# Chronic Depression and Comorbid Personality Disorders: Response to Sertraline Versus Imipramine

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***Background:*** Chronic subtypes of depression appear to be associated with high rates of Axis II personality disorder comorbidity. Few studies, though, have systematically examined the clinical correlates of Axis II personality disorder comorbidity or its effect on treatment response or time to response.

***Method:*** 635 patients diagnosed with DSM-III-R chronic major depression or "double depression" (dysthymia with concurrent major depression) were randomized to 12 weeks of double-blind treatment with either sertraline or imipramine between February 1993 and December 1994. Axis II diagnoses were made using the personality disorders version of the DSM-III-R Structured Clinical Interview. The effect of study treatment was measured utilizing the Hamilton Rating Scale for Depression and the Clinical Global Impressions scale.

***Results:*** Forty-six percent of patients met criteria for at least 1 comorbid Axis II personality disorder, with cluster C diagnoses being the most frequent at 39%; 21% met criteria for at least 2 Axis II personality disorders. A cluster C diagnosis was associated with significantly higher rates of early-onset depression (before age 21; 47% vs. 32% for no cluster C; $p = .005$) and comorbid anxiety disorder (34% vs. 18% for no cluster C; $p < .001$). Overall, the presence of Axis II personality disorder comorbidity had minimal-to-no effect on the ability to achieve either an antidepressant response or remission and had inconsistent effects on time to response. The presence of Axis II personality disorder comorbidity did not appear to reduce functional and quality-of-life improvements among patients responding to acute treatment with sertraline or imipramine.

***Conclusion:*** In this treatment sample, rates of Axis II personality disorder comorbidity were substantial in patients suffering from chronic forms of depression. Axis II personality disorder comorbidity did not appear to diminish symptomatic response to acute treatment or associated improvement in functioning and quality of life.

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The chronic subtypes of unipolar depression exhibit 3 common longitudinal patterns of illness—dysthymia, which can occur in a "pure" form; double depression, in which dysthymia is punctuated by episodes of major depression[1]; or chronic major depression.

Axis II personality disorder comorbidity commonly complicates the clinical presentation of depression, with especially high rates, in the range of 38% to 85%, in chronic forms of depression.[2–6] In evaluating Axis II comorbidity rates, few studies, though, clearly differentiate among depression subtypes, age at onset, and course of illness patterns,[2,7–9] although there is evidence that early age at onset is associated with higher Axis II rates.[3,10]

The presence of Axis II personality disorder comorbidity has been reported to be associated with a poorer response to acute treatment in some,[11,12] but not all,[13,14] studies, as well as a slower time to response[15,16] and a higher risk of relapse.[17] A growing body of work has reported the effect of Axis II comorbidity on the long-term outcome of chronic forms of depression.[2,3,18–21] Few studies, though, have reported a clinical trial that had sufficient power to examine the clinical correlates of Axis II comorbidity and its effect on treatment response or time to response, and no study that we are aware of separately reports results for patients with chronic subtypes of depression.

The conduct of a large double-blind study comparing the efficacy of sertraline and imipramine in the treatment of chronic major and double depression provided us with the opportunity to examine the clinical and psychosocial correlates of Axis II diagnoses in patients presenting with



chronic forms of depression. It also permitted us to examine the differential effect of Axis II comorbidity on clinical outcome.

## METHOD

Entry criteria and study methodology have been described in detail in previous publications,[22,23] but will be briefly summarized here.

### Patients

Six hundred thirty-five men and women between the ages of 21 and 65 years were entered if they met DSM-III-R criteria for 1 of 2 primary diagnoses: either chronic major depression (N = 294) or dysthymic disorder with a concurrent major depression (double depression; N = 341). Individuals were excluded from study entry if they met DSM-III-R criteria for any other primary Axis I disorder or if they suffered from any clinically significant acute or unstable medical condition. Patients with severe antisocial, schizotypal, or borderline personality disorders were excluded from the study.

### Study Design

After a 1-week, single-blind, placebo run-in, patients with a Hamilton Rating Scale for Depression (HAM-D)[24] score ≥ 18 were randomized to 12 weeks of double-blind treatment with either sertraline, in flexible doses of 50–200 mg/day, or imipramine, in flexible doses of 50–300 mg/day, in a 2:1 ratio between February 1993 and December 1994.

### Assessments

The Structured Clinical Interview for DSM-III-R with Psychotic Screen (SCID-P)[25] was utilized at baseline to identify the presence of chronic major depression or double depression, other psychiatric disorders, and the presence of psychiatric exclusion criteria. A physician-rated Clinical Global Impressions scale (CGI) and trained-rater-administered HAM-D assessed depressive symptoms and overall severity at baseline and weeks 1, 2, 4, 6, 8, 10, and 12 of the study.

