, Uebelacker LA, Alpert JE, Nierenberg AA, Pava JA, Rosenbaum JF. Major depressive subtypes and treatment response. *Biological Psychiatry* 1997;42:568–576. [PubMed: 9376453]
- Fava M, Farabaugh AH, Sickinger AH, Wright E, Alpert JE, Sonawalla S, Nierenberg AA, Worthington JJ 3rd. Personality disorders and depression. *Psychological Medicine* 2002;32:1049–1057. [PubMed: 12214786]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW.; Janet, BW. Structured Clinical Interview for DSM-IV Personality Disorders, (SCID-II). Washington, D.C.: American Psychiatric Press, Inc.; 1997.
- Gurrera RJ, Dickey CC, Niznikiewicz MA, Voglmaier MM, Shenton ME, McCarley RW. The five-factor model in schizotypal personality disorder. *Schizophrenia Research* 2005;80:243–251. [PubMed: 16168625]
- Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* 1960;23:56–62.
- Hammen C. Stress and depression. *Annual Review of Clinical Psychology* 2005;1:293–319.
- Hart AB, Craighead WE, Craighead LW. Predicting recurrence of major depressive disorder in young adults: a prospective study. *Journal of Abnormal Psychology* 2001;110:633–643. [PubMed: 11727952]
- Heinrichs M, Baumgartner T, Kirschbaum C, Ehler U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry* 2003;54:1389–1398. [PubMed: 14675803]
- Ilardi SS, Craighead WE, Evans DD. Modeling relapse in unipolar depression: the effects of dysfunctional cognitions and personality disorders. *Journal of Consulting and Clinical Psychology* 1997;65:381–391. [PubMed: 9170761]
- Joffe RT, Regan JJ. Personality and depression. *Journal of Psychiatric Research* 1988;22:279–286. [PubMed: 3216345]
- Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. *The American Journal of Psychiatry* 1999;156:837–841. [PubMed: 10360120]
- Kendler KS, Kuhn J, Prescott CA. The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *The American Journal of Psychiatry* 2004;161:631–636. [PubMed: 15056508]
- Kool S, Schoevers R, De Maat S, Van R, Molenaar P, Vink A, Dekker J. Efficacy of pharmacotherapy in depressed patients with and without personality disorders: a systematic review and meta-analysis. *Journal of Affective Disorders* 2005;88:269–278. [PubMed: 16165217]
- Lazarus, RS.; Folkman, S. *Stress, Appraisal and Coping*. Springer Publishing Company: 1984. p. New York
- Lynch TR, Mendelson T, Robins CJ, Krishnan KR, George LK, Johnson CS, Blazer DG. Perceived social support among depressed elderly, middle-aged, and young-adult samples: cross-sectional and longitudinal analyses. *Journal of Affective Disorders* 1999;55:159–170. [PubMed: 10628885]
- Moran P, Rendu A, Jenkins R, Tylee A, Mann A. The impact of personality disorder in UK primary care: a 1-year follow-up of attenders. *Psychological Medicine* 2001;31:1447–1454. [PubMed: 11722159]
- Morey LC, Gunderson JG, Quigley BD, Shea MT, Skodol AE, McGlashan TH, Stout RL, Zanarini MC. The representation of borderline, avoidant, obsessive-compulsive, and schizotypal personality disorders by the five-factor model. *Journal of Personality Disorders* 2002;16:215–234. [PubMed: 12136679]
- Mulder RT, Joyce PR, Luty SE. The relationship of personality disorders to treatment outcome in depressed outpatients. *The Journal of Clinical Psychiatry* 2003;64:259–264. [PubMed: 12716266]

