Partial Validation of the Atypical Features Subtype of Major Depressive Disorder

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Background: Symptoms of the atypical features subtype of major depressive disorder include mood reactivity, hypersomnia, hyperphagia, leaden paralysis, and rejection sensitivity. This subtype was introduced into the mood disorders section of the DSM-IV following a series of antidepressant trials showing that such patients responded preferentially to monoamine oxidase inhibitors. Studies aimed at validating the atypical features subtype have yielded inconsistent results. Our study sought to reevaluate the validity of atypical depression by examining the demographic and clinical features of a large cohort of depressed patients who met DSM-IV criteria for atypical features.

Methods: We evaluated 579 psychiatric outpatients with a current diagnosis of major depressive disorder for the presence of atypical features. Detailed demographic and clinical information was obtained for each patient through semistructured interviews. Using the available literature, we made a series of a priori hypotheses regarding how depressed patients with atypical features (n = 130) would differ from those without atypical features (n = 449). In addition, we tested the strength of the associations between each of the 5 atypical symptoms.

Results: Although many of the predicted hypotheses were substantiated, an equal number were not. Correlation analyses revealed modest associations between several of the atypical symptoms, but mood reactivity was not associated with any of the other symptom criteria.

Conclusion: Our results provide partial support for the validity of the atypical features subtype of major depressive disorder.

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A TYPICAL depression stands alone among the DSM-IV1 mood disorder subtypes as being born out of the modern psychopharmacologic revolution. West and Dally2 first used the qualifier atypical to characterize a cohort of depressed patients who appeared phobic, “overreactive,” and “hysterical” and exhibited prominent fatigue, reversed diurnal variation, initial insomnia, and an absence of decreased appetite. Sargant3 added that such patients also tended to complain of severe lethargy, hypersomnia, and irritability. Both sets of investigators believed that these patients had good premorbid personalities but were now experiencing a chronic form of depression. They also noted that such patients responded particularly well to monoamine oxidase inhibitors (MAOIs) and less well to tricyclic antidepressants and electroconvulsive therapy.

Quitkin et al4 subsequently argued that these early investigators were actually describing 2 distinct subtypes. One subtype included patients with panic disorder; the other, patients with hysteroid dysphoria. The latter syndrome was characteristic of histrionic patients, whose mood was described as “shallow” and excessively sensitive to both admiration (mood reactive) and rejection (rejection sensitive). When depressed, such patients purportedly displayed a propensity to oversleep and overeat. Although the validity of hysteroid dysphoria was questioned by some,5,6 it was ultimately incorporated into the DSM-IV as a depressive subtype by virtue of the preferential response such patients showed for MAOIs rather than tricyclic antidepressants. In its current form, the atypical subtype includes 5 features: mood reactivity plus at least 2 of the following 4 symptoms (hereafter referred to as atypical B symptoms): hypersomnia, hyperphagia, severe lethargy (often described as a feeling of “leaden paralysis”), and a pathological sensitivity to rejection and criticism.

The decision to include the atypical features subtype in the DSM-IV was controversial,7 in part because studies that have
SUBJECTS AND METHODS

SUBJECTS

All subjects in our study were recruited from the Rhode Island Hospital (Providence) Department of Psychiatry’s outpatient practice. During their initial telephone screen, all patients were invited to participate in an in-depth diagnostic evaluation prior to meeting with their treating clinician (psychiatrist, psychologist, or social worker). Only non-English-speaking patients and those with evidence of cognitive impairment were excluded from the study. To date, 1130 patients have been evaluated. Of these, 579 (51.2%) were diagnosed as having a current major depressive disorder and form the cohort of interest for the study. The Rhode Island Hospital institutional review board approved the research protocol, and all patients provided informed written consent.

