Perceived Stress and Cognitive Vulnerability Mediate the Effects of Personality Disorder Comorbidity on Treatment Outcome in Major Depressive Disorder

A Path Analysis Study

Michele Candrian, MA, Amy Farabaugh, PhD,* Diego A. Pizzagalli, PhD,† Lee Baer, PhD,* and Maurizio Fava, MD**

Abstract: Although personality disorder (PD) comorbidity has been associated with poor treatment outcome in major depressive disorder (MDD), little is known about mechanisms mediating this link. Converging evidence suggests that maladaptive cognitive patterns, particularly in interaction with stressors, might lead to poor treatment outcome in MDD subjects with PD pathology. The goal of this study was to test the role of PD comorbidity, cognitive vulnerability, and perceived stress in treatment outcome in MDD. Three hundred eighty-four MDD outpatients were enrolled in an 8-week open-label treatment of fluoxetine. Structural equation modeling and path analyses revealed that the effect of PD vulnerability on treatment outcome was fully mediated by increased pretreatment cognitive vulnerability and depression severity, which led to increased stress perception after treatment and poorer antidepressant response. Depressogenic cognitions might be continuously activated by chronic distress in MDD subjects reporting axis II pathology, leading to stress exacerbation and eventually poorer treatment outcome.

*Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; and †Department of Psychology, Harvard University, Cambridge, Massachusetts.

Supported by NIMH grant R01 MH48483-05. DAP was supported by NIMH (R01 MH68376) and NCCAM (R21 AT002974) grants.

Dr. Fava has received research support from Abbott Laboratories, Lichtwer Pharma GmbH, and Lorex Pharmaceuticals as well as honoraria from EPIX Pharmaceuticals, Bayer AG, Compellis, Janssen Pharmaceutica, Knoll Pharmaceutical Company, Lundbeck, Dov Pharmaceuticals, Biovail Pharmaceuticals, Inc., BrainCells, Inc., Cypress Pharmaceuticals, Fabre-Kramer Pharmaceuticals, Inc., Grunenthal GmBH, MedAvante, Inc., Sepracor, and Somerset Pharmaceuticals. In addition, Dr. Fava has received both research support and honoraria from Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, J & J Pharmaceuticals, Novartis, Organon Inc., Pharmavite, Pfizer Inc, Roche, Sanofi/Synthelabo, Solvay Pharmaceuticals, Inc., and Wyeth-Ayerst Laboratories. Dr. Pizzagalli has received research support from GlaxoSmithkline.

Send reprint requests to Michele Candrian, MS, Department of Psychiatry, Massachusetts General Hospital, 15 Parkman St., WACC 812, Boston, MA 02114. E-mail: mcandrian@partners.org.

ISSN: 0022-3018/07/19509-0729
DOI: 10.1097/NMD.0b013e318142cbd5

Key Words: Personality disorder, cognitive vulnerability, perceived stress, path analyses.

(*J Nerv Ment Dis* 2007;195: 729–737)

Studies indicate that 20% to 50% of inpatients and 50% to 85% of outpatients with a current major depressive disorder (MDD) meet criteria for one or more personality disorders (PDs) (Yen et al., 2006). These high rates of PD comorbidity underscore the need to better understand the link between these disorders and evaluate the potential implications of PD comorbidity on MDD.

Although inconsistencies among studies abound, the presence of PD comorbidity is generally hypothesized to have adverse effects on the course and treatment of MDD. In line with this hypothesis, comorbid PD in MDD has been associated with: longer time to achieve treatment response (Pilkonis and Frank, 1988); higher rates of relapse (Hart et al., 2001; Ilardi et al., 1997); shorter time to recurrence (Cyranowski et al., 2004); chronicity (Riso et al., 1996); and poorer response to antidepressant treatment (Peselow et al., 1992; Sato et al., 1993).

Several studies, however, did not find a link between comorbid PD and poor treatment response (Fava et al., 1994b, 1997, 2002; Mulder et al., 2003), and recent reviews have challenged the view that comorbid PD negatively impact treatment outcome in depression (Kool et al., 2005). A recent meta-analysis involving the highest numbers of studies ($n = 34$) and patients (1663 MDD subjects with comorbid PD and 1860 MDD subjects without comorbid PD) found, however, that comorbid PD was associated with a double risk of poor outcome irrespective of treatment modality (drugs, psychotherapy, or combined treatment) (Newton-Howes et al., 2006).

Although many, albeit not all, studies have shown a link between PD comorbidity and poor treatment outcome in MDD, it is important to stress that the causal mechanisms or mediating variables underlying this association remain largely unknown. A greater understanding of mechanisms underlying the relationship between personality pathology

and the course of MDD might not only help in reconciling inconsistent findings in the literature but could also inform the development of more efficacious treatment approaches.

Diathesis-stress theories of depression might provide a powerful framework for identifying mediating variables underlying links between comorbid PD and poor treatment outcome in depression. In general, diathesis-stress theories postulate that specific factors predispose individuals to develop depression when confronted with negative life stress (Gotlib and Hammen, 2002). Among various diatheses, the role of cognitive vulnerabilities in the etiology and course of depression has received substantial empirical scrutiny. According to cognitive theories of depression, an individual's interpretation of negative events increases his or her vulnerability to developing and maintaining depression after these events occur (Abramson et al., 1989; Beck, 1967). Beck's cognitive theory of depression, in particular, proposes that dysfunctional attitudes—rigid and extreme beliefs about the self, the future, and the world that often entail themes of deriving one's worth from being perfect or needing approval from others—are activated in response to specific stressors, leading to an increased likelihood to develop depression (Beck et al., 1979).

A convergence of several lines of evidence raises the possibility that maladaptive cognitive patterns, in particular in interaction with stressors, might lead to poor treatment outcome in MDD subjects with PD comorbidity. First, irrespective of depressive status, PDs have been associated with elevated dysfunctional attitudes (e.g.,, Ilardi and Craighead, 1999; O'Leary et al., 1991), which in turn have been shown to negatively impact the course and treatment of depression (e.g.,, Alloy et al., 2006; Dunkley et al., 2006; Riso et al., 2003; Thase et al., 1992). Of primary relevance to the present study, elevated dysfunctional attitudes at baseline predicted poor response to both psychological (e.g.,, Scott and Harrington, 1996) and pharmacological (e.g.,, Fava et al., 1994a; Zuroff et al., 1999) treatments. Among clinically depressed subjects, those with PD comorbidity have been found to report significantly higher dysfunctional attitude scores than depressed subjects without PD comorbidity (Marton et al., 1989). Thus, dysfunctional attitudes and depressogenic cognitive patterns might be important mediating variables influencing treatment outcome in MDD subjects with PD comorbidity.

