# Clinical and Demographic Features of Atypical Depression in Outpatients With Major Depressive Disorder: Preliminary Findings From STAR*D

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***Objective:*** To determine the frequency and demographic and clinical characteristics of depression with atypical features in a broadly representative sample of outpatients.

***Method:*** Data derived from the first 1500 patients with DSM-IV major depressive disorder enrolled in the Sequenced Treatment Alternatives to Relieve Depression trial at 41 primary care and nonresearch psychiatric outpatient clinics. An algorithm based on the 30-item Inventory of Depressive Symptomatology-Clinician Rating (IDS-C30) determined presence or absence of depression with atypical features. Odds ratios determined whether a variety of demographic and clinical parameters differed between patients meeting and not meeting atypical criteria.

***Results:*** Over 18% of the sample met criteria for atypical features based on items from the IDS-C30. The atypical group was more likely to be female and have an earlier age at onset, greater comorbidity with anxiety symptoms, and greater symptom severity compared with the nonatypical group.

***Conclusion:*** Previously identified features of atypical depression were confirmed in this large and broadly representative, nonresearch clinical population.

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The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[1] provides specifiers for mood disorders in an attempt to create more homogenous diagnostic groups, which might better target treatment and describe the course of illness. Atypical symptom features have been widely recognized for nearly 50 years.[2–4] DSM-IV does not recognize an atypical subtype, but rather allows for a description of atypical symptom features, because there remains a question as to whether atypical depression is a distinct entity or represents a phase of major depressive disorder (MDD) that evolves over time as patients age or as the disorder becomes more chronic.[5] The atypical features specifier can be applied to the current or most recent major depressive episode (MDE) in MDD, bipolar I disorder, or bipolar II disorder or to dysthymic disorder.

To qualify as having DSM-IV atypical features, a depressed patient must experience significant mood reactivity plus at least 2 of the following 4 features: (1) significant weight gain or increase in appetite, (2) hypersomnia,

(3) leaden paralysis, and (4) a long-standing pattern (i.e., not necessarily limited to periods of depressed mood) of interpersonal rejection sensitivity that results in significant social or occupational impairment. In addition, patients cannot meet criteria for melancholic or catatonic features during the same episode.

Despite the evolution of and debate surrounding the precise definition, ample evidence suggests that depressions with atypical features differ from those with melancholic, catatonic, or "typical" features (summarized by Stewart et al.[4]). Relative to patients without depression, or to those with nonatypical depression, patients with atypical depression also differ with respect to demographic and clinical features such as sex,[3,6–10] psychiatric and medical comorbidity,[3,6–9,11] and course of illness.[4] Most studies report the usual 2:1 female split within depressed patients with atypical features[3,6–10]; however, other studies, in particular epidemiologic as opposed to clinical studies, do not always support this sex split (e.g., references 11, 12). Depressed patients with atypical features are as educated as other depressed patients but less likely to ever have been or currently be married.[4,9] Horwath et al.[11] did not find racial/ethnic differences between depressed Epidemiologic Catchment Area subjects with and without atypical features. Follow-back studies have reported that depression with atypical features has an earlier onset[4,10,11,13] and a more chronic course[4,13,14] than does melancholia. Repeated episodes of illness are likely to have vegetative symptoms similar to an index depressive episode,[13,15] suggesting stability of the syndrome over time.

The description of atypical depression is historically linked to a particular treatment response, as atypical depression was originally described as particularly responsive to monoamine oxidase inhibitor (MAOI) antidepressants and not to tricyclic antidepressants (TCAs),[2,16,17] an observation confirmed by subsequent double-blind studies.[18,19] Newer antidepressants, such as fluoxetine and bupropion, have been suggested as effective for depression with atypical features.[20–22] Although not placebo controlled, the Pande et al.[22] study suggested that fluoxetine had efficacy comparable to phenelzine for atypical depression. In addition, 2 studies[23,24] have shown newer agents as effective in randomized, placebo-controlled studies. In the first, an 8-week study,[23] 62% (18/29) responded to gepirone, a serotonin 5-$HT_{1A}$ partial agonist, and 20% (6/30) responded to placebo ($\chi^2 = 9.14$, df = 1, $p < .002$). In the second,[24] fluoxetine (50% responding) was superior to placebo (25% responding) in a 10-week study. Neither study compared the newer agents to an MAOI, so their relative efficacies remain unclear.

Furthermore, biological or physiologic differences between patients with atypical depression and nonatypical depression have been identified with respect to the activity of the hypothalamic-pituitary-adrenal (HPA) axis,[25] sleep,[26] and laterality on auditory[27] and visual[28] perceptual processing. Unlike melancholia, atypical depression has been associated with relatively normal HPA, sleep, and perceptual processing profiles.