METHODS

Consenting patients were interviewed at baseline using the Structured Clinical Interview for DSM-IV (SCID). Diagnostic raters were PhD psychologists or college graduate research assistants who had undergone extensive training, as described elsewhere. Mood reactivity was assessed according to the SCID by asking patients whether they felt better, even temporarily, when something good happened. Hyperphagia was defined as increased appetite nearly every day for at least 2 weeks or an increase in body weight of 5% or more. Hypersomnia was defined as sleeping significantly more than usual. Leaden paralysis was considered to be present when a patient acknowledged often having a heavy, leaden feeling in the arms or legs. Rejection sensitivity was defined as a long-standing pattern of interpersonal sensitivity (not limited to episodes of mood disturbance) that caused significant social or occupational impairment. All 5 symptoms were rated as being either present, absent, or subthreshold, and only the first rating counted as being present. Reliability ratings for each of the atypical symptoms were obtained from 24 joint interviews. Values for the atypical symptoms were as follows: mood reactivity, 0.83; hyperphagia, 1.0; hypersomnia, 0.90; leaden paralysis, 0.78; and rejection sensitivity, 0.75, indicating excellent interrater reliability.

The SCID was supplemented with questions from the Schedule for Affective Disorders and Schizophrenia (SADS) to assess the severity of symptoms during the week prior to the evaluation. From this, we were able to obtain extracted 21-item Hamilton Depression Rating Scale (HAM-D) scores following the algorithm developed by Endicott et al. Current social-functioning ratings were obtained using the SADS item that rates the highest level of social relations during the last 5 years. Baseline Clinical Global Impression–Severity (CGI-S) ratings and current Global Assessment of Functioning (GAF) scores were also obtained for each patient by the diagnostic interviewer. Personality disorder assessments were incorporated into the protocol for only the last 530 patients; the first 600 patients did not undergo an Axis II diagnostic evaluation. Thus, PD diagnoses were available for only 262 (45.3%) of the 579 patients with major depression. Personality disorders were assessed using the Structured Interview for DSM-IV Personality.

All diagnoses were made according to DSM-IV criteria. Our analyses comparing depressed patients with and without atypical features are based on current rather than lifetime diagnoses of affective disorders. In comparing comorbidity rates, however, we used lifetime diagnoses. Psychomotor retardation was rated by interviewer observation rather than patient report. Prior suicidal behavior was analyzed based on the most serious lifetime attempt. The determination of seriousness was made after assessing the method and purpose of the attempt, the likelihood of rescue, and the seriousness of injury.

STATISTICAL ANALYSES

We performed χ² and t tests to analyze all categorical and continuous variables, respectively. Correlation coefficients were obtained using the Spearman ρ because all variables tested were dichotomous. For all hypothesized comparisons, statistical significance was set at P < .05, and all tests were 2-tailed. In addition, 34 tests were performed without an a priori hypothesis. For these tests, the Bonferroni correction was used to adjust for chance positive findings. Statistical significance in these analyses was set at P < .05 divided by 34, or P < .0015.

examined the demographic and clinical features of patients with atypical depression who have frequently yielded contradictory results. For example, the atypical features subtype has been associated with female sex by some investigators but not others, younger age by some but not others, bipolarity by some but not others, greater anxiety by some but not others, less severity by some but not others, a longer duration of illness by some but not others, a younger age of onset by some but not others, higher rates of recurrence by some but not others, and more suicidality by some, but less suicidality by others. Integrating these results has been difficult because investigators have used disparate criteria to define the atypical subtype and have often studied distinct and highly selected populations of subjects.

In our study, we sought to assess and reevaluate the validity of the atypical subtype by comparing the demographic and clinical features of depressed patients with and without atypical features. Our analyses are based on data collected from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, which has overcome many of the limitations of previous studies by (1) evaluating a large cohort of unselected psychiatric outpatients; (2) abiding by the current DSM-IV formulation of atypical depression; (3) using semistructured interviews conducted by researchers with extensive training to obtain diagnoses on most major Axis I and Axis II disorders; and (4) obtaining extensive information regarding baseline demographic and clinical features. Our study uses the results from the first 579 patients who were evaluated in the MIDAS project.
and who received a current diagnosis of major depressive disorder.