Personality disorder diagnoses were made utilizing the personality disorders version of the SCID for DSM-III-R (SCID-II),[26] which was administered to subjects in conjunction with the SCID-P at the initial visit by a trained master's level clinical social worker or nurse who had completed a training workshop on the SCID. A psychiatrist or Ph.D. clinical psychologist also evaluated the patient to independently confirm the SCID-P and SCID-II findings and determine the final Axis I and II diagnoses. Over the course of the study, the interviewers met regularly to discuss difficult ratings and to attempt to maintain standardization. The level of expertise and supervision in the Axis II diagnostic process met previously published recommendations.[27] HAM-D and CGI[28] ratings were performed at all visits by study physicians.

### Definition of Remission and Response

We defined a satisfactory therapeutic response to be at least a 50% reduction from baseline in the HAM-D total score and a HAM-D score ≤ 15. Also required to meet satisfactory therapeutic response criteria were a CGI-Improvement score of 1 or 2 (very much or much improved), and a CGI-Severity score ≤ 3 (mildly ill). Remission was defined as a HAM-D total score of ≤ 7 and a CGI-Improvement score of 1 or 2 (much or very much improved).

### Psychosocial Variables

Data from 3 scales that assess psychosocial functioning are presented here, including the Social Adjustment Scale-Self Report (SAS-SR),[29] the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36),[30] and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[31] Mean change before and after 12 weeks of treatment in hours worked per week (SAS-SR), SF-36 general health score, SF-36 social functioning score, SF-36 role limitation-emotional and -physical scores, and the total Q-LES-Q score are compared between those with and without Axis II comorbidity.

### Statistical Analysis

Categorical measures were evaluated with a Mantel-Haenszel chi-square test (or a Fisher exact test, depending on sample size) and continuous measures (with appropriate adjustments) by analysis of variance. Kaplan-Meier survival estimates and log-rank test were utilized in the intent-to-treat sample to test the null hypothesis that presence of a baseline personality disorder diagnosis does not affect the length of time to reach adequate therapeutic response. Psychosocial outcome measures for responder at endpoint were tested using an analysis of covariance model that includes effects for investigator site, depression type, treatment, and baseline measure. Discontinuation and discontinuation due to adverse events were compared using an unadjusted chi-square test for patients without any personality disorder versus patients with at least 1 disorder and patients with 2 or more disorders separately.

## RESULTS

Of the 635 study patients, 209 were treated with imipramine and 426 were treated with sertraline. Demographic variables were similar for both types of chronic depression. The most notable exception was the lower number of females diagnosed with double depression (59%) compared with chronic major depression (68%; $\chi^2 = 5.77$, df = 1, p = .016). Clinical variables were also

**Table 1. Demographic and Clinical Characteristics of Patients by Personality Disorder[a]**

| Patient Variable | No Axis II Personality Disorder (N = 341) | With Axis II Personality Disorder (N = 292) | With ≥ 2 Axis II Personality Disorders (N = 131) |
|---|---|---|---|
| Female, % | 64 | 62 | 63 |
| Age, y | 42.1 ± 10.8 | 39.8 ± 9.0** | 38.2 ± 8.7** |
| Married (currently), % | 40 | 35 | 31* |
| Education, % | | | |
| At least high school graduate | 97 | 95 | 95 |
| At least college graduate | 39 | 37 | 37 |
| Age at onset of major depression, y | 26.9 ± 12.2 | 22.3 ± 11.4** | 21.6 ± 11.0** |
| Age at onset of dysthymia, y | 19.6 ± 14.0 | 14.2 ± 11.5** | 15.1 ± 12.2* |
| No. of prior episodes of depression | 1.5 ± 1.9 | 2.1 ± 2.3** | 2.0 ± 2.2 |
| Patients with 2 or more previous episodes, % | 35 | 48** | 48* |
| History of any comorbid anxiety disorder, % | 18 | 31** | 37** |
| History of alcohol abuse, % | 26 | 33 | 30 |
| History of substance abuse, % | 33 | 37 | 34 |
| Prior treatment with antidepressants | | | |
| Adequate treatment,[b] % | 21 | 20 | 19 |
| Prior psychotherapy, % | 52 | 67** | 68** |
| Baseline ratings | | | |
| HAM-D score | 25.1 ± 5.1 | 25.0 ± 5.1 | 25.1 ± 5.1 |
| Q-LES-Q score | 54.2 ± 10.3 | 52.6 ± 9.4* | 52.4 ± 10.0 |
| No. of hours worked per week | 26.7 ± 20.6 | 28.3 ± 21.4 | 28.2 ± 22.5 |
| SF-36 general health | 63.1 ± 21.5 | 63.3 ± 20.4 | 62.0 ± 20.9 |
| SF-36 social functioning | 50.6 ± 26.1 | 48.9 ± 26.1 | 49.8 ± 27.0 |
| SF-36 role limitation, emotional | 21.0 ± 29.6 | 19.1 ± 29.3 | 18.5 ± 28.5 |
| SF-36 role limitation, physical | 60.6 ± 41.6 | 67.2 ± 38.5 | 65.0 ± 41.2 |

[a]Values shown as mean ± SD unless otherwise noted.
[b]*Adequate* defined as 4 weeks of treatment with a selective serotonin reuptake inhibitor or ≥ 150 mg of a tricyclic antidepressant.
*p < .05 vs. the "no Axis II" group.
**p < .01 vs. the "no Axis II" group.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey.

similar, with no significant differences noted in the baseline HAM-D or CGI-Severity scores. The most notable difference in clinical variables between the 2 depression subtypes was in duration of current major depressive illness (8.9 ± 9.1 years for chronic major vs. 3.6 ± 6.4 years for double depression; F = 71.67, df = 1, p = .001). There was no difference in the age at onset of major depression for either depression subtype (at 25 years for both).

