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Two-year prospective naturalistic study of remission from major depressive disorder as a function of personality disorder comorbidity

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Two-Year Prospective Naturalistic Study of Remission From Major Depressive Disorder as a Function of Personality Disorder Comorbidity

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In this study, the authors examined prospectively the 24-month natural course of remission from major depressive disorder (MDD) as a function of personality disorder (PD) comorbidity. In 302 participants (196 women, 106 men), psychiatric and PDs were assessed at baseline with diagnostic interviews, and the course of MDD was assessed with the Longitudinal Interval Follow-Up Evaluation at 6-, 12-, and 24-month follow-ups. Survival analyses revealed an overall 24-month remission rate of 73.5% for MDD that differed little by gender. Participants with MDD who had certain forms of coexisting PD psychopathology (schizotypal, borderline, or avoidant) as their primary PD diagnoses had a significantly longer time to remission from MDD than did patients with MDD without any PD. These PDs emerged as robust predictors of slowed remission from MDD even when controlling for other negative prognostic predictors.

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Major depressive disorder (MDD) is a serious and refractory public health problem (Kessler et al., 1994) and is projected to become the second overall cause of disability by the year 2020 (Murray & Lopez, 1996). Recently, MDD has become viewed as a chronic and complex problem rather than acute but transient (Mueller et al., 1999). Several longitudinal prospective studies have contributed much to our evolving understanding of the nature of MDD, including the epidemiological Zurich, Switzerland study (Angst, 1986) and clinical efforts such as the National Institute of Mental Health-Collaborative Depression Study (NIMH-CDS; Katz, Secunda, Hirschfeld, & Koslow, 1979). These studies have revealed that MDD is a chronic problem characterized by complex patterns of remission, recovery, and relapse (Frank et al., 1991). Roughly 80% of persons with MDD will have at least a second episode, and although recurrent episodes show some overall uniformity in duration (median = 20 weeks), the time to remission is variable (Keller et al., 1992; Mueller et al., 1999; Solomon et al., 1997).

Empirically supported predictors of outcome and course of MDD represent research needs. Although research to date has identified several potential predictors of worse overall long-term outcomes of MDD, the identification of reliable predictors for specific aspects of course such as remission rates or time to recovery (Solomon et al., 1997) or recurrence (Mueller et al., 1999) has been difficult. Research has identified some potential predictors of lower remission rates or longer time to remission, including female gender (Kornstein et al., 2000), presence of dysthymia (Keller, Shapiro, Lavori, & Wolfe, 1982), amount of Axis I psychiatric comorbidity (Keller et al., 1992), and whether the MDD is a single episode or has a recurring pattern of episodes (Keller, Lavori, Lewis, & Klerman, 1983; Klein et al., 1999; Maj, Veltro, Pirozzi, Lobrace, & Magliano, 1992). Some studies suggest that MDD with an earlier age of onset has greater comorbidity and longer duration of depressive episodes than MDD with later onset (Klein et al., 1999; Rothschild & Zimmerman, 2002). Solomon et al. (1997) noted that none of their "many sociodemographic and clinical factors" influenced time to recovery, and speculated that the "course of illness may be autonomous" (p. 1006).

Clinical experience and research have suggested that personality disorders (PDs) represent a negative prognostic factor for MDD course and outcome (Mulder, 2002). Many studies, but not all, have suggested that PDs may have a negative impact on the course or outcome of Axis I disorders (Grilo & McGlashan, 1999; Grilo, McGlashan, & Oldham, 1998). For instance, some research has found that PDs predict development of depression (Alnaes & Torgersen, 1997), poorer response to treatment for depression (Mulder, 2002), and relapse to depression (Hart, Craighead, & Craighead, 2001; Ilardi, Craighead, & Evans, 1997).

