Epidemiology of Major Depression With Atypical Features: Results From the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

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ABSTRACT

Objective: To examine prevalence, correlates, comorbidity and treatment-seeking among individuals with a lifetime major depressive episode (MDE) with and without atypical features.

Method: Data were derived from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions, a large cross-sectional survey of a representative sample (N = 43,093) of the US population that assessed psychiatric disorders using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-*DSM-IV* Version (AUDADIS-IV). Comparison groups were defined based on the presence or absence of hypersomnia or hyperphagia in individuals who met criteria for lifetime *DSM-IV* MDE.

Results: The presence of atypical features during an MDE was associated with greater rates of lifetime psychiatric comorbidity, including alcohol abuse, drug dependence, dysthymia, social anxiety disorder, specific phobia, and any personality disorder (all *P* values < .05), except antisocial personality disorder, than MDE without atypical features. Compared with the latter group, MDE with atypical features was associated with female gender, younger age at onset, more MDEs, greater episode severity and disability, higher rates of family history of depression, bipolar I disorder, suicide attempts, and larger mental health treatment-seeking rates (all *P* values < .05).

Conclusions: Our data provide further evidence for the clinical significance and validity of this depressive specifier. Based on the presence of any of the 2 reversed vegetative symptoms during an MDE, most of the commonly cited validators of atypical depression were confirmed in our study. Major depressive episode with atypical features may be more common, severe, and impairing than previously documented.

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Preparations for the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), have brought to the forefront of the research agenda the need to reexamine the classification of depressive disorders and their subtypes.[1] In the study of depressive disorders, few questions have generated more controversy than the validity of atypical depression as an independent nosologic entity. Despite decades of research, debate continues regarding its clinical presentation, associated characteristics, and prognostic value.[2–27] *DSM-IV* classifies as atypical major depressive episodes (MDEs) those in which the subject experiences mood reactivity plus 2 or more of the following features: increased appetite or weight gain, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity.[28]

In recent years, community[29–31] and clinical studies[32,33] have provided some support for the validity of a simplified diagnostic approach that emphasizes reversed vegetative symptoms to identify a major depression with atypical features. This approach, which identifies cases of major depression with atypical features based on the presence of hypersomnia and hyperphagia, has been shown in previous studies[29–33] to identify this depressive subtype with reasonable accuracy. Further support for the reversed vegetative approach is provided by data from those samples, which suggest that the reverse vegetative symptom diagnostic approach allows for identification of a depressed group of individuals who closely resemble those with *DSM-IV* atypical depression, including younger age at onset, female gender, higher rates of comorbid anxiety disorders, greater disability, and higher rates of health care service utilization.

Clinical studies have suggested that the depressive phase of bipolar disorder is characterized by atypical symptoms, but few studies have examined the prevalence of reversed vegetative symptoms in a nationally representative sample of depressed bipolar individuals. The present study was designed to address previous limitations and to present data on the epidemiology of major depression with atypical features using the 2001–2002 National Institute on Alcohol Abuse and Alcoholism's (NIAAA) National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

METHOD

NESARC Sample

The 2001–2002 NESARC is a survey of a representative sample of the United States sponsored by the NIAAA.[34] The target population was individuals age 18 years and older in the civilian noninstitutional population residing in households and group quarters. The survey included those residing in the continental United States, District of Columbia, Alaska, and Hawaii. Face-to-face personal interviews were conducted with 43,093 respondents. The survey response rate was 81%. Blacks, Hispanics, and young adults (aged 18–24) were oversampled with adjustments for nonresponse and oversampling. Weighted data were

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Clinical Points

- Individuals with a major depressive episode (MDE) with atypical features can be distinguished from individuals without them based on the presence of 1 or both reversed vegetative symptoms (ie, hypersomnia or hyperphagia).
- An MDE with atypical features (ie, presence of reversed vegetative symptoms) is associated with greater rates of lifetime psychiatric comorbidity, number of episodes, individual episode severity, disability, and suicide attempts than an episode without those features.
- Individuals with an MDE with atypical features had significantly higher rates of bipolar I disorder than those without atypical features.

then adjusted to be representative of the US civilian population based on the 2000 Census.

Sociodemographic Measures

Sociodemographic measures included age, sex, race-ethnicity, nativity, marital status, place of residence, and region of the country. Socioeconomic measures included education, personal and family income, and insurance type.