Second, PDs predispose individuals to the experience of negative life events (American Psychiatric Association, 1994) and are characterized by increased stress reactivity. In a community sample, for example, Daley et al. (1998) found that PD symptoms predicted interpersonal chronic stress and self-generated episodic stress over 2 years, which in turn increased the risk for depression. These findings are important, particularly since environmental factors, including life stressors, have been found to potentiate the effects of cognitive dysfunctions. Accordingly, in both clinical (e.g., Lewinsohn et al., 2001) and nonclinical (Flett et al., 1995) samples, dysfunctional attitudes have been found to interact with stressful life events to prospectively predict depressive symptoms or onset of depression. Of interest, recent studies suggest that dysfunctional attitudes (1) fully mediated the relation between depressive symptoms and stressors (Church et al., 2005); and (2) influenced both actual and perceived daily stress, which in turn predicted depressive symptoms (Dunkley et al., 2003). Overall, these findings suggest that individuals endorsing depressogenic cognitive styles are more likely to make negative inferences in response to negative life events, in turn increasing their vulnerability to depression (Abramson et al., 1989; Beck, 1967). Moreover, stress perception seems to be an important mediator explaining the relationship between dysfunctional attitudes and depressive symptoms (Dunkley et al., 2003).

THE PRESENT STUDY

On the basis of the literature reviewed above, we hypothesized that 3 factors—PD vulnerability, cognitive vulnerability, and stress exacerbation—would influence treatment outcome in MDD. Specifically, we expected that (1) certain personality traits would be linked to increased cognitive vulnerability, (2) cognitive vulnerability would lead to increased stress appraisal after the treatment, and (3) increased stress appraisal (as well as increased depression severity) would lead to poor treatment outcome. These hypotheses were incorporated within a model postulating that maladaptive cognitive patterns leading to increased stress exacerbation mediated the effects of PD comorbidity on treatment outcome (Figure 1). Structural equation modeling and path analyses were used to test these hypotheses and the possible causal relations among PD vulnerability, cognitive vulnerability, perceived stress, and treatment outcome.

METHODS

Participants

The current study presents new findings from a larger study that evaluated the efficacy of an 8-week open-label treatment of fluoxetine 20 mg/d for MDD. The parent study was conducted at the Depression Clinical and Research Program at Massachusetts General Hospital (Farabaugh et al., 2002, 2006; Fava et al., 2002) and included 384 outpatients between the ages of 18 and 65. All enrolled subjects met criteria for MDD as assessed with the Structured Clinical Interview for DSM-III-R, Patient Edition (SCID-P; Spitzer et al., 1989) and had a score of $\geq$16 on the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) at baseline. The following conditions led to exclusion from the study: pregnancy, breast-feeding, use 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 PD, and mood-congruent or incongruent psychotic features. Subjects were also excluded if they reported: (1) a history of multiple adverse drug reactions, (2) nonresponse to or intolerance of fluoxetine (60–80 mg/d), (3) failure to respond to at least one adequate antidepressant treatment during their current major depressive episode, (4) current use of other psychotropic drugs, and (5) hypothyroid-

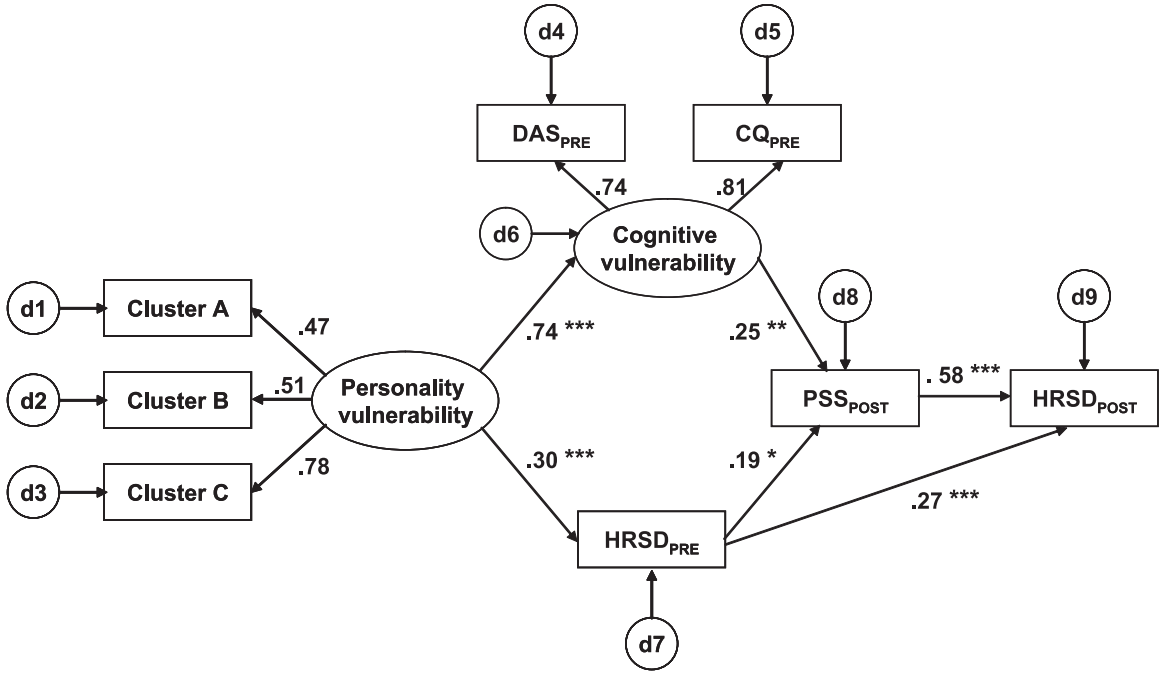

FIGURE 1. Initial, fully mediated model postulating indirect effects of personality vulnerability and cognitive vulnerability on treatment outcome in MDD. Ovals depict latent (unmeasured) variables (personality vulnerability and cognitive vulnerability), whereas rectangles symbolize measured variables. Straight arrows depict paths (presumed influences). The letters "d" denote "disturbances" (i.e., residual errors). For disturbances, a coefficient equal to 1 was selected so that the residual errors had the same scale of measurement as the respective measured variables (Keith, 2006). HRSD: Hamilton Rating Scale for Depression (Hamilton, 1960); DAS: Dysfunctional Attitude Scale (Weissman and Beck, 1978); CQ: Cognitions Questionnaire (Fennell and Campbell, 1984); PSS: Perceived Stress Scale (Cohen et al., 1983). The subscript "pre" and "post" denote pretreatment and posttreatment scores, respectively.

ism. Throughout the acute treatment, subjects were seen biweekly for safety and efficacy assessments.