Because of the inconsistencies in the results of previous studies, there is no straightforward way to generate hypotheses regarding how patients with atypical features would be expected to differ from those without atypical features. In reviewing the literature, therefore, we have given more weight to the Columbia University formulation of the disorder. Because this latter finding is contrary to the established opinion regarding atypical depression, we further predicted that patients who maintained mood reactivity would be more likely to meet the atypical B criteria threshold than those with an unreactive mood. We also expected that each of the 5 atypical symptoms would be significantly correlated with each other, and that hyper- somnia and hyperphagia would be more strongly correlated with the other atypical symptoms than would the non-atypical symptoms of insomnia and decreased appetite.

Last, because some investigators have argued that mood reactivity plus 1 of 4 atypical B symptoms, or probable atypical depression, may better capture the unique features of patients who respond preferentially to MAOIs,7,9,28,29,33,34 we sought to determine whether such a modification would be supported by our data. If patients with probable atypical depression resemble those who meet threshold criteria, we would expect the demographic and clinical features of these 2 cohorts to be similar.

### RESULTS

**PREVALENCE OF ATYPICAL FEATURES IN MAJOR DEPRESSION**

Of the 579 patients with a current major depressive disorder, 130 (22.5%) met criteria for the atypical subtype. Rates of atypical symptoms in the 579 patients were as follows: mood reactivity, 71.7%; hypersomnia, 16.8%; hyperphagia, 21.8%; leaden paralysis, 28.0%; and rejection sensitivity, 40.9%. Symptom rates in the 130 patients with atypical depression were 100% for mood reactivity, 36.2% for hypersomnia, 53.1% for hyperphagia, 60.8% for leaden paralysis, and 75.4% for rejection sensitivity.

### DEMOGRAPHIC AND CLINICAL FEATURES ASSOCIATED WITH ATYPICAL DEPRESSION

The demographic and clinical features of the 130 patients with atypical depression were compared with those of the 449 patients with nonatypical depression (Table 1). As predicted, atypical depression was associated with female sex, a younger age at onset, and a longer episode duration. Contrary to expectation, patients with atypical features were not younger, the diagnosis was not more prevalent in patients with bipolar disorder, and atypical depression was associated with a greater rather than lesser severity of illness, both on HAM-D scores and CGI-S ratings.

Because this latter finding is contrary to the established opinion regarding atypical depression, we fur-
the explored the relationship between severity and atypically. With a worsening of mood, as rated on the 6-point mood severity item from the SADS, rates of hypomania (r = 0.11; P = .01), leaden paralysis (r = 0.21; P < .001), and rejection sensitivity (r = 0.13; P = .009) all increased. The percentage of patients who met criteria for atypical features also increased with greater mood severity but not to a statistically significant degree (r = 0.07; P = .08), largely because mood reactivity was inversely correlated with mood severity (r = −0.18; P < .001).

**PRESENCE OF SYMPTOMS HYPOTHESIZED TO BE ASSOCIATED WITH ATYPICAL DEPRESSION**

In comparing patients with atypical depression with those who had nonatypical depression, the former cohort was more often rated as irritable (72.3% vs 62.1%; \( \chi^2 = 4.5; P = .03 \)) and anxious (66.9% vs 55.0%; \( \chi^2 = 5.9; P = .02 \)). However, patients with atypical depression were no more likely to display reversed diurnal variation (26.2% vs 30.5%; \( \chi^2 = 0.9; P = .34 \)), less likely to demonstrate an absence of guilt (34.6% vs 45.4%; \( \chi^2 = 4.8; P = .03 \)), and more often rated as having psychomotor retardation (40.0% vs 28.1%; \( \chi^2 = 6.7; P = .009 \)).

Rates of current suicidal ideation were nearly identical in both cohorts (51.5% and 48.6%). Of the depressed patients with atypical features, 20% had a history of a serious suicide attempt compared with 16.3% of nonatypical depressed patients; rates of nonserious suicide attempts were likewise similar between the 2 groups (8.5% and 10.9%, respectively). Thus, contrary to expectation, patients with atypical depression were neither more prone to nonserious suicide attempts nor less prone to serious ones.