### Demographic, Clinical, and Psychosocial Correlates of Axis II Personality Disorder Comorbidity

Of the 635 intent-to-treat patients, complete Axis II personality disorder diagnoses were available for 633. Table 1 compares baseline demographic, clinical, quality-of-life, and psychosocial variables for the patients with no Axis II diagnosis (53.9%) versus patients with an Axis II diagnosis (46.1%). Characteristics are also shown for the 131 patients diagnosed with 2 or more Axis II disorders, which constitute a subset of 44.9% of the patients with any Axis II diagnosis, and 20.7% of the total patient sample.

### Frequency and Distribution of Axis II Personality Disorders

Table 2 summarizes the frequency of occurrence of each personality disorder, both individually and by cluster.

**Table 2. Rates (%) of Axis II Personality Disorder Comorbidity for Chronic Major and Double Depression**

| Disorder[a] | Chronic Major Depression (N = 294) | Double Depression (N = 339) | Combined (N = 633) | p Value |
|---|---|---|---|---|
| Cluster A[b] | 6.5 | 9.7 | 8.2 | .084 |
| Paranoid | 6.1 | 9.5 | 7.9 | .075 |
| Schizoid | 0.3 | 0.9 | 0.6 | .627[d] |
| Cluster B[c] | 12.6 | 11.2 | 11.8 | .727 |
| Histrionic | 3.7 | 2.4 | 3.0 | .317 |
| Narcissistic | 3.4 | 4.7 | 4.1 | .381 |
| Borderline | 8.2 | 9.5 | 8.9 | .392 |
| Cluster C | 33.3 | 44.0 | 39.0 | .007 |
| Avoidant | 21.2 | 28.7 | 25.2 | .029 |
| Dependent | 9.5 | 12.1 | 10.9 | .227 |
| Obsessive-compulsive | 12.9 | 22.5 | 18.0 | .002 |
| Passive aggressive | 3.4 | 8.9 | 6.3 | .003 |
| Not otherwise specified | 3.1 | 1.2 | 2.1 | .076 |

[a]Patients may have more than 1 personality disorder within a cluster.
[b]Numbers of individual disorders were too small.
[c]Antisocial personality disorder was an exclusion criterion.
[d]Fisher exact test.

Cluster C Axis II personality disorder comorbidity was notably higher (39.0%) than either cluster B (11.8%) or cluster A (8.2%). The rates of cluster B comorbidity were smaller than expected since study entry criteria excluded patients with a current diagnosis of severe borderline and antisocial personality disorder.

Table 3. Distribution of Personality Disorders by Cluster

| | Chronic Major Depression (N = 294) | | Double Depression (N = 339) | | Combined (N = 633) | |
|---|---|---|---|---|---|---|
| Cluster[a] | N | % | N | % | N | % |
| A only | 4 | 1.4 | 8 | 2.4 | 12 | 1.9 |
| A and B only | 1 | 0.3 | 3 | 0.9 | 4 | 0.6 |
| A and C only | 7 | 2.4 | 9 | 2.7 | 16 | 2.5 |
| B only | 13 | 4.4 | 4 | 1.2 | 17 | 2.7 |
| B and C only | 16 | 5.4 | 18 | 5.3 | 34 | 5.4 |
| C only | 68 | 23.1 | 109 | 32.2 | 177 | 28.0 |
| A, B, and C | 7 | 2.4 | 13 | 3.8 | 20 | 3.2 |

[a]Patients may have more than 1 personality disorder within a cluster.

Some patients had more than one diagnosis within a cluster, as well as diagnoses in one or both of the other clusters. The frequency of this latter occurrence is depicted in Table 3. Patients with cluster B comorbidity were much more likely to have an additional Axis II diagnosis in another cluster (64.9% of cluster B patients with chronic major depression and 89.5% of cluster B patients with double depression), compared with cluster C (30.6% of cluster C patients with chronic major depression and 26.8% of cluster C patients with double depression).