The study protocol and procedures were approved by the Massachusetts General Hospital Institutional Review Board; participants provided written informed consent before entering the study.

Clinical Assessments and Questionnaires

The main goal of the present study was to evaluate possible causal relations among PD vulnerability, cognitive vulnerability, perceived stress, and treatment outcome in MDD. To this end, both before and immediately after the 8-week treatment, subjects were administered the self-rated Perceived Stress Scale (PSS; Cohen et al., 1983), the Dysfunctional Attitude Scale (DAS; Weissman and Beck, 1978), and the Cognitions Questionnaire (CQ; Fennell and Campbell, 1984) to assess individual differences in stress appraisal, dysfunctional attitudes, and depressive cognitive style, respectively. To assess the presence of any PD, the SCID-II (including its screening questionnaire) (First et al., 1997) was administered at both time points. All clinical assessments (SCID-P, SCID-II, and HRSD) were carried out by clinicians fully trained in their administration.

The PSS has been widely used in the literature to assess the degree to which participants appraise their daily life as unpredictable, uncontrollable, and overwhelming (e.g., "In the last week, how often have you felt that you were unable to control the important things in your life?"). Previous research has shown that this scale better predicts stress-related psychological symptoms, physical symptoms, and health service utilization than commonly used life event scales (Cohen et al., 1983). This self-rated scale includes 14 items scored on a 5-point scale and possesses satisfactory internal and short-term reliability (coefficient *alpha* reliability: 0.84; 2-day test-retest reliability: 0.85; Cohen et al., 1983).

The DAS was developed to assess dysfunctional and rigid cognitions, which have been linked to the onset and maintenance of depression in Beck's cognitive theory of depression (Beck, 1967). Specifically, this 40-item self-rated questionnaire assesses maladaptive attitudes, including perfectionistic standards of performance (e.g., "If I fail at my work, then I am a failure as a person"), sensitivity to social criticism and need for approval (e.g., "If others dislike you, you cannot be happy"), expectations of control (e.g., "I should always have complete control over my feelings"), and rigid ideas about the world. Each item is rated on a 7-point Likert scale ranging from totally agree to totally disagree. A total score and 2 scale scores (Perfectionism and Need for Social Approval) can be computed; in the present study, the total score was used. Higher scores indicate greater endorsements of dysfunctional beliefs. DAS scores, either alone or in conjunction with stressors, have been found to predict depressive symptoms (Hankin et al., 2004; Ilardi and Craig-

head, 1999), highlighting the validity of this scale. Satisfactory internal consistency (Cronbach's *alpha* 0.89) and test-retest reliability over an 8-week period ($r = 0.84$) have been reported (Weissman and Beck, 1978). In the present sample, the test-retest reliability during the 8-week treatment period was satisfactory ($r = 0.70$, $p < 0.0001$, $n = 142$).

The CQ was developed to provide an overall measure of depressive cognitive style. This self-report measure has been derived from the revised learned helplessness model (Abramson et al., 1978), which conceptualizes depression as a response to negative events perceived as uncontrollable and attributed to stable and internal causes. Specifically, the CQ assesses 5 dimensions of negative thinking in relation to different types of hypothetical events and their consequences. The 5 dimensions probed are: emotional impact (e.g., aversiveness), attribution of causality, generalization across time, generalization across situations, and perceived uncontrollability. A total score providing an overall measure of depressive distortions was used. Previous studies have shown that the total CQ score possesses satisfactory internal reliability and validity (Fennell and Campbell, 1984; MacLeod and Williams, 1990; Mitchell and Campbell, 1988). In the present study, the CQ scale had satisfactory test-retest reliability ($r = 0.66$, $p < 0.0001$, $n = 115$).

Statistics

To avoid the possibility that PD diagnoses may be confounded by the patient's depressed state (Fava et al., 1994b, 2002; Zimmerman, 1994), the statistical analyses considered only MDD subjects who either (1) met DSM-III-R criteria for cluster A ($n = 42$), cluster B ($n = 40$), or cluster C ($n = 120$) at both the pre- and posttreatment assessments; or (2) did not meet any PD criteria at either assessment ($n = 93$).

For the statistical analyses, 3 data analytic strategies were used. First, zero-order correlations between measures of depression (HRSD), cognitive vulnerability (DAS, CQ), and perceived stress (PSS) were computed to evaluate relations among the variables under investigation. Second, structural equation modeling and path analysis were used to assess the fit between: (1) models hypothesizing specific causal relations between PD vulnerability, cognitive vulnerability, stress perception, and treatment outcome; and (2) the observed set of correlations between the variables in the models. Note that the goal of the path analyses was not to test all possible models but instead to test models derived from previous theories and empirical findings. Third, to test the specificity of findings emerging from the second step, path analyses were separately performed for cluster A, cluster B, and cluster C PDs. For path analyses, PD vulnerability was entered as a dichotomous variable (see Keith, 2006, for detail concerning the use of dichotomous variables in path analyses).

Figure 1 shows an initial model postulating a specific causal flow from a latent exogenous variable (PD vulnerability) through 2 sets of intervening variables (first set: pretreatment HRSD and cognitive vulnerability; second set: posttreatment PSS) to an outcome variable (posttreatment HRSD). Thus, this model postulates indirect effects of PD vulnerability on treatment outcome in MDD. The effects are mediated by cognitive vulnerability and depression severity before treatment leading to increased stress perception after the treatment, in turn modulating treatment outcome. Both PD vulnerability and cognitive vulnerability were defined as latent variables.

For path analyses, we used AMOS (Arbukle, 2003; version 5.0), which uses maximum-likelihood estimation to test the fit of a hypothesized model to the observed variance-covariance matrix. In line with the recommendation of Hoyle and Panter (1995), various measures of fit were used to evaluate various models. First, chi square was used to assess the statistical fit of the model; nonsignificant chi square means that the model and the actual data are consistent with one another. Next, we considered the ratio of the chi square value to the *df* in the model (absolute fit); ratios between 1 and 2 reflect better-fitting models (Carmines and McIver, 1981). To assess incremental fit, the Comparative Fit Index (CFI) was used as a goodness-of-fit index. Goodness-of-fit index provides an estimate of the total covariance accounted for by the model, and CFI values over 0.95 represent a good fit of the model to the data (Bentler, 1990). Finally, to assess parsimony-adjusted fit, we used the root mean square error of approximation (RMSEA); values lower than 0.05 are interpreted as suggesting a close fit of the model (Browne and Cudeck, 1993).