Diagnostic Assessment

DSM *Diagnostic Interview.* The Alcohol Use Disorder and Associated Disabilities Interview Schedule—*DSM-IV* Version (AUDADIS-IV), a structured diagnostic interview designed for lay interviewers, was used to generate diagnoses.[35]

Lifetime Major Depressive Episode With and Without Atypical Features

The assessment of mood disorders in the NESARC has been described in detail elsewhere.[36–38] Consistent with *DSM-IV* diagnostic rules, individuals who endorsed depressed mood or anhedonia completed the major depressive episode module, whereas all other individuals skipped out of that module. An MDE was diagnosed when at least 2 weeks of persistent depressed mood or anhedonia were present, accompanied by a total of at least 5 or more of the 9 *DSM-IV* symptoms of major depressive episode during the episode. Lifetime *DSM-IV* MDE was defined as having at least 1 MDE over the life course (including major depressive disorder [MDD] and bipolar I and bipolar II disorders). To minimize respondents' burden, the assessment of MDE focused on the most severe episode.

Major depressive disorder was defined as having at least 1 MDE over the life course without history of manic, mixed, or hypomanic episodes. In contrast, *bipolar depression* was defined as having 1 lifetime MDE among respondents with history of manic or hypomanic episodes. Among respondents with a lifetime MDE thus defined, and consistent with previous epidemiologic studies,[29–31] respondents with the presence of reversed vegetative symptoms, ie, hyperphagia or hypersomnia (or both), were classified as having MDE with atypical features. *Hyperphagia* was defined as (1) gain of at least 2 pounds a week, or 10 pounds altogether, during the MDE or (2) desire to eat a lot more than usual for no special reason on most days for at least 2 weeks. *Hypersomnia* was defined as sleeping more than usual nearly every day for at least 2 weeks.

Individuals were classified as having MDE with atypical features if they reported at least 1 reversed (ie, atypical) vegetative symptom, regardless of whether or not they also reported any typical vegetative symptoms. Respondents who met criteria for lifetime MDE but did not report any atypical features were classified as having MDE without atypical features. In summary, the main 2 groups in these analyses are mutually exclusive, since an MDE with atypical features include only respondents who endorsed hypersomnia or hyperphagia or both during a lifetime MDE, whereas the comparison group MDE without atypical features includes those respondents that endorsed neither hyperphagia nor hypersomnia during a lifetime MDE.

To examine the robustness of our findings, we considered several operationalizations of the definition of atypical depression based on the number of reversed vegetative symptoms (1 versus 2) and the presence or absence of typical vegetative symptoms during an MDE with atypical features (a summary of the operationalizations is shown in Table 1). Individuals with atypical symptoms and no typical vegetative symptoms were considered to have MDE with *strict* atypical features, whereas those with atypical vegetative symptoms and at least 1 typical vegetative symptom were considered to have *broad* atypical features.

Combining the number of symptoms and whether atypical features were broad or strict, resulted in 4 mutually exclusive groups: (1) MDE with *broad* atypical features with *only 1* reversed vegetative symptom; (2) MDE with *broad* atypical features with *both* reversed vegetative symptoms; (3) MDE with *strict* atypical features with *only 1* reversed vegetative symptom; and (4) MDE with *strict* atypical features with *both* reversed vegetative symptoms. The first 2 groups considered together comprised the "MDE with broad atypical features (1 or 2 symptoms)" group, whereas the other 2 groups considered jointly constituted the "MDE with strict atypical features (1 or 2 symptoms)" group.

We focused our main analyses on individuals with MDE with broad atypical features (1 or 2 symptoms) because previous studies included in their analyses all individuals with atypical symptoms, regardless of whether or not they also had any typical symptoms. However, to guard against the possibility of variations in the results due to different definitions of the MDE with atypical features group, we conducted identical analyses separately using alternative operationalizations of atypical depression (see Table 1). The following additional comparisons were conducted: (1) each of the 4 subgroups of MDE with atypical features separately (ie, broad and strict with 1 or both atypical symptoms) versus MDE without atypical features and (2) individuals with 1 atypical feature MDE versus those with both atypical

Table 1. Definitions of Major Depressive Episode (MDE) With Atypical Features[a]

Definition	Reversed Vegetative Symptoms[b]	Typical Vegetative Symptoms[c]
1. MDE without atypical features (reference group for all analyses)	No reversed vegetative symptoms present	One or both typical vegetative symptoms may be present but are not required
2. MDE with atypical features[d]	At least 1 reversed vegetative symptom present	One or both typical vegetative symptoms may be present but are not required
3. MDE with *broad* atypical features with only 1 reversed vegetative symptom	One reversed vegetative symptom is present, but not both	At least 1 typical vegetative symptom is present
4. MDE with *broad* atypical features with 2 reversed vegetative symptoms	Both reversed vegetative symptoms present	At least 1 symptom typical vegetative symptom is present
5. MDE with *strict* atypical features with 1 reversed vegetative symptom	One symptom reversed vegetative is present, but not both	No typical vegetative symptoms present
6. MDE with *strict* atypical features with 2 reversed vegetative symptoms	Both reversed vegetative symptoms are present	No typical vegetative symptoms present
7. MDE with *broad* atypical features (1 or 2 reversed vegetative symptoms)[e]	One or both reversed vegetative symptoms are present	At least 1 typical vegetative symptom is present
8. MDE with *strict* atypical features (1 or 2 reversed vegetative symptoms)[f]	One or both reversed vegetative symptoms are present	At least 1 typical vegetative symptom is present