Epidemiologic studies suggest that atypical depression is relatively common in the general population, with rates ranging from 0.7% to 4.0%.[11–13,15] Rates of atypical depression among clinical populations of depressed patients seeking treatment range from 22%[29] to 36%.[30]

Patients having MDD with atypical features are more likely to have comorbid conditions than those with nonatypical depression. These comorbid disorders include panic disorder,[9,11] social phobia,[9,13,31] generalized anxiety disorder (GAD),[13] and obsessive-compulsive disorder (OCD),[9] as well as somatization/hypochondriasis,[11,29] bulimia,[8] and body dysmorphic disorder.[9] Substance abuse disorders and personality disorders have also been reported at increased rates among depressed patients with atypical as compared to typical features.[11–13,29]

A major limitation of the available studies of atypical depression is that most were conducted in research or other tertiary care settings or reported on epidemiologic samples. None sampled representative clinical settings. Tertiary care settings may oversample atypical depression, given that increased severity, comorbidity, and chronicity characterize both atypical depression and patients seeking care at tertiary care settings. Thus, some of the previously identified associated characteristics of atypical depression may reflect, in part, a selection bias toward more chronically ill patients. Well-conducted epidemiologic studies provide unbiased estimates of prevalence, sociodemographics, comorbidities, and other variables of interest, but because only some people having a disorder seek treatment, these studies cannot accurately inform practitioners of what to expect in their patients. Because most epidemiologic studies do not assess possible self-selection bias, we evaluated patients seeking treatment from primary care physicians and nonresearch psychiatrists and psychiatric clinics to constitute our informative sample.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial is a multisite collaborative project involving participants from settings that are not research driven. It was designed to prospectively investigate which of several treatments, including pharmacotherapy and cognitive therapy, are most effective for patients who suffer from nonpsychotic major depressive disorder that does not satisfactorily respond to treatment with citalopram or subsequent randomized treatments.[32,33] The STAR*D sample draws on outpatients receiving treatment for depression in both primary care and specialty settings who were not specifically recruited to those sites for the purpose of depression research. In addition, during their current depressive episode, eligible patients must not have had an unsatisfactory response to an adequate trial of any medication included in the first 2

steps of the STAR*D protocol. The STAR*D population thus provides a representative sampling of relatively treatment-naive depressed patients served by both primary and nonresearch specialty care outpatient settings. An advantage of this study over prior studies is its drawing from multiple different nonresearch facilities around the country, so it can inform general clinicians about the relatively treatment-naive depressed patients who come to them for treatment.

The present analysis of STAR*D subjects represents an opportunity to identify and compare the demographic and clinical characteristics of patients with atypical and nonatypical depression from public and private sectors across the country, in both specialty and primary care settings. Based on the literature, we expected to see a prevalence of atypical depression in the range of 22% to 25%, with these patients having higher psychiatric comorbidity (particularly anxiety disorders), an earlier onset of illness, and a longer length of illness.

## METHOD

### Sample and Data Collection

The population and methods of STAR*D including enrollment, inclusion and exclusion criteria, and data collection (described in detail in Fava et al.[32] and Rush et al.[33]) are briefly summarized here. The sample population for this current analysis consists of the first 1500 consecutive patients enrolled in STAR*D. The analyses are exploratory, aiming to identify potential differences for further hypothesis testing once the full sample (expected N = 4000) is acquired.

STAR*D is a collaboration among personnel at 2 coordinating centers and over 40 clinical sites, comprising more than 60 coordinators and/or interviewers and over 400 clinicians. The STAR*D infrastructure includes the National Coordinating Center (NCC) in Dallas, Tex., the Data Coordinating Center (DCC) in Pittsburgh, Pa., and 14 Regional Centers (RCs) across the United States. Each RC oversees the implementation of the protocol at 2 to 4 clinical sites. Clinical Research Coordinators (CRCs) are located at each clinical site and are trained and certified in implementing the treatment protocol and in data collection methods. They work closely with the participants and clinicians and provide a liaison between the sites on the one hand, and the RCs, the DCC, and the NCC on the other. CRCs also administer some of the clinician-rated instruments.

To achieve the goal of enrolling a broadly representative group of participants with MDD, selection of clinical sites was made from groups providing primary and specialty care in either the public or private sectors. To further ensure that the study sample is representative of the "real world," the choice of clinical sites included practice sites that did not typically engage in traditional randomized clinical trials. In addition, advertising was not permitted in STAR*D, since advertising tends to enroll fewer participants who differ in important ways from treatment-seeking patients, although we recognize that some authors have not considered such differences as age, marital status, or alcohol use to be important.[34–38]

In general, the inclusion/exclusion criteria were broad so as to acquire a sample representative of persons with MDD who would receive medication or psychotherapy in everyday practice. At baseline, participants who were clinically diagnosed with MDD had to score at least 14 (moderate severity) on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D-17)[39] as rated by the CRC. However, persons with medical contraindications that precluded randomization to any treatment in levels 2 through 4 were excluded. In addition, participants with schizophrenia, schizoaffective disorder, bipolar disorder, anorexia nervosa, or a primary diagnosis of bulimia nervosa or OCD were excluded since their primary psychiatric condition required a different initial treatment. Participants with active and clinically significant substance abuse were eligible (so long as inpatient care was not required clinically at study entry), although participation in a substance abuse program was encouraged by their clinician. Participants with active substance dependence who required detoxification were not eligible for reasons of medical safety.