Although the initial model postulated a full mediation of PD on treatment outcome, an alternate model was evaluated by adding direct paths from the exogenous latent variable (PD vulnerability) and the mediating variable (cognitive vulnerability) to the outcome variables (posttreatment HRSD). Note that the initial model was nested in the alternate model (i.e., it can be derived from the other by deleting paths). Accordingly, the difference between the respective chi square values was computed to assess whether the initial and revised models fit the data differently. The Akaike Information Criterion (AIC) was used to evaluate competing models. Following prior recommendations (Keith, 2006), the model with the lower AIC value was favored.

RESULTS

Zero-Order Correlations

Before conducting a path analysis, zero-order correlations were computed to determine whether the variables under investigation were related to each other. As shown in Table 1, most of the correlations were significant, justifying the use of path analysis.

Initial, Fully Mediated Model

Figure 1 illustrates the initial model postulating indirect effects of PD and cognitive vulnerability on treatment outcome in MDD and the resulting path coefficients. As shown in the figure, all standardized coefficients were significant and large (i.e., above 0.25; Keith, 2006). The path between pretreatment HRSD and posttreatment PSS score was also significant but in the moderate range. All fit indices indicated a good fit of the model to the data, $\chi^2 = 11.06$, $p = 0.85$ ($df = 17$; $n = 231$), $\chi^2/df = 0.65$. The RMSEA was smaller than 0.001, with a 90% confidence interval of 0.000 to 0.034, and the CFI was 1.0. As shown in Figure 1, PD vulnerability was significantly and positively correlated with pretreatment

TABLE 1. Zero-Order Correlations Among the Variables Under Investigation

	Pretreatment HRSD	Pretreatment DAS	Pretreatment CQ	Posttreatment PSS	Posttreatment HRSD
Pretreatment HRSD	1.000	0.214** (n = 160)	0.180* (n = 139)	0.260*** (n = 172)	0.407*** (n = 231)
Pretreatment DAS	—	1.000	0.589*** (n = 132)	0.135 (n = 138)	0.154 (n = 160)
Pretreatment CQ	—	—	1.000	0.258** (n = 118)	0.161 (n = 139)
Posttreatment PSS	—	—	—	1.000	0.655*** (n = 172)
Posttreatment HRSD	—	—	—	—	1.000
Mean	19.52	147.86	28.19	25.87	9.41
SD	3.32	35.71	11.10	9.37	6.40
N	231	160	139	172	231

HRSD indicates Hamilton Rating Scale for Depression (Hamilton, 1960); DAS, Dysfunctional Attitude Scale (Weissman and Beck, 1978); CQ, Cognitions Questionnaire (Fennell and Campbell, 1984); PSS, Perceived Stress Scale (Cohen et al., 1983).
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

cognitive dysfunctions and pretreatment HRSD scores, which in turn were both significantly and positively correlated with increased stress perception after treatment. Elevated stress perception was positively correlated with depression severity after the 8-week treatment. Sobel's tests (Sobel, 1982) confirmed that the indirect path between PD vulnerability and post-treatment stress perception ($Z = 4.43$, $p < 0.00001$; mediating variable: cognitive vulnerability), and the indirect path between cognitive vulnerability and treatment outcome ($Z = 2.75$, $p < 0.007$; mediating variable: posttreatment stress perception) were both significant. Thus, the effect of PD vulnerability on treatment outcome was fully mediated by increased cognitive vulnerability and depression severity, leading to increased stress exacerbation after treatment. Table 2 summarizes the effect coefficients for the initial model.

Revised Model

The initial model does not include direct paths between (1) PD vulnerability and posttreatment PSS, (2) PD vulnerability and posttreatment HRSD, and (3) Cognitive vulnerability and posttreatment HRSD. The initial, fully mediated, and overidentified model was compared with a revised, just-identified model including these 3 additional paths. The revised model fit the data equally well ($\chi^2 = 9.30$, $p = 0.81$, $df = 14$, $n = 231$, $\chi^2/df = 0.66$; RMSEA <0.001, 90% confidence interval: 0.000–0.041; CFI = 1.00). A test of the difference between the 2 competing models indicated that the initial model did not fit the data significantly less well than the just-identified revised model ($\Delta\chi^2 = 1.76$, $df = 3$, $p = 0.62$). Following established procedures (Keith, 2006), the initial model was favored because (1) was more parsimonious ($df = 17$) than the revised model ($df = 14$) and (2) had an equivalent fit. Evaluation of the critical ratio (t = coefficient/$SE_{\text{coefficient}}$) for the additional direct paths leads to a similar conclusion in favor of the initial model. In fact, the critical ratio for the path between PD vulnerability and posttreatment PSS; ($t = 1.94$, $p = 0.23$); PD vulnerability and posttreatment HRSD ($t = -0.36$, $p = 0.72$); and cognitive vulnerability and posttreatment HRSD ($t = 0.02$, $p = 0.98$) indicated that these paths were not significant. Finally, the AIC was lower for the initial model, again consistent with the notion that the model without direct path should be favored.

TABLE 2. Effect Coefficients for the Initial Model Postulating Indirect Effects of Personality and Cognitive Vulnerability on Treatment Outcome (Posttreatment HRSD)

Variable	Direct	Indirect	Total
Personality vulnerability	—	0.219	0.219
Cognitive vulnerability	—	0.146	0.146
Pretreatment HRSD	0.267	0.107	0.374
Posttreatment PSS	0.576	0.000	0.576

Note: Direct, indirect, and total effects were calculated after standardizing all variables. Personality vulnerability and cognitive vulnerability were entered as latent variables. For personality vulnerability and cognitive vulnerability, no direct effects on treatment outcome were postulated.
HRSD indicates Hamilton Rating Scale for Depression (Hamilton, 1960); PSS, Perceived Stress Scale (Cohen et al., 1983).