Numerous methodological limitations characterize the existing PD prediction literature (Grilo et al., 1998; Grilo & McGlashan, 1999). Research examining PD prediction of MDD has generally not used prospective and repeated assessments that capture the fluctuating nature of MDD. For example, most studies of MDD have assessed cross-sectionally and have not considered data longitudinally (e.g., how long to remission). The large-scale longitudinal naturalistic studies of MDD (e.g., Katz et al., 1979; Keller et al., 1982), which did consider MDD's fluctuating course, have not included standardized diagnostic interview assessments of PDs.

The Collaborative Longitudinal Personality Disorders Study (CLPS) was designed to provide comprehensive data on the course and outcome of patients with one (or more) of four PDs—schizotypal (STPD), borderline (BPD), avoidant (AVPD), and obsessive-compulsive (OCPD)—and a comparison group of MDD without any PD (Gunderson et al., 2000; McGlashan et al., 2000). This design allows for a clear test of whether PDs represent a negative prognostic factor for MDD course (Mulder, 2002). In this study, we examined the 2-year natural course of MDD (remission rate and time to remission) as a function of PD comorbidity.

Method

Participants

Participants for this study were drawn from the CLPS—a multisite, prospective naturalistic longitudinal study. Recruitment aimed to obtain a diverse clinically representative sample. The majority of participants were recruited from diverse in- and outpatient clinical programs affiliated with four recruitment university sites (Brown, Columbia, Harvard, and Yale). In addition, advertising was used to recruit participants with present or past psychiatric treatment. CLPS enrolled 668 participants age 18–45 years with at least one of four PDs (STPD, BPD, AVPD, or OCPD) or with current MDD without any PD. Detailed descriptions of the CLPS aims, methods, and characteristics of the overall study group have been reported (Grilo et al., 2004; Gunderson et al., 2000; McGlashan et al., 2000) but are summarized here.

Of the 1,605 potential participants screened (described below), 668 (42%) were eligible and enrolled in the study. Of the 668 participants, 573 met criteria for a PD study group, and 95 met criteria for the MDD (without PD) group, following the assessment procedures described below. Co-occurring Axis I and Axis II diagnoses were common. Overall, the mean number of lifetime Axis I disorders for participants was 3.5 (SD = 1.7, range = 0–9). The Axis I disorders included the major diagnostic categories assessed on the Structured Clinical Interview for *DSM-IV* Axis I Disorders-Patient Version (SCID-I/P; First, Spitzer, Gibbon, & Williams, 1996) except for psychotic disorders, which were an exclusionary requirement. We followed the traditional rules for assigning and counting diagnoses, except that we collapsed multiple substance use disorders—if present—into one category.

Among the PD participants, the mean number of PD diagnoses was 2.4 (SD = 1.6) of the possible total of 12 (10 formal diagnoses and 2 research diagnoses) listed in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994). Thus, participants with a PD were assigned a mean of 1.4 additional PD diagnoses, with a median of 1.0 additional PD. In cases in which more than one study PD was present, a primary PD study group was assigned following an a priori algorithm (Gunderson et al., 2000) described below. Specific patterns of co-occurrence among the psychiatric disorder and PD diagnoses are described in detail by McGlashan et al. (2000).

The present report was based on all 302 of the participants who met criteria for current MDD at baseline (regardless of PD status) for whom at least 6 months of follow-up data were available. Mean age was 33.4 (SD = 8.1) years. Of the 302 participants, 196 (65%) were women and 106 (35%) were men; 218 (72%) were Caucasian and 84 (28%) were minority—48 (16%) were African American, 29 (10%) were Hispanic American, and 7 (2%) were other.

Procedures

Written informed consent was provided by all participants following a full description of all study procedures. The study protocol, which included consent procedures, was approved by each collaborating site's institutional review board. Participants were interviewed in person by experienced interviewers with master's or doctoral degrees in mental health disciplines. Interviewers underwent extensive standardized training to achieve reliability in the administration of the diagnostic measures for both Axis I and II disorders (Zanarini et al., 2000). Interviewers were monitored and received regular ongoing supervision by the investigators at each site, as well as supervision across sites to maintain reliability and prevent drift over time.