- Mulder RT, Joyce PR, Frampton CM, Luty SE, Sullivan PF. Six months of treatment for depression: outcome and predictors of the course of illness. *The American Journal of Psychiatry* 2006;163:95–100. [PubMed: 16390895]
- Newton-Howes G, Tyrer P, Johnson T. Personality disorder and the outcome of depression: Meta-analysis of published studies. *British Journal of Psychiatry* 2006;188:13–20. [PubMed: 16388064]
- Patience DA, McGuire RJ, Scott AI, Freeman CP. The Edinburgh Primary Care Depression Study: personality disorder and outcome. *The British Journal of Psychiatry* 1995;167:324–330. [PubMed: 7496640]
- Peselow ED, Fieve RR, DiFiglia C. Personality traits and response to desipramine. *Journal of Affective Disorders* 1992;24:209–216. [PubMed: 1578076]
- Pfohl B, Stangl D, Zimmerman M. The implications of DSM-III personality disorders for patients with major depression. *Journal of Affective Disorders* 1984;7:309–318. [PubMed: 6241212]
- Romanov K, Varjonen J, Kaprio J, Koskenvuo M. Life events and depressiveness - the effect of adjustment for psychosocial factors, somatic health and genetic liability. *Acta Psychiatrica Scandinavica* 2003;107:25–23. [PubMed: 12558538]
- Russell JM, Kornstein SG, Shea MT, McCullough JP, Harrison WM, Hirschfeld RM, Keller MB. Chronic depression and comorbid personality disorders: response to sertraline versus imipramine. *The Journal of Clinical Psychiatry* 2003;64:554–561. [PubMed: 12755659]
- Sato T, Sakado K, Sato S. Is there any specific personality disorder or personality disorder cluster that worsens the short-term treatment outcome of major depression? *Acta Psychiatrica Scandinavica* 1993;88:342–349. [PubMed: 7905225]
- Sato T, Sakado K, Sato S, Morikawa T. Cluster A personality disorder: a marker of worse treatment outcome of major depression? *Psychiatry Research* 1994;53:153–159. [PubMed: 7824675]
- Shea MT, Pilkonis PA, Beckham E, Collins JF, Elkin I, Sotsky SM, Docherty JP. Personality disorders and treatment outcome in the NIMH Treatment of Depression Collaborative Research Program. *The American Journal of Psychiatry* 1990;147:711–718. [PubMed: 2343912]
- Skodol AE, Grilo CM, Pagano ME, Bender DS, Gunderson JG, Shea MT, Yen S, Zanarini MC, McGlashan TH. Effects of personality disorders on functioning and well-being in major depressive disorder. *Journal of Psychiatric Practice* 2005;11:363–368. [PubMed: 16304504]
- Spitzer, RL.; Williams, JBW.; Gibbon, M.; First, MB. Biometrics Research Department. New York: New York State Psychiatric Institute; 1989. Structured Clinical Interview for DSM-III-R - Patient Edition.
- Tennant C. Life events, stress and depression: a review of recent findings. *The Australian and New Zealand Journal of Psychiatry* 2002;36:173–182. [PubMed: 11982537]
- Trull TJ, Durrett CA. Categorical and dimensional models of personality Disorder. *Annual Review of Clinical Psychology* 2005;1:355–380.
- Wade TD, Kendler KS. The relationship between social support and major depression: cross-sectional, longitudinal, and genetic perspectives. *The Journal of Nervous and Mental Disease* 2000;188:251–258. [PubMed: 10830561]
- Ystgaard M, Tambs K, Dalgard OS. Life stress, social support and psychological distress in late adolescence: a longitudinal study. *Social Psychiatry and Psychiatric Epidemiology* 1999;34:12–19. [PubMed: 10073116]
- Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR. Prediction of the 10-year course of borderline personality disorder. *American Journal of Psychiatry* 2006;163:827–832. [PubMed: 16648323]
- Zimmerman M. Diagnosing personality disorders A review of issues and research methods. *Archives of General Psychiatry* 1994;51:225–245. [PubMed: 8122959]
- Zuroff DC, Blatt SJ. Vicissitudes of life after the short-term treatment of depression: Roles of stress, social support, and personality. *Journal of Social and Clinical Psychology* 2002;21:473–496.

Table 1

Pre-treatment ("pre") and post-treatment ("post") HAMD-17 and perceived stress scale (PSS) scores as a function of presence vs. absence of DSM-III-R personality disorder (PD) clusters

	PD	Mean (SD)	Cluster A t-value	P	Mean (SD)	Cluster B t-value	P	Mean (SD)	Cluster C t-value	P
HAMD-17: Pre	Yes:	19.98 (3.56) (n = 42)	2.44	0.016	20.80 (3.86) (n = 40)	3.72	0.0003 [†]	20.24 (3.43) (n = 120)	3.76	0.0002 [†]
	No:	18.60 (2.75) (n = 93)			18.60 (2.75) (n = 93)			18.60 (2.75) (n = 93)		
HAMD-17: Post	Yes:	10.31 (5.83) (n = 42)	2.22	0.028	10.85 (7.22) (n = 40)	2.48	0.014	10.22 (6.74) (n = 120)	2.60	0.01
	No:	7.96 (5.65) (n = 93)			7.96 (5.65) (n = 93)			7.96 (5.65) (n = 93)		
PSS score: Pre	Yes:	36.28 (6.72) (n = 36)	0.82	0.413	40.56 (5.92) (n = 34)	4.35	0.0005 [†]	38.01 (6.86) (n = 101)	2.81	0.006
	No:	35.25 (5.91) (n = 76)			35.25 (5.91) (n = 76)			35.25 (5.91) (n = 76)		
PSS score: Post	Yes:	28.50 (7.70) (n = 34)	3.01	0.003 [†]	29.06 (9.37) (n = 31)	3.03	0.003 [†]	27.31 (9.38) (n = 98)	2.86	0.005 [†]
	No:	23.09 (8.83) (n = 64)			23.09 (8.83) (n = 64)			23.09 (8.83) (n = 64)		

[†] $p < 0.05$ after Bonferroni correction ($p = 0.05/12 = 0.0042$).