**COMORBIDITY IN PATIENTS WITH ATYPICAL DEPRESSION**

Patients with atypical depression were significantly more likely to have panic disorder with agoraphobia and social phobia but were not more likely to have panic disorder without agoraphobia (Table 2). No differences were found in rates of other anxiety disorders or substance use disorders, including amphetamine abuse or dependence. Lifetime diagnoses of hypochondriasis (5.4% vs 1.6%; \( \chi^2 = 6.2; P = .01 \)) and body dysmorphic disorder (6.9% vs 1.8%; \( \chi^2 = 9.4; P = .002 \)) were more common in patients with atypical depression; bulimia was not found to be more common (6.2% vs 2.7%; \( \chi^2 = 3.7; P = .06 \)).

Of the 579 depressed patients in our sample, 262 underwent an Axis II evaluation. A dimensional analysis, which compares the number of DSM-IV criteria met for each PD, confirmed that histrionic and avoidant traits were associated with atypical depression (\( F_{261} = 4.2; P = .04 \), and \( F_{260} = 35.2; P < .001 \), respectively). In fact, patients with atypical depression had higher mean dimensional rating scores for each of the 10 PDs than patients with nonatypical depression (Table 3).

From a categorical standpoint, 100 (38.2%) of the 262 depressed patients met the diagnostic threshold for at least 1 comorbid PD. Avoidant PD (but not histrionic PD) was significantly associated with a greater likelihood of having atypical features (\( \chi^2 = 20.1; P < .001 \)). No other PDs were associated with the atypical subtype, although some of the sample sizes were small (Table 4).

**CORRELATIONS AMONG ATYPICAL SYMPTOMS**

We first evaluated whether the presence of mood reactivity was significantly associated with having at least 2 of 4 atypical B symptoms. Of the 579 patients diagnosed as having a current major depressive disorder, 415 (71.7%) were mood reactive and 164 (28.3%) were mood nonreactive. Of the mood-reactive patients, 130 (31.3%) met the atypical B criteria; 53 (32.3%) of the mood-nonreactive patients also met the criteria. Thus, mood reactivity was not associated with a greater likelihood of meeting the atypical B diagnostic threshold.

Next, we assessed the strength of association between the 5 atypical symptoms (Table 5). Mood reactivity was not correlated with any of the atypical B symptoms. Hyperphagia was significantly associated with...
hypersomnia (r = 0.09; P = .03) as well as leaden paralysis (r = 0.10; P = .02), and leaden paralysis was significantly associated with rejection sensitivity (r = 0.09; P = .03). No other symptom domains were significantly correlated.

To assess the discriminant validity of the atypical subtype, we compared the strength of associations between hyperphagia and hypersomnia with the remaining 3 atypical symptoms and contrasted these with the strength of associations between the nonatypical symptoms of decreased appetite and insomnia. In making these comparisons, only the previously mentioned associations reached statistical significance. Hyperphagia was positively associated with each of the other 4 atypical symptoms (r = 0.04 to 0.10), whereas decreased appetite was negatively correlated with them (r = −0.04 to 0.00). Hypersomnia was more strongly correlated with hyperphagia (r = 0.09) and rejection sensitivity (r = 0.02) than was insomnia (r = −0.02 for both); however, leaden paralysis was more strongly correlated with insomnia (r = 0.06) than with hypersomnia (r = 0.01). These results suggest a positive but modest correlation between the atypical B symptoms, and fairly good discriminant validity compared with the nonatypical symptoms of decreased appetite and insomnia.