Clinical and demographic information was collected, as well as information on prior course of illness, current and past substance abuse, prior suicide attempts, family history of MDD or bipolar disorder, current general medical illnesses, and prior treatment of the current MDE (both medications and psychotherapy). Concurrent medical conditions were identified and quantified by the use of the Cumulative Illness Rating Scale (CIRS),[40,41] with which patients identified the presence and severity of medical conditions according to physiologic system.

Concurrent psychiatric symptoms were identified by the use of the Psychiatric Diagnostic Screening Questionnaire (PDSQ)[42] obtained at baseline. The PDSQ is a self-rated screening questionnaire (126 yes/no questions) with which patients rate the presence or absence of current and recent symptoms relevant to each of several major DSM-IV disorders, including posttraumatic stress disorder, bulimia nervosa, OCD, panic disorder, agoraphobia, social anxiety disorder, alcohol and drug abuse, generalized anxiety disorder, somatoform disorder, and hypochondriasis, among others. Internal consistency and test-retest reliability have been investigated, and the PDSQ has been validated against structured interviews.[42–44]

Within 72 hours of the baseline visit, subjects participated in a telephone interview with a Research Outcomes Assessor (ROA) and completed the HAM-D-17, the 30-item Inventory of Depressive Symptomatology-Clinician Rating (IDS-C30),[45–47] and a questionnaire regarding in-

come and public assistance. A 16-item self-report version of the IDS-C30 (QIDS-SR16) was also completed by subjects.[47,48] An interactive voice response (IVR) system obtained additional participant-reported information not specifically referenced in this article.

### Definition of Atypical Depression

Atypical depression was operationally defined by an algorithm applied to selected items of the IDS-C30 that addressed DSM-IV symptoms for depression with atypical features. These criteria included mood reactivity, leaden paralysis, hyperphagia (weight gain or increased appetite), hypersomnia, and rejection sensitivity. The reliability of IDS-C30 scores has been compared and validated (J.W.S.; P. J. McGrath, M.D.; F. M. Quitkin, M.D., unpublished data, June 2004) with scores using the clinician-rated Atypical Depression Diagnostic Scale.[4]

The IDS items that most closely approximated DSM-IV criteria were chosen by consensus. Inclusion criteria required a score of 0, 1, or 2 for mood reactivity, 2 or 3 for leaden paralysis, 2 or 3 for weight gain or increased appetite, 2 or 3 for hypersomnia, and 3 for interpersonal sensitivity. Of note, the IDS mood reactivity item scores 0 for a highly mood reactive individual and 3 for someone considered to be highly nonreactive. To qualify as having atypical depression, patients had to be rated as having mood reactivity, and they had to qualify as having at least 2 of the other 4 symptoms.

Patients with atypical depression were then compared to those with nonatypical depression according to baseline sociodemographic characteristics, clinical course, concurrent medical and psychiatric disorders and symptoms, and the presence or absence of nondefining individual IDS-C30 symptoms.

### Data Analysis

Data are presented as percentages for categorical variables and as means, standard deviations, medians, and observed ranges for continuous measures. A bivariate logistic regression analysis was used to assess the association, as measured by an odds ratio, between each variable and the presence of atypical depression. A multivariable logistic regression model was used to assess the association between each variable and the presence of atypical depression, after controlling for the effects of sex, age, and age at onset of the first MDE and then for severity. The evaluation of the association of atypical depression with the presence of a given depressive symptom measured by the IDS-C30, in which a symptom was considered to be present with a score greater than or equal to 1, was analyzed using a $\chi^2$ test, and logistic regression analyses were used when adjusting for sex, age, and age at onset of the first MDE and then for severity. The statistical significance for all tests was set at $p < .05$. As the analyses were exploratory in nature, no correction for multiple tests was made, so results must be interpreted accordingly. Severity was measured using the IDS-C30 minus the items defining atypicality.

## RESULTS

### Characteristics of the Entire Sample

The baseline characteristics of all 1500 patients as well as separated by atypical/nonatypical groups are presented in Table 1. Thirty-four percent of patients (N = 512) received treatment in a primary care setting, while 66% (N = 988) came from specialty care settings. White patients comprised 76% (N = 1137) of the total patients, 18% (N = 272) were black/African American, and 6% (N = 91) were neither black/African American nor white. Nine percent (N = 138) were Hispanic. Women comprised 63% (N = 941) of the sample, and 42% (N = 628) were married. More than half of the patients had a self-reported family history of depression (55%, N = 828), and more than half were employed (59%, N = 884).