Baseline Assessments

Potential participants were screened for possible PDs with the Personality Screening Questionnaire (PSQ), a self-report instrument consisting of all items for the four study PDs taken from the Personality Diagnostic Questionnaire (Hyler, Skodol, Kellman, Oldham, & Rosnick, 1990). Participants who were positive on the PSQ for one or more of the PDs received further assessment. Participants were also screened for the possible presence of current MDD with a self-report instrument (Depression Screening Questionnaire) that comprised items tapping *DSM-IV* criteria for MDD. Participants who screened positive on the Depression Screening Questionnaire and had no PD on the PSQ received further assessment for the MDD study group.

At baseline, research interviewers administered the SCID-I/P (First et al., 1996) to assess Axis I psychiatric disorders and the Diagnostic Interview for *DSM-IV* Personality Disorders (DIPD-IV; Zanarini, Frankenburg, Sickel, & Yong, 1996) to assess all 12 Axis II diagnoses of PD in the *DSM-IV*. Because diagnostic instruments do not always yield identical findings (Oldham et al., 1992), we conservatively required additional convergent support for the DIPD-IV diagnosis from either the Schedule for Nonadaptive and Adaptive Personality (Clark, 1993) or from an independent clinician-rated Personality Assessment Form (Shea, Glass, Pilkonis, Watkins, & Docherty, 1987).

The CLPS design involved a comparison of four specific PD diagnoses (STPD, BPD, AVPD, and OCPD) with a study group of MDD without PD. These four PD diagnoses were selected partly because of their prevalence and research base with clinical samples and partly to provide coverage across the three *DSM-IV* clusters (Gunderson et al., 2000). It is well documented that Axis II PDs frequently co-occur (Becker, Grilo, Edell, & McGlashan, 2000; Grilo, Anez, & McGlashan, 2002; Oldham et al., 1992). Thus, if more than one study PD was present, then a primary PD study group was assigned following an a priori algorithm (Gunderson et al., 2000) based on diverse clinical and empirical writings about PD and presumed severity (Millon, 1981; Widiger, Frances, Spitzer, & Williams, 1998). In such cases, STPD and BPD diagnostic study groups generally had hierarchical precedence over AVPD and OCPD on the basis of their presumed severity. If participants had both STPD and BPD diagnoses, or if they had both AVPD and OCPD diagnoses, then they were allocated to a PD study group on the basis of the number and severity of the criteria they met on the diagnostic interviews and the additional assessments.

Follow-Up Assessments

Participants were reinterviewed at 6, 12, and 24 months following baseline assessment. The course of MDD (as well as the course of all co-occurring Axis I disorders), psychosocial functioning, and treatment use during these intervals were assessed with the Longitudinal Interval Follow-Up Evaluation (LIFE; Keller et al., 1987). These follow-up interviews were not blind and were conducted by the same (baseline) interviewer whenever possible.

Measures

SCID-I/P. The SCID-I/P (First et al., 1996), a diagnostic interview to assess current and lifetime Axis I psychiatric disorders, was administered at baseline. Kappa coefficients (Cohen, 1960) for interrater reliability for Axis I psychiatric diagnoses ranged from .57 to 1.00; kappa for MDD was .80, and kappa for dysthymia was .76 (Zanarini et al., 2000).

DIPD-IV. The DIPD-IV (Zanarini et al., 1996) is a semistructured diagnostic interview for the assessment of *DSM-IV* Axis II PDs. Each of the criteria for all *DSM-IV* PD diagnoses is assessed with one or more questions, which are then rated on a 3-point scale (0 = *not present*; 1 = *present but of uncertain clinical significance*; 2 = *present and clinically significant*). The DIPD-IV requires that criteria be pervasive for at least 2 years and that the criteria be characteristic of the person for most of his or her adult life to be counted toward a diagnosis.