### CATEGORIZING PATIENTS WITH PROBABLE ATYPICAL DEPRESSION

Probable atypical depression is defined as mood reactivity plus exactly 1 of 4 atypical B symptoms. Of the 449 patients who did not meet the full criteria for atypical depression, 141 (31.5%) met the probable criteria for this disorder. To determine whether these patients more closely resembled those who met the full criteria or those with nonatypical depression, we performed the following analysis: we compared the 141 patients with probable atypical depression with both the 130 patients who had atypical depression and the 308 patients with nonatypical depression across each demographic and clinical variable. Patients with probable atypical depression differed significantly from those with threshold criteria on 7 variables. They were less severely ill; had a shorter episode duration; had higher rates of comorbid social phobia; had lower rates of borderline, narcissistic, and avoidant traits; and had lower rates of avoidant PD. In contrast, patients with probable atypical depression differed significantly from patients with nonatypical depression on only 1 variable: they were more likely to be female. Thus, our results suggest that patients with probable atypical depression are distinct from those who meet threshold criteria.

### Table 4. Comorbidity Rates in Depressed Patients With and Without Atypical Features

<table>
<thead>
<tr>
<th>Atypical</th>
<th>Nonatypical</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid</td>
<td>5 (9.3)</td>
<td>11 (5.3)</td>
</tr>
<tr>
<td>Schizotypal</td>
<td>4 (7.4)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Schizoid</td>
<td>4 (7.4)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Borderline</td>
<td>10 (18.5)</td>
<td>24 (11.5)</td>
</tr>
<tr>
<td>Narcissistic</td>
<td>1 (1.9)</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Antisocial</td>
<td>0 (0)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Histrionic</td>
<td>1 (1.9)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>OCPD</td>
<td>6 (11.1)</td>
<td>21 (10.1)</td>
</tr>
<tr>
<td>Dependent</td>
<td>1 (1.9)</td>
<td>4 (1.9)</td>
</tr>
</tbody>
</table>
| Avoidant          | 23 (42.6)           | 31 (14.9)| <.001†%
| Cluster A         | 9 (16.7)            | 20 (9.6)  | .14 |
| Cluster B         | 11 (20.4)           | 29 (13.9)| .24 |
| Cluster C         | 24 (44.4)           | 55 (24.0)| .003‡ |
| Any PD            | 28 (51.9)           | 72 (34.6)| .03‡ |

* N = 262. Data are presented as number (percentage) unless otherwise indicated. OCPD indicates obsessive-compulsive personality disorder; PD, personality disorder.
† Statistically significant in the hypothesized direction.
‡ Not statistically significant after adjusting for the Bonferroni correction.

### Table 5. Correlations Among Atypical Symptoms and Comparisons With the Nonatypical Symptoms of Decreased Appetite and Decreased Sleep

<table>
<thead>
<tr>
<th>Mood reactivity</th>
<th>Hyperphagia</th>
<th>Hypersomnia</th>
<th>Leaden paralysis</th>
<th>Rejection sensitivity</th>
<th>Decreased appetite</th>
<th>Decreased sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood reactivity</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
</tr>
<tr>
<td>Hyperphagia</td>
<td></td>
<td>.09†</td>
<td>.09†</td>
<td>.09†</td>
<td>.09†</td>
<td>.09†</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>.05</td>
<td></td>
<td>.05</td>
<td>.05</td>
<td>.05</td>
<td>.05</td>
</tr>
<tr>
<td>Leaden paralysis</td>
<td>.02</td>
<td>.10†</td>
<td>.10†</td>
<td>.10†</td>
<td>.10†</td>
<td>.10†</td>
</tr>
<tr>
<td>Rejection sensitivity</td>
<td>.08</td>
<td>.08</td>
<td>.08</td>
<td>.08</td>
<td>.08</td>
<td>.08</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
<td>.04</td>
</tr>
<tr>
<td>Decreased sleep</td>
<td>.01</td>
<td>.01</td>
<td>.01</td>
<td>.01</td>
<td>.01</td>
<td>.01</td>
</tr>
</tbody>
</table>

* N = 579. Ellipses indicate not applicable.
† P < .05.
‡ P < .01.
Our most salient finding regards mood reactivity. Mood reactivity has been considered an essential component of the atypical features subtype; of the 5 atypical symptoms, it is the only one required to make the diagnosis. Consistent with other reports, we did not find any evidence to suggest that mood reactivity is associated with the atypical B symptoms. In some antidepressant trials, the presence of mood reactivity has been shown to predict a preferential MAOI response, whereas other studies have found that it is not predictive or that mood unreactivity predicts a superior MAOI response.