The mean age was 40.5 ± 13.2 years, and patients had 13.6 ± 3.2 years of education. Monthly income was $2440 ± $2974. Patients endorsed 3.2 ± 2.3 medical comorbidities. The mean severity index for medical comorbidities was 1.3 ± 0.6 (where 1 = "current mild problem or past significant problem" and 2 = "moderate disability or morbidity/requires first-line therapy"). The mean total score for medical comorbidities was 4.6 ± 3.7 (number of categories endorsed × severity). Mean age at onset for the first MDE was 25.1 ± 13.9 years, and the mean number of episodes was 5.7 ± 9.3. The mean length of the current MDE was 20.9 ± 48.7 months. The mean time since onset of first MDE was 15.4 ± 13.2 years. Mean scores on the HAM-D-17, IDS-C30, and QIDS-SR16 (Table 2) are consistent with a moderate-to-severe level of depressive severity.

### Comparisons Between Depression With and Without Atypical Features

Atypical features were found to be present in 18.1% of the subjects (264/1455 due to missing data in 45 subjects). Baseline characteristics of race, ethnicity, sex, marital status, employment status, and family history of depression for these 2 patient groups are represented in the first section of Table 1. Odds ratios are presented unadjusted; adjusted for sex, age, and age at onset of first MDE; and adjusted for these parameters as well as severity (modified IDS-C30).

Women were more likely to present with atypical features (OR = 1.664, $p < .0006$), suggesting that women are nearly 70% more likely to have atypical depression. Unadjusted values for marital status suggested that patients with atypical features were about 1.5 times more likely to be unmarried, but this difference was not significant after adjusting for sex, age, and age at onset of first MDE.

**Table 1. Baseline (discrete) Characteristics and Association With Atypical Depression**

| Characteristic | Total Sample, %[a] (N = 1500) | Nonatypical Depression, % (N = 1191 [81.9%[b]]) | Atypical Depression, % (N = 264 [18.1%[b]]) | Unadjusted Odds Ratio | Unadjusted p Value[c] | Adjusted[d] Odds Ratio | Adjusted[d] p Value | Adjusted[e] Odds Ratio | Adjusted[e] p Value |
|---|---|---|---|---|---|---|---|---|---|
| Setting | | | | | .6856 | | .6446 | | .7012 |
| Primary care | 34.1 | 81.3 | 18.7 | | | | | | |
| Specialty care | 65.9 | 82.2 | 17.8 | 0.944 | | 0.934 | | 0.944 | |
| Race | | | | | .6643 | | .8224 | | .8239 |
| White | 75.8 | 82.2 | 17.8 | | | | | | |
| Black/African American | 18.1 | 81.5 | 18.5 | 1.049 | | 1.076 | | 0.930 | |
| Other | 6.1 | 78.4 | 21.6 | 1.273 | | 1.154 | | 1.125 | |
| Ethnicity, Hispanic | | | | | .9274 | | .8209 | | .9298 |
| No | 90.8 | 81.9 | 18.1 | | | | | | |
| Yes | 9.2 | 81.5 | 18.5 | 1.022 | | 0.947 | | 0.979 | |
| Sex | | | | | .0006 | | | | |
| Female | 62.8 | 79.2 | 20.8 | 1.664 | | | | | |
| Male | 37.2 | 86.4 | 13.6 | | | | | | |
| Marital status | | | | | .0234 | | .1581 | | .0849 |
| Never married | 28.6 | 76.9 | 23.1 | 1.490 | | 1.377 | | 1.404 | |
| Married | 41.9 | 83.3 | 16.7 | | | | | | |
| Divorced | 26.8 | 84.5 | 15.5 | 0.909 | | 0.898 | | 0.849 | |
| Widowed | 2.7 | 84.6 | 15.4 | 0.904 | | 0.931 | | 0.837 | |
| Employment status | | | | | .1122 | | .0827 | | .2757 |
| Employed | 59.0 | 83.2 | 16.8 | | | | | | |
| Unemployed | 34.7 | 79.0 | 21.0 | 1.319 | | 1.367 | | 1.208 | |
| Retired | 6.3 | 84.8 | 15.2 | 0.889 | | 1.436 | | 1.536 | |
| Family history of depression | | | | | .8733 | | .5071 | | .5862 |
| No | 44.5 | 82.0 | 18.0 | | | | | | |
| Yes | 55.5 | 81.7 | 18.3 | 1.022 | | 0.911 | | 0.925 | |
| Insurance type | | | | | .9512 | | .9182 | | .8941 |
| Private | 56.4 | 82.5 | 17.5 | | | | | | |
| Public | 12.5 | 81.6 | 18.4 | 1.059 | | 1.062 | | 0.899 | |
| None | 31.1 | 81.9 | 18.1 | 1.037 | | 1.059 | | 0.974 | |

[a]Denominators used to calculate percentages for total sample were 1498 for ethnicity and employment status, 1499 for sex and marital status, 1493 for family history of depression, and 1452 for insurance type due to missing data.
[b]Based on denominator of 1455 due to missing data on 45 patients.
[c]Significant at $p < .05$.
[d]Adjusted for sex, age, and age at onset of first major depressive episode.
[e]Adjusted for above items as well as severity (modified 30-item Inventory of Depressive Symptomatology-Clinician Rating).