Interrater reliability (based on 84 pairs of raters independently rating 27 videotaped assessments) kappa coefficients (Cohen, 1960) for all the PD diagnoses ranged from .58 to 1.00 (Zanarini et al., 2000). Kappa coefficients for the four PDs of primary focus ranged from .68 (BPD) to .73 (AVPD) with 100% agreement for STPD, and test–retest reliability kappas (based on two direct interviews of 52 participants performed 7–10 days apart with the second interview blind to the first interview) ranged from .69 (BPD) to .74 (OCPD).

LIFE. The LIFE (Keller et al., 1987) is a semistructured interview rating system for assessing the longitudinal course of mental disorders. It also assesses the nature and quantity of all forms of treatment received. The LIFE has served as the primary measure of major longitudinal studies of Axis I disorders, including depressive (Mueller et al., 1999; Solomon et al., 1997) and anxiety (Warshaw, Keller, & Stout, 1994) disorders. Good to excellent reliability has been reported for the LIFE (Warshaw, Dyck, Allsworth, Stout, & Keller, 2001; Warshaw et al., 1994). All CLPS interviewers were trained and certified in the use of the LIFE by the developers and official training staff at the Brown University site. The LIFE training staff were available throughout this study for ongoing training and consultation regarding the interview and ratings. These methods have maintained long-term reliability and prevented drift over time (Warshaw et al., 2001).

The LIFE was administered, as in the NIMH-CDS (Keller et al., 1982; Mueller et al., 1999; Solomon et al., 1997), to measure the presence and severity of psychopathology on a weekly basis. In the LIFE, the severity of psychopathology is quantified on weekly Psychiatric Status Ratings (PSRs), which are made for each Axis I disorder present. For MDD, PSRs were based on the following 6-point scale: PSR = 1 signifies *no symptoms*; PSR = 2 corresponds to *1 or 2 symptoms of mild degree with no impairment in functioning*; PSR = 3 corresponds to *moderate symptoms but considerably less than meeting full criteria for diagnosis with up to moderate impairment in functioning*; PSR = 4 corresponds to *marked symptoms but not meeting full criteria for diagnosis with major impairment in functioning*; PSR = 5 corresponds to *symptoms meeting full criteria for disorder*; PSR = 6 corresponds to *full disorder criteria plus psychosis or extreme impairment in functioning*. Remission from MDD was defined as 8 consecutive weeks with PSR ratings no higher than 2 (reflecting minimal or no symptoms), following the NIMH-CDS (Keller et al., 1982).

The LIFE also assesses mental health treatment use by obtaining detailed ratings of pharmacological and psychosocial treatments for all mental health contacts, frequency of sessions, length of treatment, and number of days of inpatient and partial hospitalization. Medication usage and dosing were recorded on a weekly basis. A global measure of treatment intensity was developed, with weights assigned to levels of care (e.g., inpatient, day hospital, or outpatient); these weights were multiplied by the amount of treatment received at each level during the follow-up.

Data Analyses

Life table survival methods (Kalbfleisch & Prentice, 1980) were used to analyze time to remission during the 24-month follow-up. Kaplan and Meier's (1958) method was used to estimate cumulative remission rates. Keller et al. (1982) cogently presented the specific strengths of life table analyses (over cross-sectional methods), including—but not limited to—the ability to consider the length of illness (and time to remission).

Patients with MDD were divided into groups with no PDs or with one of the four PD study groups (STPD, BPD, AVPD, or OCPD) created on the basis of a priori algorithms developed prior to starting the study. This categorization was used to predict time to MDD remission overall, as well as separately by gender.

For the omnibus predictor analysis of time to MDD remission, we used Cox's (1972) proportional hazards regression tests for significance. Two-tailed tests with alphas of .05 were considered statistically significant.

Results

24-Month MDD Remission

Overall, 222 (73.5%) of the 302 patients with MDD at baseline had a remission during the 24-month, follow-up period. Of the 106 men, 79 (74.5%) had a remission from MDD; of the 196 females, 142 (72.4%) had a remission from MDD.