Cluster-Specific Model

To assess whether the initial model was specific to a given DSM-based PD cluster, a path analysis of the initial model was performed for cluster A, cluster B, and cluster C separately. For each cluster, the model provided a good fit of the data (cluster A: $\chi^2 = 2.18$, $p = 0.90$, $df = 6$, $\chi^2/df = 0.36$; RMSEA < 0.001; CFI = 1.0; cluster B: $\chi^2 = 7.46$, $p = 0.28$, $df = 6$, $\chi^2/df = 1.24$; RMSEA = 0.043; CFI = 0.99; cluster C: $\chi^2 = 6.91$, $p = 0.33$, $df = 6$, $\chi^2/df = 1.15$; RMSEA = 0.027; CFI = 0.996). For each cluster, the direct path between PD and posttreatment PSS was not significant (Table 3). Interestingly, only for cluster A, a fully mediated model was observed (Figure 2). For both cluster B and C, the path coefficient between cognitive vulnerability and posttreatment PSS was not significant (Table 3).

DISCUSSION

In recent years, inconsistent findings have emerged around the question of whether PD comorbidity might have adverse effects on the course and treatment of MDD (Kool et al., 2005; Mulder, 2006; Newton-Howes et al., 2006). Although several studies have shown a link between PD comorbidity and poor treatment outcome in MDD (Newton-Howes et al., 2006), little is known about causal mechanisms or mediating variables underlying this link. The main goal of the present study was to evaluate the effects of potential mediating variables on treatment outcome after an 8-week open-label treatment with fluoxetine in a clinical sample charac-

TABLE 3. Standardized Regression Weights Emerging From the Cluster-Specific Path Analyses

	Cluster A	Cluster B	Cluster C
Personality vulnerability → Cognitive vulnerability	0.622***	0.703***	0.566***
Personality vulnerability → Pretreatment HRSD	0.207*	0.309***	0.251***
Pretreatment HRSD → Posttreatment PSS	0.236**	0.211*	0.191**
Cognitive vulnerability → Posttreatment PSS	0.429*	0.307	0.189
Personality vulnerability → Posttreatment PSS	−0.016	−0.018	0.076
Pretreatment HRSD → Posttreatment HRSD	0.244***	0.276***	0.257***
Posttreatment PSS → Posttreatment HRSD	0.510***	0.545***	0.580***

HRSD indicates Hamilton Rating Scale for Depression (Hamilton, 1960); DAS, Dysfunctional Attitude Scale (Weissman and Beck, 1978); CQ, Cognitions Questionnaire (Fennell and Campbell, 1984); PSS, Perceived Stress Scale (Cohen et al., 1983).

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

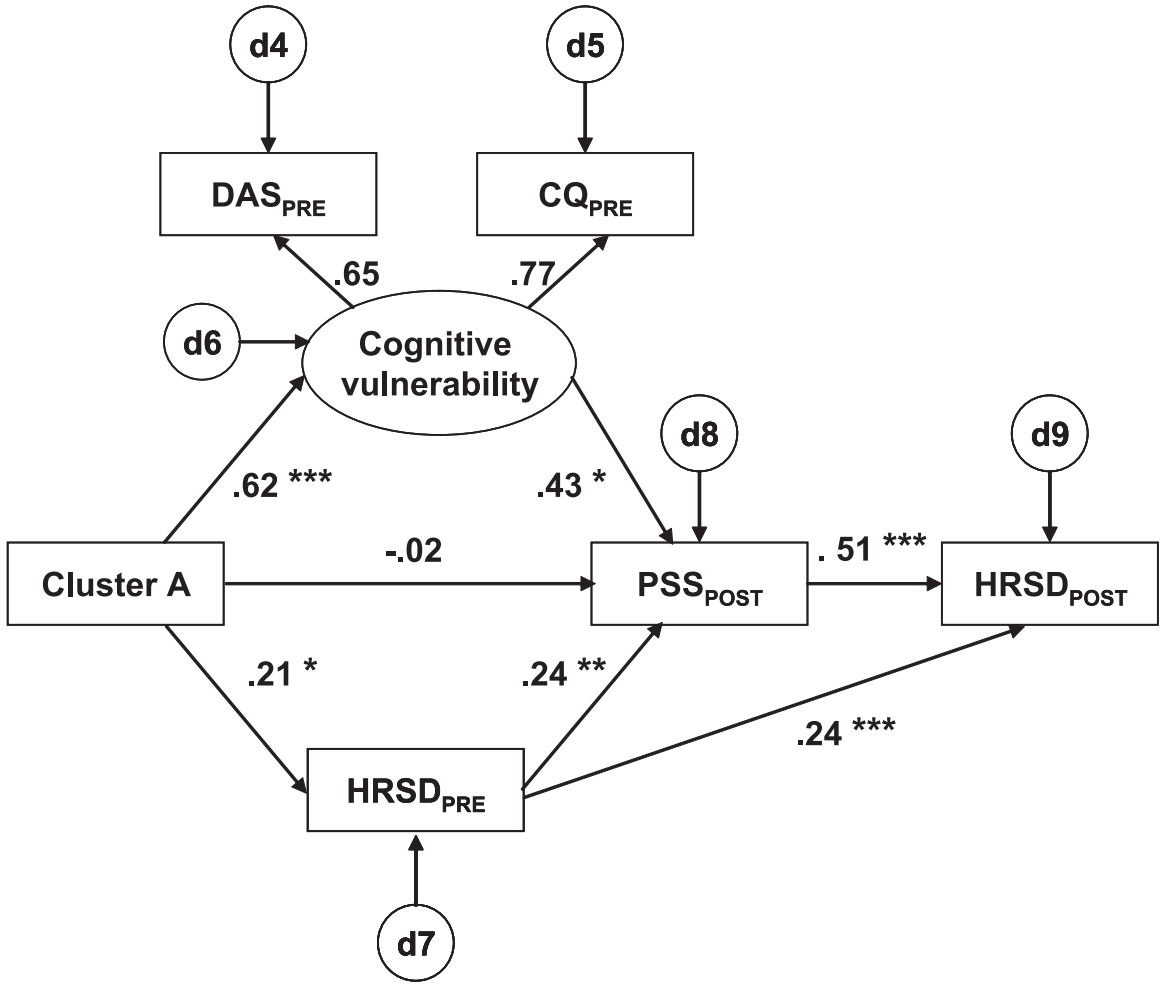

FIGURE 2. Fully mediated model investigating the effects of cluster A PD comorbidity, cognitive vulnerability, baseline depression severity, and perceived stress on treatment outcome. See Figure 1 for more details.