No significant differences in the unadjusted or adjusted odds ratios between the atypical and nonatypical groups were found for race, ethnicity, employment status, family history of depression, enrollment setting, insurance type, or total years of education.

Age, education, and characteristics of the course of depressive illness, as well as comorbid diagnoses, are presented in Table 2. The odds of atypical depression increased with an earlier age at illness onset. Although initially the length of total illness was longer for the atypical group, the observed difference was no longer significant after adjusting for severity. In addition, the length of the current episode and number of episodes was not significantly associated with atypical depression.

Before adjusting for severity, the proportion of patients with atypical depression increased with the number of comorbid psychiatric symptoms in every PDSQ comorbid disorder, save for alcohol abuse. That is, the presence of atypical depression increased with the number of symptoms of anxiety disorders (e.g., OCD, panic disorder, social phobia, posttraumatic stress disorder), drug abuse, somatoform disorder, hypochondriasis, and bulimia nervosa. After adjusting for severity, comorbidity with symptoms of GAD, panic disorder, PTSD, drug abuse, and hypochondriasis was no longer significantly associated with atypical features.

Atypical features were also associated with increased scores for 3 of the symptom severity scales (HAM-D-17, IDS-C30, QIDS-SR16). However, after adjusting for severity, the higher HAM-D-17 scores in the atypical depression group were no longer statistically significant ($p = .2481$).

Table 3 compares the percentages of patients with atypical and nonatypical depression reporting the presence of individual baseline IDS-C30 (ROA) items. The statistical difference in association of each item to the atypical group and nonatypical group is presented both before and after adjusting for severity. Patients with atypical features more frequently endorsed several baseline symptoms compared to patients without atypical features. Interestingly, some items were statistically different both before and after the adjustment. On the other hand, some differences were present only before and some only after. The associated symptoms were not limited to those that usually make up the core features of the atypical subtype.

**Table 2. Clinical Features of Atypical and Nonatypical Depression**

| Characteristic | Total Sample (N = 1500) Mean | SD | Nonatypical Depression (N = 1191 [81.9%[a]]) Mean | SD | Atypical Depression (N = 264 [18.1%[a]]) Mean | SD | Unadjusted Odds Ratio | p Value[b] | Adjusted[c] Odds Ratio | p Value | Adjusted[d] Odds Ratio | p Value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age, y | 40.5 | 13.2 | 40.9 | 13.2 | 38.5 | 12.9 | 0.986 | .0065 | | | | |
| Education, y | 13.6 | 3.2 | 13.6 | 3.2 | 13.5 | 3.2 | 0.989 | .5994 | 0.992 | .6987 | 1.016 | .4814 |
| Age at onset of first MDE | 25.1 | 13.9 | 25.6 | 14.1 | 22.6 | 13.2 | 0.983 | .0012 | | | | |
| No. of MDEs | 5.7 | 9.3 | 5.7 | 9.7 | 5.8 | 7.9 | 1.001 | .8506 | 1.002 | .8218 | 1.002 | .7914 |
| Length of episode, mo | 20.9 | 48.7 | 21.0 | 51.7 | 20.3 | 34.8 | 1.000 | .8419 | 0.999 | .6242 | 0.999 | .4462 |
| Length of illness, y | 15.4 | 13.2 | 15.3 | 13.4 | 15.9 | 12.5 | 1.003 | .5038 | 1.013 | .0416 | 1.010 | .0975 |
| Psychiatric comorbidities[e] | | | | | | | | | | | | |
| GAD (10) | 6.6 | 3.1 | 6.5 | 3.1 | 7.3 | 2.8 | 1.105 | < .0001 | 1.089 | .0006 | 1.043 | .1095 |
| OCD (8) | 1.4 | 1.9 | 1.3 | 1.8 | 1.7 | 2.1 | 1.124 | .0006 | 1.129 | .0005 | 1.077 | .0419 |
| Panic disorder (8) | 2.5 | 2.6 | 2.4 | 2.5 | 2.8 | 2.6 | 1.065 | .0150 | 1.054 | .0454 | 0.987 | .6456 |
| Social phobia (15) | 5.6 | 4.7 | 5.2 | 4.6 | 7.5 | 4.6 | 1.108 | < .0001 | 1.100 | < .0001 | 1.080 | < .0001 |
| PTSD (15) | 5.6 | 5.1 | 5.3 | 5.1 | 6.6 | 5.3 | 1.051 | .0002 | 1.045 | .0010 | 1.020 | .1766 |
| Agoraphobia (11) | 2.2 | 2.7 | 2.0 | 2.6 | 2.9 | 3.0 | 1.122 | < .0001 | 1.116 | < .0001 | 1.071 | .0068 |
| Alcohol abuse (6) | 0.7 | 1.5 | 0.7 | 1.4 | 0.7 | 1.6 | 1.021 | .6483 | 1.036 | .4595 | 1.025 | .6087 |
| Drug abuse (6) | 0.3 | 1.1 | 0.3 | 1.1 | 0.4 | 1.3 | 1.114 | .0458 | 1.115 | .0487 | 1.098 | .0963 |
| Somatoform disorder (5) | 1.4 | 1.3 | 1.3 | 1.3 | 1.8 | 1.3 | 1.291 | < .0001 | 1.267 | < .0001 | 1.173 | .0033 |
| Hypochondriasis (5) | 0.9 | 1.5 | 0.9 | 1.4 | 1.2 | 1.6 | 1.132 | .0043 | 1.124 | .0083 | 1.058 | .2233 |
| Bulimia (10) | 2.6 | 3.1 | 2.3 | 3.0 | 3.9 | 3.4 | 1.155 | < .0001 | 1.142 | < .0001 | 1.130 | < .0001 |
| HAM-D-17 (ROA) | 20.4 | 6.6 | 20.0 | 6.7 | 22.2 | 5.9 | 1.051 | < .0001 | 1.049 | < .0001 | 0.973 | .2481 |
| IDS-C30 (ROA) | 35.8 | 11.6 | 34.4 | 11.6 | 41.9 | 9.6 | 1.061 | < .0001 | 1.059 | < .0001 | 1.440 | < .0001 |
| QIDS-SR16 | 15.4 | 4.2 | 15.0 | 4.2 | 17.1 | 3.6 | 1.131 | < .0001 | 1.122 | < .0001 | 1.098 | < .0001 |
| Modified IDS-C30 (ROA)[f] | 29.3 | 9.4 | 28.6 | 9.4 | 32.4 | 8.4 | 1.046 | < .0001 | 1.045 | < .0001 | | |