Time to MDD Remission by PD Comorbidity

Of the 302 patients with MDD, 91 (30.1%) had no PD, 33 (11.0%) met criteria for the STPD group, 68 (22.5%) met criteria

for the BPD group, 62 (20.5%) met criteria for the AVPD group, and 48 (15.9%) met criteria for the OCPD group. Figure 1 shows the survival curves (time to remission) for MDD as a function of PD comorbidity. MDD remission rates by PD comorbidity were as follows: 89% (for the non-PD group), 52% (for the STPD group), 60% (for the BPD group), 71% (for the AVPD group), and 81% (for the OCPD group).

MDD Remission and PD Comorbidity by Gender

Of the 106 male patients with MDD, 35 (33.0%) had no PD, 16 (15.1%) met criteria for the STPD group, 16 (15.1%) met criteria for the BPD group, 19 (17.9%) met criteria for the AVPD group, and 20 (18.9%) met criteria for the OCPD group. Of the 196 female patients with MDD, 56 (28.6%) had no PD, 17 (8.7%) met criteria for the STPD group, 52 (26.5%) met criteria for the BPD group, 43 (21.9%) met criteria for the AVPD group, and 28 (14.3%) met criteria for the OCPD group.

Figure 2 shows the survival curves for MDD across the five study groups separately for men and women. For men, remission rates differed across the study groups, log-rank $\chi^2(4, N = 106) = 20.48$, $p = .0004$, and were as follows: 94% (for the non-PD group), 50% (for the STPD group), 59% (for the BPD group), 73% (for the AVPD group), and 75% (for the OCPD group). For women, remission rates differed across the study groups, log-rank $\chi^2(4, N = 196) = 14.50$, $p = .0058$, and were as follows: 85% (for the non-PD group), 53% (for the STPD group), 60% (for the BPD group), 70% (for the AVPD group), and 86% (for the OCPD group).

Treatment Effects

Consideration and adjustment for treatment effects in naturalistic studies is complex and generally precludes any clear inferences. For example, it is known that those patients with the most severe problems tend to receive the most treatment (Cochran, 1983). Indeed, we found this to clearly be the case for our participants. We have documented elsewhere (Bender et al., 2001) that participants with PD had significantly more extensive treatment histories than participants with MDD without PDs for most forms of psychiatric and psychosocial treatment modalities. Nonetheless, in the present study, we explored whether the differences in the course of MDD between the different study groups could have been confounded by differences in either treatment seeking or in the amount of treatment received.

At a global level, we explored the possibility that MDD remission was associated with differences in whether treatment was received during the 24-month, follow-up period. We compared the MDD participants without PD with MDD participants grouped by having PDs on whether they received any mental health treatment during the follow-up period. During the first 12 months, 83% ($n = 76$) of the MDD patients without PD versus 94% ($n = 198$) of those with any one PD received treatment, $\chi^2(1, N = 302) = 12.10$, $p < .001$. During the 2nd follow-up year, a similar pattern of treatment was observed (54% vs. 75%, respectively), $\chi^2(1, N = 302) = 14.30$, $p < .001$. Thus, MDD participants with PDs (who