### Frequency of Axis II Personality Disorder Comorbidity: Effects of Age at Depression Onset, Subtype of Depression, and Gender

In the combined group of chronically depressed patients, early age at depression onset (before 21 years) was associated with a significantly higher rate of Axis II comorbidity only for the cluster C disorders (early, 47.1%, vs. late, 31.9%; $\chi^2 = 7.79$, df = 1, p = .005). Depression subtype was also associated with a difference only in the prevalence of cluster C disorders, with patients diagnosed with early double depression having a higher rate than patients with early chronic major depression (53% vs. 40%, respectively; $\chi^2 = 4.05$, df = 1, p = .044) and patients with late double depression having a higher rate of cluster C disorders than patients with late chronic major depression (36% vs. 27%; $\chi^2 = 3.76$, df = 1, p = .053).

Finally, there were no differences observed in the prevalence of cluster A, B, or C Axis II disorders by gender. This was true whether chronic depressive subtypes were combined or examined separately and for both early and late depression onset. The only notable difference in prevalence of individual Axis II disorders was the significantly higher rate of obsessive-compulsive personality in male versus female patients who reported an early onset of depression (30% vs. 13% for combined depression subtypes; p < .01).

### Effect of Axis II Personality Disorder Comorbidity on Depression Outcome

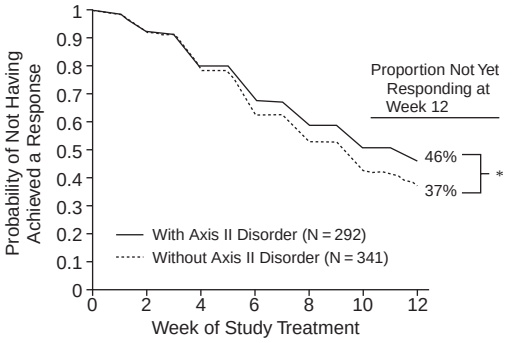
The effect of Axis II comorbidity on depression outcome is shown in Table 4 for the intent-to-treat sample at endpoint. In this analysis, both sertraline and imipramine groups have been combined since no between-treatment-group differences were identified in rates of remission or satisfactory therapeutic response for patients either with or without Axis II comorbidity. As can be seen, Axis II comorbidity had no significant effect on either response or remission rates with the exception that patients diagnosed with cluster B comorbidity had a modestly higher rate of remission (46%) compared with patients with no Axis II comorbidity (34%; $\chi^2 = 4.19$, df = 1, p = 041). The subset of patients diagnosed with 2 or more Axis II disorders achieved both satisfactory therapeutic response and remission rates that were comparable to those of patients without Axis II comorbidity.

Table 4. Rates of Treatment Response for the Combined Treatment Groups by Axis II Personality Disorder Comorbidity Status

| Axis II | Responders[a] | | p | Remitters[c] | | p |
|---|---|---|---|---|---|---|
| Comorbidity Status | N | % | Value[b] | N | % | Value[b] |
| No Axis II disorder | 183 | 55 | … | 112 | 34 | … |
| With Axis II disorder | 140 | 49 | .210 | 90 | 31 | .585 |
| With ≥ 2 Axis II disorders | 74 | 58 | .425 | 52 | 41 | .135 |
| Presence of cluster A | 26 | 53 | .841 | 20 | 41 | .288 |
| Presence of cluster B | 47 | 64 | .113 | 34 | 46 | .041 |
| Presence of cluster C | 122 | 50 | .384 | 79 | 33 | .792 |

[a]Responders had a 50% reduction at endpoint in HAM-D score, HAM-D score ≤ 15, and CGI-I = much/very much improved, and CGI-S ≤ mildly ill.
[b]Remitters had endpoint HAM-D score ≤ 7 and CGI-I = much or very much improved.
[c]p Value vs. no Axis II personality disorder.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = CGI-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression.

Figure 1. Kaplan-Meier Estimated Time-to-Response Estimates for Patients With and Without a Comorbid Axis II Personality Disorder




*p = .052, log-rank chi-square test.

### Effect of Axis II Personality Disorder Comorbidity on Time to Response

A separate analysis was conducted to determine whether Axis II comorbidity had an effect on the time to response—either satisfactory therapeutic response or remission. Figure 1 displays the Kaplan-Meier curves for

Table 5. Effect of Axis II Personality Disorder Comorbidity on Functional and Quality-of-Life Measures For Responders in the Combined Treatment Groups as Determined Using Mean ± SD Acute-Phase Change Scores

| Variable | No Axis II (N = 183) | With Axis II (N = 140) | ≥ 2 Axis II (N = 74) | Cluster A (N = 26) | Cluster B (N = 47) | Cluster C (N = 122) |
|---|---|---|---|---|---|---|
| No. of hours worked per week | 6.3 ± 17.1 | 3.8 ± 16.2 | 4.1 ± 15.4 | 3.9 ± 10.1 | 5.5 ± 12.9 | 3.8 ± 16.7 |
| SF-36 general health | 13.4 ± 18.0 | 13.6 ± 19.4 | 13.9 ± 19.6 | 16.2 ± 22.2 | 13.2 ± 20.6 | 13.4 ± 19.1 |
| SF-36 social functioning | 32.8 ± 26.3 | 33.8 ± 27.3 | 34.3 ± 26.8 | 35.2 ± 30.0 | 36.5 ± 27.7 | 33.8 ± 25.6 |
| SF-36 role limitation, emotional | 48.5 ± 43.8 | 53.9 ± 44.0 | 58.1 ± 42.4 | 64.1 ± 46.1 | 59.9 ± 42.9 | 53.5 ± 43.4 |
| SF-36 role limitation, physical | 18.6 ± 46.4 | 14.5 ± 41.8 | 17.5 ± 41.6 | 14.4 ± 43.1 | 15.9 ± 39.7 | 14.1 ± 41.7 |
| Quality-of-life measure | 20.6 ± 12.9 | 20.4 ± 12.3 | 21.2 ± 12.5 | 17.6 ± 14.7 | 20.5 ± 12.3 | 20.6 ± 12.1 |