[a]Based on denominator of 1455 due to missing data on 45 patients.
[b]Significant at $p < .05$.
[c]Adjusted for sex, age, and age at onset of first MDE.
[d]Adjusted for above items as well as severity (modified IDS-C30).
[e]Numbers in parentheses indicate the total number of items on the Psychiatric Diagnostic Screening Questionnaire used to screen for each concurrent condition. The mean values shown indicate the average number of items relevant to each condition that was endorsed by subjects in the atypical and nonatypical groups.
[f]Modified IDS-C30 score is obtained by subtracting the items for defining atypical depression from IDS-C30 total score.
Abbreviations: GAD = generalized anxiety disorder, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IDS-C30 = 30-item Inventory of Depressive Symptomatology-Clinician Rating, MDE = major depressive episode, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology, ROA = research outcomes assessor.

For example, anxious mood, concentration/decision-making, self-outlook, future outlook, and involvement were statistically associated with atypical features prior to adjusting for severity but not afterward. Gastrointestinal symptoms, psychomotor agitation, and sympathetic arousal also became nonsignificant after the severity adjustment. Unexpectedly, "low energy and fatigability" is also no longer associated, but "leaden paralysis/physical energy" is. Adjusting for severity revealed associations between atypical depression and symptoms of disturbed pleasure/enjoyment and all 3 types of insomnia that had not been present prior to adjustment. As expected, the only symptoms that were reported significantly more frequently by patients with nonatypical depression (before and after adjusting for severity) were decreased appetite and decreased weight.

## DISCUSSION

Our results suggest that the characteristics that differentiate patients with and without atypical depression in this broad population of depressed outpatients are similar to characteristics frequently reported in other research populations of patients with atypical depressions. That is, many of the previously identified characteristics of atypical depression seem to apply to a broader group of patients with atypical features and may not be restricted to research populations.

A number of features were associated with depression with atypical features. Although concurrent psychiatric symptoms, especially those associated with several specific anxiety disorders (e.g., GAD, OCD, panic disorder, social phobia, PTSD, and agoraphobia) have frequently been cited as associated with atypical depression, only some of these associations remained significant after accounting for severity. In this STAR*D population, drug and alcohol abuse were not associated with atypical features. This lack of an association is consistent with most,[12,13,29] but not all,[11] studies.

Previous studies of atypical depression have suggested that patients with atypical features have an earlier onset and a more chronic course.[4,10,11,13,14] The present results also support an earlier age at onset in atypical depression, as reported by Stewart et al.[4] and Nierenberg et al.[49] However, there was no association with the length of the current MDE or the total length of illness.

