# Psychiatric Comorbidity as a Predictor of Clinical Response to Nortriptyline in Treatment-Resistant Major Depressive Disorder

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***Background:*** A number of studies of major depressive disorder suggest that psychiatric comorbidity may contribute to treatment resistance. The purpose of this study was to test whether the presence of comorbid Axis I and Axis II disorders predicts clinical response to an open trial of nortriptyline among patients with treatment-resistant depression.

***Method:*** Ninety-two outpatients with treatment-resistant DSM-III-R major depressive disorder were enrolled in a 6-week open trial of nortriptyline (Nov. 1992–Jan. 1999). The presence of comorbid Axis I and Axis II disorders was established at baseline with the use of the Structured Clinical Interview for DSM-III-R. Chi-square analyses were used to test Axis I or Axis II comorbid conditions as a predictor of clinical response to nortriptyline.

***Results:*** Thirty-nine patients (42.4%) responded to nortriptyline. The presence of avoidant personality disorder ($p < .01$) predicted poorer response to nortriptyline. The response rate was 16.7% for patients with and 48.6% for patients without comorbid avoidant personality disorder. No other comorbid diagnoses were found to predict clinical response in a statistically significant manner.

***Conclusion:*** The presence of avoidant personality disorder conferred a poorer prognosis in treatment-resistant depression patients treated with nortriptyline.

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Although antidepressants have been widely prescribed for decades, the ability to predict which patients will respond to any particular medication remains elusive. Predicting antidepressant response is even more difficult in patients with treatment-resistant depression. The presence of comorbid Axis I disorders has long been thought a feature that could distinguish potential treatment responders from nonresponders. Indeed, a number of studies have identified comorbid dysthymia,[1] anxiety disorders,[2] and panic disorder[3,4] as predictors of poor treatment outcome in major depressive disorder, although some studies fail to find any relation between dysthymia[2] and outcome.

Considerable emphasis has also been placed on comparing depressed patients with comorbid personality disorders with those without on a number of characteristics. Patients with significant personality disturbance are more likely to present with depressive episodes of greater severity and longer duration, experience an earlier age at onset of depression and a greater number of lifetime depressive episodes, and present with suicidal ideation compared with those without personality disturbance.[5–7] In addition, major depressive disorder accompanied by personality disturbance has been associated with lower levels of psychosocial functioning and a greater frequency of suicide attempts.[8,9]

A recent review of over 50 studies reveals that the impact of personality pathology on treatment outcome in major depression varies according to the study design.[10] Some studies have found that characterological and temperamental factors such as dysfunctional attitudes,[11] reward dependence,[12] and symptoms of cluster A and cluster C personality disorders[13–15] are related to poorer outcome, while other studies have not.[2,16,17] In addition, 2 of the positive studies examining Axis II disorders or traits focus on naturalistic treatment[13] or long-term outcome.[14]

Therefore, it remains unclear whether psychiatric comorbidity contributes to treatment resistance per se. We previously reported that patients with treatment-resistant depression did not have higher rates of Axis I[18] or Axis II[19] disorders when compared with depressed patients without

treatment-resistant depression. The purpose of this study was to test whether the presence of comorbid Axis I and Axis II disorders predicts clinical response to an open trial of nortriptyline among patients with treatment-resistant depression.

## METHOD

### Patient Selection and Study Design

Subjects were recruited at the Massachusetts General Hospital Depression Clinical and Research Program for the purpose of an outpatient clinical trial to assess the efficacy of lithium versus placebo augmentation of nortriptyline among subjects with treatment-resistant depression who had previously failed an open clinical trial of nortriptyline of 6 weeks' duration. This report focuses on the open phase of the study.

A total of 92 outpatients were enrolled. Inclusion criteria were as follows: men and women 18 to 70 years of age with major depressive disorder (MDD) according to the Structured Clinical Interview for DSM-III-R, Patient Edition (SCID-P)[20] and a score on the 17-item Hamilton Rating Scale for Depression (HAM-D-17)[21] greater than or equal to 18. The presence of comorbid Axis I and Axis II disorders was established at baseline with the use of the SCID-P and SCID-II,[22] respectively.