Abbreviation: SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey.

time to response. The median time to response was 10 weeks for patients without an Axis II personality disorder and 12 weeks for patients with a personality disorder. The Kaplan-Meier estimated probability of achieving a response was 62.7% (95% CI = 57.0% to 68.3%) for patients without Axis II comorbidity and 53.7% (95% CI = 47.6% to 59.8%) for patients with Axis II comorbidity. The difference in time to response failed to achieve significance ($\chi^2 = 3.771$, df = 1, p = .052). When the subgroup of patients with 2 or more Axis II diagnoses were analyzed separately, the Kaplan-Meier estimated probability of response at 12 weeks was 61.7% (95% CI = 52.9% to 70.6%) for patients without 2 or more Axis II disorders, compared with 46.9% (95% CI = 38.6% to 55.3%) for patients with exactly 1 Axis II diagnosis. This result was statistically significant when these 2 subgroups were compared with patients with no Axis II comorbidity ($\chi^2 = 9.455$, df = 1, p = .009). One hundred sixty-one patients were diagnosed as having only 1 Axis II personality disorder. This was 55.1% of the total of 292 patients diagnosed with Axis II comorbidity. Of the 161 patients with only 1 Axis II diagnosis, 75.8% were cluster C patients, suggesting that a cluster C diagnosis might be contributing to a somewhat slower time to response.

### Effect of Axis II Personality Disorder Comorbidity on Psychosocial Outcome

As can be seen from Table 5, the presence of Axis II comorbidity had no significant influence on any functional or quality-of-life measure among responders. This was true both for each cluster as well as for patients who were found to have multiple Axis II diagnoses.

Among patients with Axis II comorbidity who achieved at least a satisfactory therapeutic response at study endpoint, there were no significant differences between sertraline and imipramine in the improvement in psychosocial and quality-of-life measures.

### Study Discontinuation and Adverse Events: Effect of Axis II Personality Disorder Comorbidity

For patients with no Axis II personality disorder, positive Axis II comorbidity, or 2 or more Axis II disorders, the premature study discontinuation rate for all reasons was 21.1%, 18.5%, and 17.6%, respectively. Among the subset of patients discontinuing from the study due to adverse events, the rate was higher for patients with no Axis II disorder (10.6%) compared with patients with Axis II comorbidity or with 2 or more disorders (5.5%, p = .020 and 4.6%, p < .041, respectively).

## DISCUSSION

We report the incidence, clinical correlates, and effect on outcome of Axis II comorbidity in outpatients suffering from chronic major depression and double depression who were participating in a pharmacologic treatment study. Overall, 46.1% of patients were diagnosed with an Axis II personality disorder. Highly variable Axis II comorbidity rates have been reported previously, ranging from below 10%[32,33] in community surveys to rates above 50% in outpatient treatment samples.[3–9,24,34,35] One study that excluded patients with high chronicity[2] found a much lower Axis II comorbidity rate of 18%, a finding consistent with research suggesting that Axis II comorbidity may be associated with a worse clinical outcome.[11] The rates in the current, highly chronic patient sample were higher than 18%, but still were below the rates reported in many treatment samples. The current data, therefore, do not help resolve the issue of whether the poor outcome risk associated with Axis II comorbidity is due to an increased risk of relapse and/or recurrence, or an increased risk of chronicity (i.e., lower recovery rates).

Among patients in the current study, a cluster C diagnosis was by far the most frequent (39.0%), followed by cluster B (11.8%). This result differs from most previous reports, which find the rate of cluster B comorbidity especially in dysthymia[2,4,22] to equal or exceed that of cluster C. Since severe borderline and antisocial patients were excluded from study entry, and since the study was designed as a treatment study and not an epidemiologic study, inferences cannot be confidently drawn about the relative incidence of Axis II cluster comorbidity.

The results of the current investigation found that almost half of the subgroup of patients diagnosed with

Axis II comorbidity (44.9%) received 2 or more Axis II diagnoses. Cluster B comorbidity was much more likely to be associated with an additional Axis II diagnosis (65% and 90% for chronic major and double depression, respectively) than was cluster C comorbidity (31% and 27% for chronic major and double depression, respectively). Whether this is a genuine finding or is a nosologic artifact reflecting lower discriminant validity for cluster B versus cluster C diagnoses is unclear.