Of the remaining atypical symptoms, correlation analyses revealed significant but modest associations. Although correlation coefficients of 0.09 to 0.10 account for only about 1% of the variance, the association between insomnia and decreased appetite \( (r = 0.13) \) was only slightly higher. This suggests that this level of correlation may be clinically meaningful. Our analyses lend support to the discriminant validity of the subtype because hyperphagia and hypersomnia were generally more closely correlated with the remaining atypical symptoms than were the nonatypical symptoms of decreased appetite and insomnia.

Three of the most commonly cited validators of atypical depression were confirmed in our study: a preponderance of women, a younger age at onset, and a longer duration of illness. Two other important validators were not confirmed. Depressed patients with atypical features were not younger, and they were found to be more rather than less severely depressed. Although psychopharmacologic studies have consistently reported that patients with atypical depression have a milder illness, these studies are vulnerable to sampling bias because subjects with mild depression are invariably excluded from these trials. The lower rates of severity found in these studies could also reflect the fact that the HAM-D rating scale does not account for reversed neurovegetative symptoms. In our study, a greater severity of illness in patients with atypical depression was corroborated by lower baseline GAF scores and poorer social-functioning ratings.

Our analysis of comorbid Axis I disorders confirmed that panic disorder with agoraphobia, social phobia, hypochondriasis, and body dysmorphic disorder were all associated with atypical depression, as predicted. Panic disorder without agoraphobia was not associated with this condition. Although most research assessing the predictive value of comorbid anxiety for MAOI response rates in patients with atypical features has focused on the presence of comorbid panic attacks, our results suggest that the phobic element may be more relevant.

Despite the statistically significant findings, we would argue that our results do not support a strong association between histrionic PD and atypical depression because (1) personality traits were also found to be higher in PDs that have not been postulated to be associated with atypical features; (2) the mean \( \pm \) SD number of DSM-IV histrionic traits in the 54 patients with atypical depression was only \( 1.0 \pm 1.2 \); and (3) only 1.9% of the depressed patients with atypical features met the criteria for histrionic PD. Our finding that avoidant PD is associated with atypical depression is consistent with previous studies. One possible explanation for this finding, however, is that rejection sensitivity may be closely related to avoidant traits. If so, the comorbidity findings could simply be a consequence of the overlapping nature of these constructs; in fact, all of the comorbid conditions associated with the atypical features subtype appear to have this phobic-hyperconscious element in common. To determine whether the other atypical symptoms were independently associated with these disorders, we reanalyzed our data set using a modified definition of atypical depression that required mood reactivity plus 2 of 3 atypical B symptoms (excluding rejection sensitivity). Of all the validators we assessed in this study, only 1 remained significantly associated with the atypical subtype: being female. This suggests that the comorbidity findings may be a consequence of the fact that rejection sensitivity is an element of most, if not all, of these disorders.

Two limitations of our study should be kept in mind. First, although multiple raters were used to interview patients, the study was entirely carried out at one site, and the results therefore warrant replication. Second, the small sample sizes for conditions such as panic disorder without agoraphobia, bipolar disorder, and certain PDs may have provided insufficient power to detect real differences that might have been present; these analyses should be interpreted cautiously.

We conclude that our results lend partial support for the validity of the DSM-IV atypical features subtype. We could find no evidence, however, to suggest that mood reactivity is a valid component of the subtype, and this feature should perhaps be dropped from the diagnostic criteria set. With MAOIs falling into disuse, it seems unlikely that more pharmacologic trials will be performed to further address these issues. Thirty years ago, using antidepressant response rates in probands and family members, Pare and Mack suggested that certain patients may have a distinct genetic makeup that predisposes them to respond to particular antidepressants. Since then, little progress has been made in our ability to profile specific antidepressant responders. It would be unfortunate if the one instance in which a clear beneficial response pattern was known were not more fully investigated to uncover any underlying clues that might be available.

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