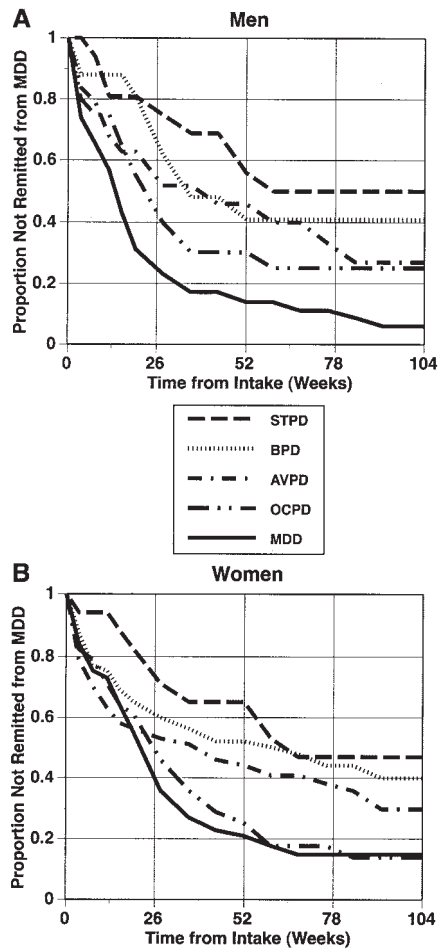

Figure 2. Survival curves for major depressive disorder (MDD) across the five study groups, separately for men (A) and women (B). STPD = schizotypal personality disorder; BPD = borderline personality disorder; AVPD = avoidant personality disorder; OCPD = obsessive-compulsive personality disorder.

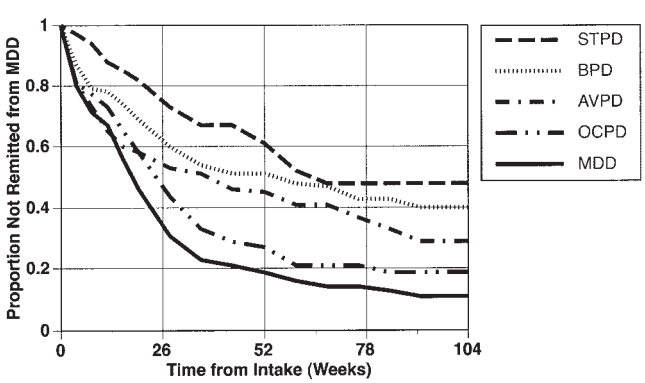

Figure 1. Survival curves (time to remission) for major depressive disorder (MDD) as a function of personality disorder comorbidity. STPD = schizotypal personality disorder; BPD = borderline personality disorder; AVPD = avoidant personality disorder; OCPD = obsessive-compulsive personality disorder.

had lower remission rates) were more likely to seek treatment than MDD participants without PD.

These global treatment findings may not reflect intensity or extensiveness of treatment. Thus, to test whether the amount or intensity of treatment received was related to the course of MDD, we included the global measure of treatment intensity calculated at each follow-up (from the LIFE) as a covariate in the overall model below.

Multivariate Prediction of MDD Remission

We performed an overall multivariate analysis to predict time to MDD remission. In this analysis, we considered the following variables: (a) four different PD groups (STPD, BPD, AVPD, OCPD), (b) total number of Axis I psychiatric disorders, (c) the presence or absence of dysthymia, (d) whether the MDD was first episode (single) or recurrent, (e) the age of onset of MDD, (f) treatment intensity score during the follow-up period, (g) gender, and (h) ethnicity. Our rationale follows.

Our literature review above highlighted the potential relevance of PDs, the number of Axis I disorders, dysthymia, single versus recurrent MDD, age of onset of MDD, treatment status, and gender. We specifically considered the presence or absence of specific forms of PDs using our a priori algorithm for PD study groups in this omnibus analysis because of the following reasons: (a) the well-known high degree of PD co-occurrences, (b) the literature suggesting that specific forms of PD (i.e., BPD) may be associated with a more insidious pattern of MDD (Skodol et al., 1999), and (c) although earlier age of onset of MDD is associated with BPD, BPD is not always present in early onset MDD, and these two methods of subdividing MDD patients account for unique variances (Rothschild & Zimmerman, 2002). We considered ethnicity (Caucasian vs. non-Caucasian due to power constraints), given reports that BPD may be differentially distributed across ethnicity by gender (Castaneda & Franco, 1985).

In our primary analysis, we used Cox's (1972) proportion hazards regression to test for differences in time to remission from MDD across the study groups while covarying for potential confounding variables. The five study groups were represented by four dummy variables, with the MDD group without PD serving as the reference group. This allowed us to determine whether the MDD participants in the PD study groups differed from the MDD participants without any PD in time to remission. To control for possible confounds, we also added seven covariates (as explained above) to the model: gender, ethnicity, total number of Axis I psychiatric disorders, dysthymia, single versus recurrent MDD, age of onset of MDD, and a composite measure of treatment intensity and contact during the follow-up period.