### Demographic, Clinical, and Psychosocial Correlates of Axis II Personality Disorder Comorbidity

The presence of Axis II comorbidity was associated both with an older age and with a significant tendency (Table 1) for the depression to have an earlier age at onset, and, in terms of major depressive episodes, to have a higher rate of recurrence. The historical nature of the data on age at depression onset and course of illness, though, does not permit us to test causal hypotheses. The most notable clinical correlate of Axis II comorbidity was the significantly higher rate of comorbid anxiety disorders. This was, not surprisingly, contributed mostly by patients with a cluster C diagnosis: 34% of patients with cluster C diagnoses were found to also have a concurrent anxiety disorder diagnosis, compared with 18% of patients without cluster C ($\chi^2 = 22.72$; df = 1; $p < .001$).

Perhaps surprisingly, Axis II comorbidity was associated with very little reduction in perceived quality of life, as measured by the Q-LES-Q, or in self-rated functioning, as measured by factors on the SF-36. In fact, the psychosocial impact of Axis II comorbidity in these chronically depressed patients was limited, almost exclusively, to a modest reduced likelihood of being currently married (35% and 31% for patients with any and 2 or more Axis II disorders, respectively, compared with 40% among patients with no Axis II comorbidity). Since 67% of individuals in the community aged 40 years are currently married and living with their spouse,[36] these figures suggest that the negative impact on marital status in our study is contributed more by the chronic depression itself than by the additional Axis II comorbidity.

### Associations Between Age at Onset, Depression Subtype, and Gender and the Frequency and Pattern of Axis II Personality Disorder Comorbidity

Early age at onset had a relatively modest impact on the rate of Axis II comorbidity. This result differs from previous reports that have linked early onset of major depression to higher rates of Axis II comorbidity.[9,37,38] Our current results may seem paradoxical since, on average, patients with Axis II comorbidity had a significantly earlier mean age at onset than patients without Axis II comorbidity (22 years vs. 27 years; $p < .01$). Yet the definition of "early onset" required that the depression begin prior to age 21, which may have served to "bottom out" the group mean difference in age at onset. Using this criterion, early age at onset was associated with a significant increase only in the rate of cluster C comorbidity (47.1% vs. 31.9% for late onset; $p < .01$). This is intriguing since cluster C comorbidity was, in turn, associated with a significantly higher rate of Axis I anxiety disorder comorbidity, and preliminary research suggests that an anxiety diagnosis may be a significant predispositional factor in the development of early-onset depression.[39] Once again, though, the available data do not permit us to test causal hypotheses concerning whether the antecedent vulnerability is most commonly anxiety, depression, or related to interpersonal or coping difficulties reflected in an Axis II disorder.

Similar to age at onset, depression subtype was only modestly correlated with Axis II comorbidity rates. Double depression was associated with modestly higher Axis II cluster C rates than chronic major depression, both in patients with early-onset depression (53% vs. 40%) and late-onset depression (36% vs. 27%). There was no notable depression subtype difference in rates of Axis II comorbidity either for clusters A and B or for individual personality disorders.

The results obtained in the current investigation differ from previously reported research in separately examining the association between Axis II comorbidity and time of onset and depression subtype in a large depression sample that was homogeneous for duration of illness. Keeping the duration variable relatively constant permits one to obtain a somewhat better estimate of the influence of age at onset, while minimizing the potentially confounding effects of chronicity. Our current results raise the possibility that the development of Axis II comorbidity may be associated as much with chronicity as it is with age at onset—except for personality disorders that fall in the anxious/fearful cluster.

The current investigation found gender to be minimally correlated with Axis II comorbidity, either by age at onset or by depression subtype. The only significant exception was for patients with early-onset major depression, for whom the rate of comorbid obsessive-compulsive personality disorder was significantly higher in males than in females (30% vs. 13%; $p < .01$). This might be expected since early-onset OCD (prior to age 18) is more common in males.[40] No previous study has examined gender correlates on Axis II comorbidity rates in chronic forms of depression. Studies have examined gender differences in specific Axis II disorders, but results are variable, and the studies generally do not control for the presence of Axis I diagnoses, not to mention the other illness dimensions such as duration of illness or age at onset. Previous studies examining Axis II comorbidity rates by gender in patients with major depression have found males to have a significantly higher incidence of narcissistic and obsessive-compulsive personality.[9,41]

### The Association Between Axis II Personality Disorder Comorbidity and Outcome

The current investigation found the presence of Axis II comorbidity to have minimal-to-no effect on antidepressant response. This was true for both sertraline and imipramine. This result is in contrast to some,[11,12,15,16] but not all,[13,14] previous research which suggested that such comorbidity has a negative effect on antidepressant response. Only 1 of these studies[12] examined whether the putative Axis II effect might have been due to depression chronicity, age at onset, or the presence of concurrent dysthymia; it was not.