Treatment resistance was defined as nonresponse to at least 1, but no more than 5, adequate antidepressant trials during the current major depressive episode. The adequacy of a trial was assessed with the use of the Harvard Antidepressant Treatment History form,[23] which provides specific criteria with respect to dose and duration of treatment. Some examples of adequate dosage of an antidepressant trial include 150 mg or more of imipramine (or its tricyclic antidepressant [TCA] equivalent), 60 mg or more of phenelzine (or its monoamine oxidase inhibitor equivalent), 20 mg or more of fluoxetine (or its selective serotonin reuptake inhibitor [SSRI] equivalent), 150 mg or more of bupropion, and 300 mg or more of trazodone (or nefazodone). A trial of adequate duration was defined as one during which the patient was taking any given antidepressant at an adequate dose for a minimum of 6 weeks.

Exclusion criteria were as follows: bipolar I or bipolar II disorder, psychotic disorders, a history of organic mental or seizure disorder, serious or unstable medical illness, active substance abuse or dependence disorders within the past 12 months, acute suicide risk, pregnancy, lactation, history of adverse reaction or allergy to the study medications, concomitant use of psychotropic medications, and clinical or laboratory evidence of thyroid abnormalities.

The procedure and possible side effects of the study were fully explained to participants before obtaining their informed consent. Participants in this study signed an Institutional Review Board–approved informed consent form immediately prior to the initial study visit.

After obtaining informed consent, subjects were started on 25 mg of nortriptyline, which was increased by 25 mg per day until an initial daily dose of 100 mg was reached, unless patients were unable to tolerate the dose increase due to side effects. Blood levels of nortriptyline were obtained at weeks 2 and 6, and dose adjustments were made after the second week if blood levels were 100 ng/mL or less. Subjects were then kept at a stable dose of nortriptyline for the remaining 4 weeks.

Study visits occurred at screening, at baseline, and then weekly for 6 weeks. The 31-item version of the HAM-D, allowing the scoring of the HAM-D-17, was administered at screening, baseline, and each study visit by experienced psychologists and psychiatrists. In our group, training in the use of instruments such as the HAM-D-17 and SCID-P is done by peer review of videotaped interviews. Interrater reliability in our group for the use of the SCID-P was recently estimated as $\kappa = 0.80$ for the diagnosis of depressive disorders.[24]

### Definition of Outcome

Outcome analysis was based on an intent-to-treat model ($N = 92$). For this analysis, the last available HAM-D-17 data point was carried forward (i.e., the last available data point substituting for the week-6 data point) for those patients who prematurely discontinued the study. Response was defined as greater than or equal to a 50% reduction in total HAM-D-17 score (from baseline visit to last recorded visit).

### Statistical Analysis

Chi-square analyses were used to test whether the presence of any comorbid Axis I or Axis II condition was a predictor of clinical response to nortriptyline. In these analyses, the presence or absence of a comorbid disorder and the response status were the 2 variables entered. Chi-square analyses were also used to test whether the presence of any comorbid Axis I or Axis II condition was a predictor of premature discontinuation of treatment. These analyses were performed similarly to the above analyses, substituting clinical response for completer status. A correction for multiple comparisons (Bonferroni correction) was used where appropriate. The efficacy results of the open-label trial are reported elsewhere.[25]

## RESULTS

Thirty-nine patients (42.4%) responded to the 6-week open trial of nortriptyline. Table 1 presents the response rates for patients presenting with and without each comorbid Axis I disorder. None of these Axis I disorders were found to predict clinical response ($p > .05$). Table 2 presents the response rates for patients presenting with and without each Axis II disorder. The presence of avoidant personality disorder ($p < .01$) was found to significantly

  