**Table 3. Percentage of Patients With Nonatypical or Atypical Depression Reporting the Presence of Individual Baseline IDS-C30 (ROA) Items[a]**

| IDS-C30 (ROA) Item | Nonatypical Depression, % (N = 1191 [81.9%[b]]) | Atypical Depression, % (N = 264 [18.1%[b]]) | Unadjusted p Value | Adjusted[c] p Value | Adjusted[d] p Value |
|---|---|---|---|---|---|
| Sleep onset insomnia | 69.9 | 71.6 | .5904 | .7366 | .0195 |
| Mid-nocturnal insomnia | 83.4 | 82.9 | .8474 | .9561 | .0468 |
| Early morning insomnia | 55.7 | 54.2 | .6386 | .7641 | .0113 |
| Hypersomnia | 21.2 | 43.6 | < .0001 | < .0001 | < .0001 |
| Sad mood | 96.5 | 98.5 | .1011 | .1391 | .6656 |
| Irritable mood | 78.8 | 89.8 | < .0001 | .0003 | .0425 |
| Anxious mood | 76.9 | 85.6 | .0021 | .0024 | .2321 |
| Reactivity of mood | 71.8 | 74.2 | .4364 | .6007 | .0794 |
| Mood variation | 45.8 | 47.2 | .6823 | .9300 | .3202 |
| Quality of mood | 74.0 | 73.9 | .9545 | .9610 | .1359 |
| Decreased appetite | 49.8 | 35.2 | < .0001 | < .0001 | < .0001 |
| Increased appetite | 17.6 | 45.5 | < .0001 | < .0001 | < .0001 |
| Decreased weight | 35.7 | 22.4 | < .0001 | < .0001 | < .0001 |
| Increased weight | 16.6 | 47.4 | < .0001 | < .0001 | < .0001 |
| Concentration/decision-making | 88.5 | 95.1 | .0023 | .0034 | .3158 |
| Self-outlook | 80.2 | 89.8 | .0004 | .0015 | .1353 |
| Future outlook | 77.7 | 87.5 | .0005 | .0015 | .3445 |
| Suicidal ideation | 47.6 | 53.8 | .0697 | .0546 | .6926 |
| Involvement | 86.1 | 93.9 | .0008 | .0013 | .3232 |
| Low energy/fatigability | 90.1 | 96.6 | .0013 | .0036 | .1680 |
| Disturbed pleasure/enjoyment | 68.8 | 70.8 | .5227 | .5861 | .0081 |
| Sexual interest | 62.7 | 68.9 | .0544 | .0804 | .5877 |
| Psychomotor slowing | 60.8 | 77.6 | < .0001 | < .0001 | .0012 |
| Psychomotor agitation | 59.4 | 69.7 | .0021 | .0012 | .1777 |
| Somatic (pain) complaints | 73.0 | 84.5 | .0001 | .0004 | .0393 |
| Sympathetic arousal | 65.5 | 73.5 | .0128 | .0165 | .9587 |
| Panic/phobic symptoms | 34.6 | 51.5 | < .0001 | < .0001 | .0078 |
| Gastrointestinal | 43.6 | 54.2 | .0020 | .0023 | .1186 |
| Interpersonal sensitivity | 54.3 | 82.6 | < .0001 | < .0001 | < .0001 |
| Leaden paralysis/physical energy | 38.2 | 75.4 | < .0001 | < .0001 | < .0001 |

[a]p Values significant at < .05.
[b]Based on denominator of 1455 due to missing data on 45 patients.
[c]Adjusted for sex, age, and age at onset of first major depressive episode.
[d]Adjusted for above items as well as severity (modified IDS-C30).
Abbreviations: IDS-C30 = 30-item Inventory of Depressive Symptomatology-Clinician Rating, ROA = research outcomes assessor.

In several instances, analyses showing significant differences between patients with and without atypical features were not significant when rerun adjusting for severity. How should one interpret this finding? Since it is unclear whether to attribute the increased severity of depression in patients with atypical features to their atypicality, or if increased severity confers an increased likelihood of having atypical features, or if some third unmeasured variable is influencing both, it is unclear whether to consider the adjusted or unadjusted values as more informative. Both values are presented, allowing the reader to decide which to use. Thus, for example, length of illness (i.e., years since onset), which was not significantly different between groups in the unadjusted analysis, became significant with adjustment for age, sex, and age at onset, but was then not significant after an adjustment for severity. Likelihood of several comorbid disorders (GAD, panic disorder, PTSD, drug abuse, and hypochondriasis) differed between groups in the unadjusted and adjusted analyses, but these between-group differences were lost when the analyses adjusted for severity. Finally, several symptoms were only significantly different between groups in the analysis that included all the adjustments. The appearance of the 3 insomnia items plus the pleasure/enjoyment item as being different between groups only in the final analysis, which adjusted for severity, may be partially definitional since hypersomnia and significant mood reactivity are definitional items for atypical depression; hence, insomnia and loss of pleasure/enjoyment ought to be more common in the nonatypical group.

We leave it to the reader to decide whether these results demonstrate that (1) depressed patients with atypical features are more likely to also have anxiety symptoms, and that is why they have greater severity (so it is inappropriate to adjust for severity) or (2) more severe patients are more likely to have both anxious and atypical symptoms (so the adjustment for severity appropriately removes its significance).