terized by substantial PD comorbidity. On the basis of previous findings, we hypothesized that maladaptive cognitive patterns and increased stress appraisal might mediate the effects of PD on treatment outcome. These hypotheses were confirmed. Specifically, path analyses revealed that PD comorbidity significantly and positively correlated with cognitive vulnerability (dysfunctional attitudes and depressogenic cognitive patterns), which in turn was positively correlated with stress appraisal after the treatment; increased stress perception was in turn significantly and positively correlated

with depression severity after treatment. Notably, a fully mediated model was compared with a partially mediated model that included direct paths between (1) PD and treatment outcome, (2) PD and stress perception, and (3) cognitive vulnerability and treatment outcome. The partially mediated model was not a significantly better fit to the data than the fully mediated model, and the additional 3 paths, including the one between PD and treatment outcome, were not significant. Moreover, Sobel's tests confirmed that the indirect path between PD vulnerability and posttreatment stress perception and the one between cognitive vulnerability and treatment outcome were significant. Together with the presence of nonsignificant direct paths, findings from the Sobel's tests indicate that the relation between PD and treatment outcome can be considered fully mediated (Dunkley et al., 2006). Interestingly, although each DSM-based PD cluster was associated with elevated cognitive vulnerability, the path coefficient between pretreatment cognitive vulnerability and posttreatment perceived stress was significant only for cluster A, indicating that the fully mediated model provided an excellent statistical fit for MDD subjects reporting enduring cluster A pathology (paranoid, schizoid, and schizotypal PD).

The present findings implicate cognitive vulnerability and perceived stress in the mediation of treatment outcome for MDD subjects presenting with enduring personality pathology. These results are consistent with and extend a large body of previous work. First, PDs are characterized by deeply ingrained and inflexible patterns of relating, perceiving, and thinking (DSM-IV, American Psychiatric Association, 1994), and previous studies have documented elevated dysfunctional attitudes in subjects with axis II pathology (e.g., Ilardi and Craighead, 1999; O'Leary et al., 1991). According to cognitive theories of depression, and in particular Beck's cognitive theory, maladaptive, negatively focused cognitive schemata involving themes of failure, personal inadequacy, and hopelessness about the self, the world, and the future are activated in response to specific stressors, leading to an increased likelihood to develop depression (Abramson et al., 1989; Beck, 1967, Beck et al., 1979). Consistent with this hypothesis, a multitude of studies have found that dysfunctional attitudes and depressogenic cognitive patterns influence the onset and course of depression. In prospective studies, for example, individuals endorsing dysfunctional attitudes and negative cognitive style experienced more episodes, more severe episodes, and more chronic courses of depression during a 2.5-year follow-up period compared with control subjects (e.g., Alloy et al., 2006). Similarly, in a clinical sample characterized by substantial PD comorbidity, DAS (perfectionism) scores predicted depressive symptoms 3 years later (Dunkley et al., 2006). Of primary relevance to the present study, elevated dysfunctional attitudes at baseline predicted poor response to both psychological (Jarrett et al., 1991; Scott and Harrington, 1996) and pharmacological (Fava et al., 1994a,b; Zuroff et al., 1999) treatments. Finally, elevated dysfunctional attitudes have been related with early onset and longer duration of depression (Luty et al., 1999), increased risk for relapse (e.g., Thase et al., 1992), and chronic course (Riso et al., 2003). Findings emerging from the present study are consistent with these prior reports and indicate that the presence of elevated dysfunctional attitudes and depressogenic cognitions before treatment predict higher depressive symptoms after an 8-week fluoxetine treatment in MDD subjects reporting PD comorbidity.

Interestingly, in the present study, the effect of cognitive vulnerability on treatment outcome was mediated by increased stress perception after the treatment. Accordingly, MDD subjects with axis II pathology reporting rigid and extreme beliefs about the self and the world before the treatment reported higher level of stress, which in turn was associated with higher depressive symptoms after the treatment. These findings are intriguing, particularly since cognitive vulnerability models have suggested that maladaptive cognitive schemata may remain latent until primed by a distress or negative life event (Ingram et al., 1998; Miranda and Persons, 1988), and activation of cognitive vulnerability during follow-up periods has been hypothesized to contribute to relapse and recurrence of depression (Segal et al., 1992). Because PD is characterized by chronic, clinically significant distress (American Psychiatric Association, 1994, p. 633), it is possible that depressogenic cognitions are continuously primed and activated in MDD subjects reporting enduring axis II pathology, leading to poor treatment outcome.

In the current study, presence of any DSM-based PD cluster was associated with increased cognitive vulnerability. Only for MDD subjects with cluster A comorbidity, however, elevated dysfunctional attitudes and depressogenic cognition at baseline predicted increased stress perception after the treatment, indicating that the fully mediated model provided an excellent fit only for cluster A. These findings are intriguing, particularly in light of prior evidence that symptoms of cluster A (as well as cluster B, but not cluster C) pathology predicted interpersonal chronic stress and self-generated episodic stress over 2 years, which in turn increased the risk for depressive symptoms (Daley et al., 1998). Although stress mediated the relationship between cluster A pathology and later symptoms of depression in both the present and Daley et al.'s (1998) study, it is important to emphasize that the reasons for this specificity are not entirely clear and that previous studies investigating the effects of DSM-based PD pathology on treatment outcome in depression have yielded somewhat inconsistent findings (Daley et al., 1999; Hart et al., 2001; Ilardi et al., 1997; Peselow et al., 1992). One possibility is that the emotional withdrawal, lack of warmth, and odd/eccentric behavior characteristic of cluster A pathology may lead to restricted social support, which is an important buffer against the physiological (Heinrichs et al., 2003) and psychological (Ystgaard et al., 1999) effects of stress. Although the present findings await replication from future studies, they suggest that the link between cognitive vulnerability and stress exacerbation might be particularly important for MDD subjects reporting cluster A comorbidity.

The limitations of the present study deserve mention. First, a key mediating variable (posttreatment stress appraisal) and the outcome variable (posttreatment HRSD) were measured concurrently. Accordingly, the present findings cannot demonstrate any causal relation between increased

stress perception and depressive symptoms after the treatment. It is possible that depressive symptoms influenced stress perception, or that bidirectional relations exist between these variables. To assess causality, prospective designs assessing mediating variables and outcome variables at different time points will be required. Second, we did not investigate single PD diagnoses or subgroups of patients differing in clinical and sociodemographic variables that have been associated with differential treatment response (Fava et al., 1997). Although conceptually of great interest, subgrouping would have produced sample sizes too small for the *SEM* analyses. Moreover, the use of DSM-based clusters has received support in several factor and cluster-analytic studies (Bagby et al., 1993). Third, although the present *SEM* provided an excellent fit to the data, it is important to keep in mind that it is always possible that other models not tested in the present study might fit the data equally well or even better. The present model was, however, developed based on previous empirical findings and current etiological theories of depression, and the findings confirmed the a priori hypotheses. Fourth, analyses were primarily based on self-report assessments. Although the questionnaires used in the present study have been widely used in the literature and possess satisfactory reliability and validity, reporting biases cannot be excluded. Finally, in light of the rather extensive exclusion criteria used in the current study, future work should evaluate the generalizability of the present findings to community samples, which will likely be more heterogeneous.