The overall model, which contained seven covariates in addition to the four dummy variables that represented the study groups, was significant, likelihood ratio $\chi^2(11, N = 302) = 35.71, p < .0002$. A test that the four PD groups jointly differed from the MDD group was also significant, $\chi^2(4, N = 302) = 14.14, p = .0069$. Looking at the specific PDs, we found that the STPD group, $\chi^2(1, N = 124) = 10.33, p = .0013$, the BPD group, $\chi^2(1, N = 159) = 10.56, p = .0012$, and the AVPD group, $\chi^2(1, N = 153) = 5.03, p = .025$, had significantly longer time to remission from MDD than the MDD reference group. The OCPD group was not found to be significantly different from the MDD reference group, $\chi^2(1, N = 139) = 1.94$, *ns*. None of the variables we covaried for potential confounding were found to have a statistically significant effect on time to MDD remission. We also covaried for the total number of PDs in an additional analysis, but this variable neither altered the overall findings nor made any contribution, $\chi^2(1, N = 302) < 0.01, p = .99$.

In Cox's (1972) survival regression analyses, hazards ratios are a standard measure of effect size. The following hazard ratios were observed: .31 for STPD, .41 for BPD, .58 for AVPD, and .73 for OCPD. Thus, for example, participants with MDD in the STPD group remitted from MDD at less than one third of the rate of the participants in the MDD group.

Discussion

Although we observed similar overall rates of MDD remission in this 2-year prospective study for men (74.5%) and women (72.4%), our findings suggest that PDs significantly predict a pattern of slowed time to remission from MDD. Participants with MDD who had certain forms of coexisting PD psychopathology (STPD, BPD, or AVPD) as their primary PD diagnoses had a significantly longer time to remission from MDD than did patients with MDD without any PD. These patterns of slowed remission from MDD were similar for women and men. These forms of PDs emerged as robust predictors of slowed remission from MDD even when controlling for other potential negative prognostic predictors selected from the depression literature.

Our overall remission rate for MDD is comparable with that reported by the NIMH-CDS (Keller et al., 1982) for the same time frame on the basis of the same assessment methodology (LIFE) and analytic procedures (life table analyses), albeit with slightly different diagnostic systems. An interesting finding was that the MDD remission rates for patients grouped by the presence of PDs in our study bear some resemblance to the remission rates reported by Keller et al. (1982) for MDD patients grouped by dysthymia (with superimposed illness [59%] versus without superimposed illness [79%]) over 24 months, as do the time to remission data (survival curves).

Our study considered a number of predictors, including gender, ethnicity, and treatment, along with clinical predictors from the MDD literature (e.g., dysthymia, Axis I comorbidity, whether the MDD had a recurrent pattern, and age of onset of MDD). We found that certain forms of PD comorbidity contributed significantly to slowing remission from MDD but that none of the other variables we covaried for potential confounding were found to have a statistically significant effect on time to remission from MDD. Previous studies have reported associations among PDs, dysthymia, and certain characteristics of MDD such as earlier onset and recurrence (Klein et al., 1999). Our analyses suggest that specific forms of PD psychopathology (STPD, BPD, and AVPD)—but not necessarily other forms of PD (i.e., OCPD) or just a generic total number of PD diagnoses—emerge as significant predictors of slower MDD remission.

We found that certain forms of PD psychopathology predict a similar pattern of slower remission from MDD for both men and women. The presence of STPD, BPD, and AVPD, along with their associated additional forms of personality dysfunction, signifi-

cantly and substantially delay the time to remission from MDD relative to the time to remission observed for patients with MDD without any coexisting PD. The OCPD group, which reduced the MDD remission rate by a factor of roughly 1.6–1.0, did not have a statistically significant effect, which reflects a combination of lower power (smaller sample) coupled with the lower effect size observed for the other PD study groups. The presence of additional PDs per se does not appear to contribute to further delaying the time to remission.