**Table 1. Response Rates for Patients Treated With Nortriptyline (N = 92) With and Without Comorbid Axis I Disorders[a]**

| | Response Rate | | | |
|---|---|---|---|---|
| | Diagnosis Present | | Diagnosis Not Present | |
| Axis I Diagnosis | N | % | N | % |
| Social phobia | 5/18 | 27.8 | 34/74 | 45.9 |
| Panic disorder | 8/17 | 47.0 | 31/75 | 41.3 |
| Obsessive-compulsive disorder | 0/6 | 0 | 39/86 | 45.3 |
| Posttraumatic stress disorder | 2/6 | 33.3 | 37/86 | 43.0 |
| Simple phobia | 3/8 | 37.5 | 36/84 | 42.9 |
| Agoraphobia | 4/8 | 50.0 | 35/84 | 41.7 |
| Generalized anxiety disorder | 2/4 | 50.0 | 37/88 | 42.0 |
| Any anxiety disorder | 14/40 | 35.0 | 25/52 | 48.1 |
| Somatoform disorder | 1/2 | 50.0 | 38/90 | 42.2 |
| Eating disorder | 1/3 | 33.3 | 38/89 | 42.7 |

[a]$p > .05$ for all comparisons using chi-square analyses with the clinical response and the presence of each of the diagnoses individually as the 2 variables.

**Table 2. Response Rates for Patients Treated With Nortriptyline (N = 92) With and Without Comorbid Axis II Disorders[a]**

| | Response Rate | | | |
|---|---|---|---|---|
| | Diagnosis Present | | Diagnosis Not Present | |
| Axis II Diagnosis | N | % | N | % |
| Schizotypal | 0/0 | 0 | 39/92 | 42.4 |
| Schizoid | 0/2 | 0 | 39/90 | 43.3 |
| Paranoid | 4/9 | 44.4 | 35/83 | 42.2 |
| Cluster A | 4/11 | 36.4 | 31/81 | 38.3 |
| Borderline | 5/10 | 50.0 | 34/82 | 41.5 |
| Histrionic | 0/0 | 0 | 39/92 | 42.4 |
| Narcissistic | 2/3 | 66.7 | 37/89 | 41.6 |
| Antisocial | 0/4 | 0 | 39/88 | 44.3 |
| Cluster B | 5/12 | 41.7 | 34/80 | 42.5 |
| Avoidant[b] | 3/18 | 16.7 | 36/74 | 48.6 |
| Dependent | 1/8 | 12.5 | 38/84 | 45.2 |
| Obsessive-compulsive | 5/14 | 35.7 | 34/78 | 43.6 |
| Passive-aggressive | 2/6 | 33.3 | 37/86 | 43.0 |
| Cluster C[c] | 7/27 | 25.9 | 32/65 | 49.2 |
| Any Axis II | 11/34 | 32.4 | 28/58 | 48.3 |

[a]Except as noted otherwise, $p > .05$ for all comparisons using chi-square analyses.
[b]$p < .01$ using chi-square analyses with clinical response and the presence of avoidant personality disorder individually as the 2 variables.
[c]$p < .05$ using chi-square analyses with clinical response and the presence of cluster C diagnosis individually as the 2 variables, but this difference did not reach statistical significance with Bonferroni correction.

predict nonresponse. The response rate was approximately 16.7% (3/18) for patients with comorbid avoidant personality disorder and 48.6% (36/74) for patients without. There was a trend toward statistical significance for the presence of a cluster C personality disorder to predict nonresponse ($p < .05$), but this difference did not reach statistical significance with Bonferroni correction. No other Axis II disorders were found to significantly predict clinical response. Thirty-two patients (35%) discontinued the study prematurely. There was no difference in discontinuation rates between patients who did and did not present with avoidant personality disorder ($p > .05$) or any cluster C personality disorder ($p > .05$).

## DISCUSSION

To our knowledge, this is the first study to test comorbid psychiatric diagnoses as predictors of clinical response to nortriptyline in treatment-resistant depression. The presence of avoidant personality disorder predicted nonresponse. In fact, the response rate for patients with avoidant personality disorder was almost one third the response rate for patients without avoidant personality disorder. We found no other statistically significant predictive value with respect to clinical response for any other Axis I or Axis II disorder.

It is not unusual for clinicians to think of patients with treatment-resistant depression as having an additional underlying psychiatric disturbance, particularly an Axis II disturbance. In part, this perception may stem from some studies suggesting that depressed patients with significant personality disturbance have a less favorable course compared with those without personality disturbance.[10] The majority of these studies, however, either involve naturalistic treatment or retrospective chart review and measure long-term outcome rather than clinical response in the setting of a 4- to 16-week controlled trial. In fact, several clinical trials do not support any relationship between Axis II pathology and clinical response.