In spite of these limitations, the present findings indicate that the relation between PD and treatment outcome was fully mediated by intervening variables. Specifically, the *SEM* analyses revealed that the presence of PD comorbidity was associated with increased maladaptive cognitive patterns (dysfunctional attitudes and depressogenic cognitions) leading to elevated stress appraisal after the treatment, which in turn was associated with higher depression severity after an 8-week fluoxetine treatment. More generally, the present findings underscore the need to address underlying cognitive and personality vulnerability, in addition to symptoms of depression, in treatments for depression (Hayes et al., 1996; Zuroff et al., 1999).

REFERENCES

Abramson LY, Metalsky GI, Alloy LB (1989) Hopelessness depression: A theory-based subtype of depression. *Psychol Rev*. 96:358–372.

Abramson LY, Seligman MEP, Teasdale JD (1978) Learned helplessness in humans: Critique and reformulation. *J Abnorm Psychol*. 87:49–74.

Alloy LB, Abramson LY, Whitehouse WG, Hogan ME, Panzarella C, Rose DT (2006) Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *J Abnorm Psychol*. 115:145–156.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th ed). Washington (DC): American Psychiatric Press.

Arbuckle JL (2003) *Analysis of Moment Structures (AMOS)* (User's Guide Version 5.0). Chicago (IL): SmallWaters Corporation.

Bagby RM, Joffe RT, Parker JDA (1993) Re-examination of the evidence for the DSM-III personality disorder clusters. *J Personal Disord*. 7:320–328.

Beck AT (1967) *Depression: Clinical, Experimental and Theoretical Aspects.* New York: Hoeber Medical Division, Harper & Row.

Beck AT, Rush A, Shaw B, Emery G (1979) *Cognitive Therapy of Depression.* New York: Guilford Press.

Bentler PM (1990) Comparative fit indexes in structural models. *Psychol Bull*. 107:238–246.

Browne MW, Cudeck R (1993) Alternative ways of assessing model fit. In KA Bollen, JS Long (Eds), *Testing Structural Equation Models* (pp 136–162). Newbury Park (CA): Sage.

Carmines E, McIver J (1981) Analyzing models with unobserved variables: Analysis of covariance structures. In G Bohrnstedt, E Borgatta (Eds), *Social Measurement: Current Issues* (pp 65–115). Beverly Hills (CA): Sage.

Church NF, Brechman-Toussaint ML, Hine DW (2005) Do dysfunctional cognitions mediate the relationship between risk factors and postnatal depression symptomatology? *J Affect Disord*. 87:65–72.

Cohen S, KamarckT, Mermelstein R (1983) A global measure of perceived stress. *J Health Soc Behav.* 24:385–396.

Cyranowski JM, Frank E, Winter E, Rucci P, Novick D, Pilkonis P, Fagiolini A, Swartz HA, Houck P, Kupfer DJ (2004) Personality pathology and outcome in recurrently depressed women over 2 years of maintenance interpersonal psychotherapy. *Psychol Med*. 34:659–669.

Daley SE, Hammen C, Burge D (1999) Depression and axis II symptomatology in an adolescent community sample: Concurrent and longitudinal associations. *J Personal Disord*. 13:47–59.

Daley SE, Hammen C, Davila J, Burge D (1998) Axis II symptomatology, depression and life stress during the transition from adolescence to adulthood. *J Consult Clin Psychol*. 66:595–603.

Dunkley DM, Sanislow CA, Grilo CM, McGlashan TH (2006) Perfectionism and depressive symptoms 3 years later: Negative social interactions, avoidant coping and perceived social support as mediators. *Compr Psychiatry*. 47:106–115.

Dunkley DM, Zuroff DC, Blankstein KR (2003) Self-critical perfectionism and daily affect: Dispositional and situational influences on stress and coping. *J Pers Soc Psychol*. 84:234–252.

Farabaugh A, Mischoulon D, Yeung A, Alpert J, Matthews J, Pava J, Fava M (2002) Predictors of stable personality disorder diagnoses in outpatients with remitted depression. *J Nerv Ment Dis*. 190:248–256.

Farabaugh AH, Sonawalla SB, Fava M, Pedrelli P, Papakostas GI, Schwartz F, Mischoulon D (2006) Differences in cognitive factors between "true drug" versus "placebo pattern" response to fluoxetine as defined by pattern analysis. *Hum Psychopharmacol*. 21:221–225.

Fava M, Bless E, Otto MW, Pava JA, Rosenbaum JF (1994a) Dysfunctional attitudes in major depression. Changes with pharmacotherapy. *J Nerv Ment Dis*. 182:45–49.

Fava M, Bouffides E, Pava JA, McCarthy MK, Steingard RJ, Rosenbaum JF (1994b) Personality disorder comorbidity with major depression and response to fluoxetine treatment. *Psychother Psychosom*. 62:160–167.

Fava M, Farabaugh AH, Sickinger AH, Wright E, Alpert JE, Sonawalla S, Nierenberg AA, Worthington JJ III (2002) Personality disorders and depression. *Psychol Med*. 32:1049–1057.

Fava M, Uebelacker LA, Alpert JE, Nierenberg AA, Pava JA, Rosenbaum JF (1997) Major depressive subtypes and treatment response. *Biol Psychiatry*. 42:568–576.

Fennell MJ, Campbell EA (1984) The cognitions questionnaire: Specific thinking errors in depression. *Br J Clin Psychol*. 23:81–92.

First MB, Spitzer RL, Gibbon M, Williams JBW, Janet BW (1997) *Structured Clinical Interview for DSM-IV Personality Disorders, (SCID-II)*. Washington (DC): American Psychiatric Press, Inc.

Flett GL, Hewitt PL, Blankstein KR (1995) Perfectionism, life events and depressive symptoms: A test of a diathesis-stress model. *Curr Psychol*. 14:112–137.

Gotlib I, Hammen C (2002) *Handbook of Depression.* New York: Guilford Press.

Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 23:56–62.

Hankin BL, Abramson LY, Miller N (2004) Cognitive vulnerability-stress theories of depression: Examining affective specificity in the prediction of depression versus anxiety in three prospective studies. *Cogn Ther Res*. 28:309–345.