Much has been written about possible complex biopsychosocial factors that might account for gender differences in the frequency, expression, and natural history of MDD (Hankin & Abramson, 1999, 2001). Our findings suggest that the presence of certain severe forms of PD psychopathology might override usual gender differences. It is worth noting that although time to remission from MDD did not differ by gender, gender rates were different for certain PDs (e.g., a higher proportion of men had STPD and a higher proportion of women had BPD), suggesting that there might be gender differences in risk for certain types of PD psychopathology and hence in time to remission from MDD.

Hankin and Abramson (1999, 2001), in their elaborated developmental cognitive vulnerability-transactional stress model, detailed gender differences in personality and associated cognitive vulnerabilities that can interact with negative affect and/or negative events (particularly interpersonal events) and lead to increases in depression and to further negative events that continue to fuel the distress. Our findings suggest that the presence of these personality and cognitive vulnerabilities can greatly and negatively impact both men and women. Of course, the finding that such vulnerabilities can affect both men and women does not necessarily mean that they are driven by the same mechanisms.

We briefly note method limitations as a context for our findings. Interviews conducted during this 2-year period were nonblind to baseline status. Although it is possible that this method may have contributed a bias, the use of the same interviewer provides the advantage of repeated contacts with the participant. This may increase the validity of the MDD ratings on the LIFE and diminish the error due to rater variance.

A second limitation of naturalistic longitudinal studies of clinically ascertained participants is the potential for confounding by treatment. In our initial study of treatment use (Bender et al., 2001), MDD patients without PDs used significantly less treatment than patients with PD, and the patients with the more severe forms of PDs (including those with more PDs) reported receiving the most treatment. Such findings suggest that the amount of treatment received is driven by the severity of the disorder, which is a typical finding in naturalistic studies (Cochran, 1983). Consistent with this, in the present study, our prospective analyses revealed that (a) MDD patients with more PDs (and slower time to remission) were more likely to receive treatment than those without PD and (b) a treatment intensity composite variable entered into the omnibus multiple regression analysis did not have a statistically significant effect on time to remission from MDD. We note, however, that this study was designed to address the question of the course of MDD in patients in real-world clinical settings. Our study was not designed to address the important, but distinct, questions of the untreated course of MDD or of treatment outcome in MDD (Mulder, 2002) with experimentally controlled treatment.

Another issue concerns the definition of *remission* from MDD as 8 consecutive weeks with PSR ratings no higher than 2 (reflecting minimal or no symptoms). This definition follows the NIMH-CDS (Keller et al., 1982; Solomon et al., 1997) and therefore allows for direct comparison with that prospective longitudinal study. Researchers in the field of MDD have debated and struggled with the important issues of how to best define terms such as remission (Frank et al., 1991). Further research making use of longitudinal data sets might improve on these definitions. On the basis of present knowledge, however, this definition appears to have some merits. Whereas the duration criterion (8 consecutive weeks) might seem brief, the consecutive requirement at 2 or fewer PSRs is strict. In support of this argument, we note the impressive longitudinal studies that have documented that subthreshold depression (i.e., below threshold for MDD but falling about the remission criteria) is clinically quite meaningful as demonstrated by its chronic course and high levels of associated impairment (Judd, Akiskal, et al., 2000; Judd et al., 1998; Judd, Paulus, et al., 2000).

In summary, we found that the presence of certain PDs predicts a pattern of slowed remission from MDD. Patients with MDD who had coexisting STPD, BPD, or AVPD as primary PD diagnoses had a significantly slower time to remission from MDD than did patients with MDD without any PD. These PDs emerged as robust predictors of slowed remission from MDD even when controlling for other negative prognostic predictors. In this ongoing CLPS study, future analyses will attempt to delineate factors that might influence the timing of changes—such as relapses (Ilardi et al., 1997) and associated changes (e.g., life events, treatment, psychosocial functioning)—and how these factors contribute to the longer-term course of depression.

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