The prevalence of atypical depression in this sample (18.1%, with a 95% confidence interval of 15.6% to 19.6%) was lower than rates reported in previous clinical studies (22%–36%).[29,30] Our prevalence rate is much closer to that calculated by Horwath et al.,[11] who rean-

alyzed data from the Epidemiologic Catchment Area study of 5 U.S. communities. Our lower rate may not be surprising if one considers that different methods for identifying atypical depression were used in all of these studies. However, it is important to consider the possible reasons why we identified a lower rate. Likely explanations for our lower rate include the chance that we failed to detect all the patients who have atypical features or the possibility that our sample may not have contained the expected ratio of depressed patients with atypical features.

Failure to detect all of the depressed patients with atypical features could have occurred due to the process used to enroll patients and identify atypical features. The post hoc application of our diagnostic algorithm may have underestimated the prevalence of the atypical subtype. A cursory review of the frequency distribution of atypical versus nonatypical depression using looser operational definitions of atypical features yielded larger percentages, ranging from 26.7% to 49.0% of patients with atypical depression.

Several possibilities come to mind when we consider the possibility that our algorithm underestimated the prevalence of depression, for example, that our sample may not have contained the expected ratio of patients with atypical features. A study such as STAR*D, which excludes participants who already have not responded to a trial of medication during their current depressive episode, is likely to underestimate the prevalence of a subtype of depression that is historically treatment resistant. One could also speculate that the enrollment of patients from nontertiary settings (nearly one third of these first 1500 STAR*D patients were treated in a primary care setting) could lead to the inclusion of patients with less chronic or less severe symptoms of depression, therefore diluting the ratio of patients with atypical versus typical depression. This dilution could happen as a result of a selection bias on the part of the evaluator (primary care physician) to enroll mildly depressed patients or due to an overpresentation of such patients in the primary care setting. However, preliminary data comparing the HAM-D-17 scores for the presenting depressive episode in the specialty clinics and the primary care settings have indicated that patients did not differ in the severity of their current depressive episode.[50] In addition, our results show that atypical depression was present in 18.7% of patients in our primary care settings compared to 17.8% in our specialty care settings (OR = 0.934, p = .6446).

One might also have speculated that different rates of atypical depression could have been found among patients with different insurance types on the basis of 2 assumptions. The first assumption is that patients with more chronic depressions are less likely to have private insurance, and the second is that chronic depression is associated more frequently with atypical features. However, rates of atypical depression did not differ among the 3 insurance types (private insurance, public insurance, and no insurance, Table 1), and, at least in this population, there was no difference in chronicity between patients with and without atypical features.

A large number of comparisons were made without correcting p values as protection against type 1 error. As these were intended as exploratory analyses, we considered this acceptable. We therefore present the data without correction, pointing out that if one took a more conservative view, differences with larger p values would not be considered significant. For example, if one used an alpha of .01 instead of .05, marital status, sympathetic arousal, and comorbid panic disorder and drug abuse would not be considered significant in the unadjusted analyses, and comorbidity of OCD as well as symptoms of insomnia and irritable mood would fail significance in the analyses adjusting for severity. Most differences would remain significant, however, so we consider our overall conclusions to hold whether one chooses to apply an exploratory significance level or a more stringent one.

One potential problem with our algorithm is that, unlike the DSM-IV criteria for depression with atypical features, we did not try to exclude patients who also met criteria for melancholic features. Our reasoning was that, although an algorithm was made for converting IDS scores into a diagnosis of melancholic features, this does not have validation, and not all melancholic features could be addressed. Because the resulting assessment of melancholic features must be considered suspect to an unknown degree, we elected to ignore those who met the algorithm for melancholic features but report that 57 patients, or 4% of the total sample and 21% of those meeting the criteria we used for atypical features, also met the algorithm for melancholic features.

In considering comorbid disorders and individual symptoms, which were found to be more common in depressed patients with atypical features in the unadjusted analyses, but not to be different when controlling for severity, one might wonder whether an overreporting bias might account for both. That is, if depressed patients with atypical features have a tendency (perhaps resulting from their inherent tendency to overreact) to overreport in general, then, relative to other patients, they would endorse both general depressive symptoms and the symptoms of other disorders. While this confound is intriguing, we have no way to assess the degree to which it might play a role in the findings. An overreporting bias would not account for age, sex, or marital status differences, however.

One might wonder how reliable the various variables were. Because the majority were obtained only by self-report, it is not possible to assess reliability in this data set. However, the majority of rating instruments have been shown in other samples to have adequate interrater reliability.[39–48]

## CONCLUSION

In summary, our findings in the large group of subjects in the STAR*D trial confirm that many observations previously reported in research-oriented settings also apply to this subject pool from an effectiveness study. More specifically, our observations are consistent with findings that patients with atypical depression have an earlier onset of illness, and that both medical and psychiatric comorbidities are commonplace. Future reports from the complete STAR*D cohort will describe whether there are significant differences in treatment outcome for atypical depression patients. The findings from this preliminary initial group of 1500 patients will be tested in the larger remaining group of 2500 patients.

*Drug names:* bupropion (Wellbutrin and others), citalopram (Celexa and others), fluoxetine (Prozac and others), phenelzine (Nardil).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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