Hart AB, Craighead WE, Craighead LW (2001) Predicting recurrence of major depressive disorder in young adults: A prospective study. *J Abnorm Psychol*. 110:633–643.

Hayes AM, Castonguay LG, Goldfried MR (1996) Effectiveness of targeting the vulnerability factors of depression in cognitive therapy. *J Consult Clin Psychol*. 64:623–627.

Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U (2003) Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol Psychiatry*. 54:1389–1398.

Hoyle RH, Panter AT (1995) Writing about structural equation models. In RH Hoyle (Ed), *Structural Equation Modeling* (pp 158–176). Thousand Oaks (CA): Sage.

Ilardi SS, Craighead WE (1999) The relationship between personality pathology and dysfunctional cognitions in previously depressed adults. *J Abnorm Psychol*. 108:51–57.

Ilardi SS, Craighead WE, Evans DD (1997) Modeling relapse in unipolar depression: The effects of dysfunctional cognitions and personality disorders. *J Consult Clin Psychol*. 65:381–391.

Ingram RE, Miranda J, Segal ZV (1998) *Cognitive Vulnerability to Depression.* New York: Guilford Press.

Jarrett RB, Eaves GG, Grannemann BD, Rush AJ (1991) Clinical, cognitive and demographic predictors of response to cognitive therapy for depression: A preliminary report. *Psychiatry Res*. 37:245–260.

Keith TZ (2006) *Multiple Regression and Beyond.* Boston: Pearson Education, Inc.

Kool S, Schoevers R, de Maat S, Van R, Molenaar P, Vink A, Dekker J (2005) Efficacy of pharmacotherapy in depressed patients with and without personality disorders: A systematic review and meta-analysis. *J Affect Disord*. 88:269–278.

Lewinsohn PM, Joiner TE, Rohde P (2001) Evaluation of cognitive diathesis-stress models in predicting major depressive disorder in adolescents. *J Abnorm Psychol*. 110:203–215.

Luty SE, Joyce PR, Mulder RT, Sullivan PF, McKenzie JM (1999) The relationship of dysfunctional attitudes to personality in depressed patients. *J Affect Disord*. 54:75–80.

MacLeod AK, Williams JM (1990) Overgeneralization: An important but non-homogeneous construct. *Br J Clin Psychol*. 29:443–444.

Marton P, Korenblum M, Kutcher S, Stein B, Kennedy B, Pakes J (1989) Personality dysfunction in depressed adolescents. *Can J Psychiatry*. 34: 810–813.

Miranda J, Persons JB (1988) Dysfunctional attitudes are mood-state dependent. *J Abnorm Psychol*. 97:76–79.

Mitchell S, Campbell EA (1988) Cognitions associated with anxiety and depression. *Pers Indiv Diff*. 9:837–838.

Mulder R (2006) Personality disorder and outcome in depression. *Br J Psychiatry*. 189:186–187.

Mulder RT, Joyce PR, Luty SE (2003) The relationship of personality disorders to treatment outcome in depressed outpatients. *J Clin Psychiatry*. 64:259–264.

Newton-Howes G, Tyrer P, Johnson T (2006) Personality disorder and the outcome of depression: Meta-analysis of published studies. *Br J Psychiatry*. 188:13–20.

O'Leary KM, Cowdry RW, Gardner DL (1991) Dysfunctional attitudes in borderline personality disorder. *J Personal Disord*. 5:233–242.

Peselow ED, Fieve RR, DiFiglia C (1992) Personality traits and response to desipramine. *J Affect Disord*. 24:209–216.

Pilkonis PA, Frank E (1988) Personality pathology in recurrent depression: Nature, prevalence and relationship to treatment response. *Am J Psychiatry*. 145:435–441.

Riso LP, du Toit PL, Blandino JA, Penna S, Dacey S, Duin JS, Pacoe EM, Grant MM, Ulmer CS (2003) Cognitive aspects of chronic depression. *J Abnorm Psychol*. 112:72–80.

Riso LP, Klein DN, Ferro T, Kasch KL, Pepper CM, Schwartz JE, Aronson TA (1996) Understanding the comorbidity between early-onset dysthymia and cluster B personality disorders: A family study. *Am J Psychiatry*. 153:900–906.

Sato T, Sakado K, Sato S (1993) Is there any specific personality disorder or personality disorder cluster that worsens the short-term treatment outcome of major depression? *Acta Psychiatr Scand*. 88:342–349.

Scott J, Harrington J (1996) A preliminary study of the relationship among personality, cognitive vulnerability, symptom profile and outcome in major depressive disorder. *J Nerv Ment Dis*. 184:503–505.

Segal ZV, Shaw BF, Vella DD, Katz R (1992) Cognitive and life stress predictors of relapse in remitted unipolar depressed patients: Test of the congruency hypothesis. *J Abnorm Psychol*. 101:26–36.

Sobel ME (1982) Asymptotic intervals for indirect effects in structural equations models. In S Leinhart (Ed), *Sociological Methodology* (pp 290–312). San Francisco: Jossey-Bass.

Spitzer RL, Williams JBW, Gibbon M, First MB (1989) *Structured Clinical Interview for DSM-III-R—Patient Edition.* New York: Biometrics Research Department, New York State Psychiatric Institute.

Thase ME, Simons AD, McGeary J, Cahalane JF, Hughes C, Harden T, Friedman E (1992) Relapse after cognitive behavior therapy of depression: Potential implications for longer courses of treatment. *Am J Psychiatry*. 149:1046–1052.

Weissman AN, Beck AT (1978) Development and validation of the Dysfunctional Attitude Scale (DAS). Paper presented at the 12th Annual Meeting of the Association for the Advancement of Behavior Therapy, Chicago, IL.

Yen S, McDevitt-Murphy ME, Shea MT (2006) Depression and personality. In DJ Stein, DJ Kupfer, AF Schatzberg (Eds), *The American Psychiatric Publishing Textbook of Mood Disorders* (pp 673–686). Washington (DC): American Psychiatric Publishing, Inc.

Ystgaard M, Tambs K, Dalgard OS (1999) Life stress, social support and psychological distress in late adolescence: A longitudinal study. *Soc Psychiatry Psychiatr Epidemiol*. 34:12–19.

Zimmerman M (1994) Diagnosing personality disorders. A review of issues and research methods. *Arch Gen Psychiatry*. 51:225–245.

Zuroff DC, Blatt SJ, Sanislow CA III, Bondi CM, Pilkonis PA (1999) Vulnerability to depression: Reexamining state dependence and relative stability. *J Abnorm Psychol*. 108:76–89.