Our group, for instance, failed to find an association between personality disorders and lack of clinical response in depressed patients treated with 20 mg of fluoxetine for 8 weeks.[2] Kocsis and colleagues[26] did not find a significant difference in the rate of Axis II disorders between patients with chronic depression who did respond and those who did not respond to an 8-week trial of imipramine, while Hirschfeld and colleagues[27] did not find higher rates of Axis II disorders in nonresponders when compared with responders for patients with chronic depression enrolled in a 12-week double-blind trial of sertraline versus imipramine. Hoencamp and colleagues[28] failed to find dysthymia, anxiety disorders, or any other Axis I or Axis II disorder to predict which patients would eventually respond to a 3-phase sequential antidepressant trial.

One explanation for the discrepancy in findings between the present study and the study by Hirschfeld and colleagues[27] may lie in the differences in depressive populations studied, i.e., treatment-resistant depression and MDD. However, in contrast to the study by Hoencamp and colleagues,[28] which by its design established a treatment-refractory population prospectively, our study supports the view that some forms of personality disorder comorbidity may be associated with poorer outcome in patients with

treatment-resistant depression treated with the TCA nortriptyline, a relatively noradrenergic TCA.

The trial conducted by Hirschfeld and colleagues,[27] as well as our previous studies,[2,29,30] examined the relationship between comorbid personality pathology and outcome in depressed outpatients who, at some point, received treatment with the SSRIs. This may be a possible reason for the discrepant findings, as SSRIs alone have shown efficacy in the treatment of nondepressed personality disorder patients.[31] In support of this argument, Peselow and colleagues[15] found a greater prevalence of cluster C personality disorders in patients with MDD who did not respond to a 5-week trial of the TCA desipramine, which also possesses significant noradrenergic activity. Additional support for this argument is provided by a recent review that suggests SSRIs are particularly effective in social phobia,[32] a diagnosis that has considerable overlap with avoidant personality disorder.[33] However, in the present study, we did not find social phobia to predict poorer response to TCAs.

Finally, the present findings may also be influenced by the relatively shorter duration of treatment (6 weeks as opposed to 12 weeks in the study by Hirschfeld and colleagues[27] and up to 18 weeks in the study by Hoencamp and colleagues).[28] Frank and colleagues,[34] for instance, found slower response to treatment with a combination of imipramine and interpersonal psychotherapy in patients with comorbid personality disorders.

A limitation of the study is the relatively small sample size, which may account for the lack of significance in the degree of psychiatric comorbidity between responders and nonresponders. This may be particularly true of the present study, since the focus was to examine whether the presence of any particular comorbid diagnosis, several with lower prevalence rates than others, had any impact on clinical response. Thus, disorders with relatively low prevalence in the present sample, such as antisocial personality disorder or generalized anxiety disorder, for instance, may have had a statistically significant impact on the response rate in larger sample sizes.

An additional limitation is the lack of reliability data for the study interviewers on the SCID-II or the other Axis I disorders investigated. Weak reliability, if present, combined with a relatively small sample size may have further minimized the strength of any relationships present. In addition, although raters were not blinded with respect to Axis I or Axis II status during their assessments, if any bias had been present, it would have been toward the direction of minimizing response to nortriptyline in patients with psychiatric comorbidity, thus strengthening the relationship between psychiatric comorbidity and treatment nonresponse. However, the present results fail to demonstrate a relationship between psychiatric comorbidity and treatment response for the majority of possible comorbid diagnoses, save for avoidant personality disorder.

## CONCLUSION

The presence of avoidant personality disorder conferred a poorer prognosis in treatment-resistant depression patients treated with nortriptyline. This finding is in line with a previous study examining Axis II comorbidity as a predictor of response to the TCA desipramine but contrary to other studies that did not find a relationship between Axis II comorbidity and response to the SSRI fluoxetine. Further studies are necessary to explore the role of psychiatric comorbidity in clinical response in antidepressant trials.

*Drug names:* bupropion (Wellbutrin and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), nefazodone (Serzone), nortriptyline (Aventyl, Pamelor, and others), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others).

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