The presence of Axis II comorbidity also did not reduce the improvement in perceived quality of life or in measures of functional status. This is perhaps one of the most surprising findings, since one might have hypothesized that the maladaptive coping that is central to an Axis II disorder might have had a deleterious effect on the normalization of psychosocial or quality-of-life measures.

Also surprising is that Axis II comorbidity, even the presence of 2 or more disorders, had no effect on medication tolerability or premature study discontinuation due to adverse events. In fact, the reverse was true: patients with comorbidity dropped out at somewhat lower rates.

Finally, Axis II comorbidity was associated with a somewhat slower time to response. This effect was more prominent for patients with only 1 Axis II disorder compared with patients with 2 or more disorders. This may seem paradoxical at first, but the paradox is perhaps understandable if one remembers that 76% of all patients with only 1 Axis II disorder had a cluster C diagnosis, and cluster C was associated with significantly higher rates of anxiety comorbidity. Anxiety comorbidity has been found, in this patient sample, to be associated with a significantly longer time to response.[42]

### Limitations of the Current Study

Perhaps the most important limitation of the study is that patients represented a convenience sample recruited for entry into a pharmacologic treatment study. The results, therefore, cannot be generalized to the community. Furthermore, generalizability even to outpatients suffering from chronic forms of depression should be made cautiously, since entry criteria for the treatment study excluded patients with antisocial personality disorder, a recent history of alcohol or substance abuse or dependence, and psychotic or bipolar illness. All of these exclusionary criteria had the almost certain effect of reducing the rate of Axis II comorbidity. No simple "correction" can be made, though, since it has been suggested that one of the most notable differences between patients seeking treatment and individuals with the same index illness in the community is the rate of comorbidity.[43]

In terms of the influence of a comorbid Axis II disorder on treatment response, it should be noted that the current results apply only to pharmacologic treatment and cannot be generalized to cognitive-behavioral or other psychotherapies.

One of the findings of the study was the lack of negative effect of Axis II comorbidity (predominantly cluster B) on depression response. It is possible that patients with cluster B personality disorders might have intrinsically more fluctuating levels of depression severity, and a more conservative response criterion might have required 4 weeks or longer of sustained improvement. One final study limitation consists of the lack of an independent assessment of personality status by a friend or family member informant other than the patient. Dependence on cross-sectional (instead of prospective) Axis II data is especially problematic when assessment is performed in the midst of major depression. Information from an informant may partially address this concern.

## CONCLUSION

In this treatment sample, rates of Axis II comorbidity were substantial in patients suffering from chronic forms of depression. In contrast to previous research, Axis II comorbidity did not appear to diminish symptomatic or functional response to acute treatment.

*Drug names:* imipramine (Tofranil and others), sertraline (Zoloft).

## REFERENCES


1. Klein DN. Diagnosis and classification of dysthymic disorder. In: Kocsis J, Klein DN, eds. Diagnosis and Treatment of Chronic Depression. New York, NY: Guilford Press; 1995
2. Pepper CM, Klein DN, Anderson RL, et al. DSM-III-R Axis II comorbidity in dysthymia and major depression. Am J Psychiatry 1995;152:239–247
3. Klein DN, Taylor EB, Dickstein S, et al. Primary early-onset dysthymia: comparison with primary nonbipolar nonchronic major depression on demographic, clinical, familial, personality, and socioenvironmental characteristics and short-term outcome. J Abnorm Psychol 1988;97: 387–398
4. Markowitz JC, Moran ME, Kocsis JH, et al. Prevalence and comorbidity of dysthymic disorder among psychiatric outpatients. J Affect Disord 1992:24:63–71
5. Mezzich JE, Ahn CW, Fabrega H, et al. Patterns of psychiatric comorbidity in a large population presenting for care. In: Maser JD, Cloninger CR, eds. Comorbidity of Anxiety and Mood Disorders. Washington, DC: American Psychiatric Press; 1990:189–194
6. Alnaes R, Torgerson S. Personality and personality disorders among patients with various affective disorders. J Personal Disord 1991;5: 107–121
7. Farmer R, Nelson-Grey RO. Personality disorders and depression: hypothetical relations, empirical findings, and methodological considerations. Clin Psychol Rev 1990;10:453–476
8. Corruble E, Ginestet D, Guelfi JD. Comorbidity of personality disorders and unipolar major depression: a review. J Affect Disord 1996;37: 157–170
9. Fava M, Alpert JE, Borus JS, et al. Patterns of personality disorder comorbidity in early-onset versus late-onset major depression. Am J Psychiatry 1996;153:1308–1312
10. Akiskal HS, King D, Rosenthal TL, et al. Chronic depressions, pt 1: clinical and familial characteristics in 137 probands. J Affect Disord 1981;3:297–315
11. Shea MT, Widiger TA, Klein MH. Comorbidity of personality disorders

and depression: implications for treatment. J Consult Clin Psychol 1992;60:857–868
12. Shea MT, Pilkonis PA, Beckham E, et al. Personality disorders and treatment outcome in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry 1990;147:711–718
13. Fava M, Uebelacker LA, Alpert JE, et al. Major depressive subtypes and treatment response. Biol Psychiatry 1997;42:568–576
14. Fava M, Bouffides E, Pava JA, et al. Personality disorder comorbidity with major depression and response to fluoxetine treatment. Psychother Psychosom 1994;62:160–167
15. Pilkonis PA, Frank E. Personality pathology in recurrent depression: nature, prevalence, and relationship to treatment response. Am J Psychiatry 1988;145:435–441
16. Patience DA, McGuire RJ, Scott AI, et al. The Edinburgh Primary Care Depression Study: personality disorder and outcome. Br J Psychiatry 1995;167:324–330
17. Alnaes R, Torgersen S. Personality and personality disorders predict development and relapses of major depression. Acta Psychiatr Scand 1997;95:336–342
18. Klein DN, Riso LP, Donaldson SK, et al. Family study of early-onset dysthymia: mood and personality disorders in relatives of outpatients with dysthymia and episodic major depression and normal controls. Arch Gen Psychiatry 1995;52:487–496
19. Lizardi H, Klein DN, Ouimette PC, et al. Reports of the childhood home environment in early-onset dysthymia and episodic major depression. J Abnorm Psychol 1995;104:132–139
20. Hayden EP, Klein DN. Outcome of dysthymic disorder at 5-year follow-up: the effect of familial psychopathology, early adversity, personality, comorbidity, and chronic stress. Am J Psychiatry 2001;158:1864–1870
21. Haykal RF, Akiskal HS. The long-term outcome of dysthymia in private practice: clinical features, temperament, and the art of management. J Clin Psychiatry 1999;60:508–518
22. Rush AJ, Koran LM, Keller MB, et al. The treatment of chronic depression, pt 1: study design and rationale for evaluating the comparative efficacy of sertraline and imipramine as acute, crossover, continuation, and maintenance phase therapies. J Clin Psychiatry 1998;59:589–597
23. Keller MB, Gelenberg AJ, Hirschfeld RM, et al. The treatment of chronic depression, pt 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998;59:598–607
24. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
25. Spitzer RL, Williams JBW, Gibbon M, et al. Structured Clinical Interview for DSM-III-R-Patient Version (SCID-P). New York, NY: Biometric Research, New York State Psychiatric Institute; 1989
26. Spitzer RL, Williams JBW, Gibbon M. Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II). New York, NY: Biometric Research, New York State Psychiatric Institute, 1986
27. Zimmerman M. Diagnosing personality disorders, l: a review of issues and research methods. Arch Gen Psychiatry 1994;51:225–245
28. Guy W. Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-368. Rockville, Md: National Institute of Mental Health; 1976:218–222
29. Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. Arch Gen Psychiatry 1976;33:1111–1115
30. Ware J. Sherbourne C. The MOS 36-Item Short-Form Health Survey (SF-36). Med Care 1992;30:473–481
31. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993;29:321–326
32. Samuels JF, Nestadt G, Romanoski AJ, et al. DSM-III personality disorders in the community. Am J Psychiatry 1994;151:1055–1062
33. Maier W, Lichtermann D, Klinger T, et al. Prevalence of personality disorders (DSM-III-R) in the community. J Personal Disord 1992;6: 187–196
34. Sanderson WC, Wetzler S, Beck AT, et al. Prevalence of personality disorders in patients with major depression and dysthymia. Psychiatry Res 1992;42:93–99
35. Kaye AL, McCullough JP, Roberts WC, et al. Differentiating affective and characterologic DSM-III-R psychopathology in non-treatment, community unipolar depressives. Depression 1994;2:80–88
36. US Bureau of the Census. Current Population Survey, March 1998. Table 1: Marital Status and Living Arrangements. Washington, DC: US Bureau of the Census; 1998
37. Rohde P, Lewinsohn PM, Seeley JR. Comorbidity of unipolar depression, 2: comorbidity with other mental disorders in adolescents and adults. J Abnorm Psychol 1991;100:214–222
38. Kovacs M, Feinberg TL, Crouse-Novak MA, et al. Depressive disorders in childhood, 1: a longitudinal prospective study of characteristics and recovery. Arch Gen Psychiatry 1984;41:229–237
39. Parker G, Wilhelm K, Asghari A. Early onset depression: the relevance of anxiety. Soc Psychiatry Psychiatr Epidemiol 1997;32:30–37
40. Bebbington PE. Epidemiology of obsessive-compulsive disorder. Br J Psychiatry 1998;173(suppl 35):2–6
41. Golomb M, Fava M, Abraham M, et al. Gender differences in personality disorders. Am J Psychiatry 1995;152:579–582
42. Russell JM, Koran LM, Rush J, et al. Effect of concurrent anxiety on response to sertraline and imipramine in patients with chronic depression. Depress Anxiety 2001;13:18–27
43. Roberts RS, Spitzer WO, Delmore T. An empirical demonstration of Berkson's bias. J Chronic Dis 1978;31:119–128