[a]Refer to the Method section for reference.
[b]Reversed vegetative symptoms = hypersomnia or hyperphagia.
[c]Typical vegetative symptoms = insomnia or loss of weight/appetite.
[d]Individuals were classified as having MDE with atypical features if they reported *1 or both* reversed vegetative symptoms: hyperphagia or hypersomnia. This was done regardless of whether or not respondents also reported at least 1 typical vegetative symptom during the MDE.
[e]Comprises all individuals in groups 3 and 4.
[f]Comprises all individuals in groups 5 and 6.

features, regardless of whether they belonged to the broad or strict atypical groups.

Furthermore, to examine whether MDE with atypical features is different in individuals with bipolar disorder than in those with MDD, we compared individuals with MDE with broad atypical features (1 or 2 symptoms) versus individuals with MDE without atypical features, each group being stratified by whether individuals had MDD or bipolar disorder. In addition, we directly compared individuals with bipolar depression with atypical features versus individuals with MDD with atypical features.

We present the results of the main analyses comparing the MDE with broad atypical features group (1 or 2 symptoms) versus the MDE without atypical features group and indicate the main differences from all other comparisons. Results from the direct comparisons between bipolar depression with atypical features and MDD with atypical features are presented in supplementary tables. All other results are available upon request.

As reported in detail elsewhere, the test-retest reliability[38,39] and validity[36,40–42] of AUDADIS-IV measures of MDD and MDE[39] are good (0.64–0.67), and a clinical reappraisal study[40] of major depression diagnoses showed good agreement between AUDADIS-IV and psychiatrist diagnoses ($\kappa = 0.64–0.68$).

Other Psychiatric Disorders

The use of AUDADIS-IV for assessments of *DSM-IV* lifetime anxiety disorders (generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobia), substance use disorders, and personality disorders, including avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial personality disorders, have been described in detail previously.[35,39,43,44] Reliability ($\kappa > 0.74$) and validity were good to excellent for substance use disorders[39,43,45,46] and were fair to good for anxiety ($\kappa = 0.40–0.60$) and personality ($\kappa = 0.40–0.67$) disorders.[39,40]

Other Measures

Age at onset, number of episodes, duration of only or longest episode (if more than 1), and use of alcohol or drugs to help relieve symptoms of depression were assessed. To be consistent with previous research,[47,48] the study also incorporated measures of known risk factors for MDE, including (1) family history of depression; (2) parental absence or separation from a biologic parent before age 18; (3) parental loss due to death before age 18; (4) early-onset anxiety, operationalized as onset of any anxiety disorder before age 18; (5) conduct disorder; and (6) history of divorce or loss of spouse. Although it was not used to classify individuals as having atypical symptoms, we assessed the presence of lifetime rejection sensitivity regardless of whether depressed or not, defined as avoiding getting involved with people unless the respondent was certain of being liked.

Overall health status was assessed by self-report by asking respondents, "In general, would you say your health is excellent, very good, fair, or poor?" Individuals were classified as having received mental health treatment for MDE if they (1) visited a counselor, therapist, doctor, or psychologist; (2) were a patient in a hospital for at least 1 night; (3) visited an emergency room; or (4) were prescribed any psychotropic medications for the treatment of MDE.

Statistical Analysis

Weighted cross-tabulations were used to calculate prevalence rates for each study group. A series of logistic regression analyses, adjusting for sociodemographic characteristics and total number of criteria, yielded adjusted odds ratios, indicating associations between MDE subtype and (1) sociodemographic characteristics; (2) each specific

12-month and lifetime psychiatric disorder; (3) course, clinical symptoms, psychopathological correlates, and disability; and (4) 12-month and lifetime mental health service utilization. In these sets of analyses, the group without atypical features served as the reference group. We consider 2 percentages to differ significantly if the 95% confidence interval (95% CI) of their odds ratio (OR) does not include 1.[49] Standard errors and 95% CIs for all analyses were estimated using SUDAAN.[50]

RESULTS

Prevalence and Sociodemographic Correlates

The prevalence of lifetime MDE with atypical features was 10.23%, while the prevalence of MDE without atypical features was 6.31%. Among individuals with atypical features, 43.54% had only hypersomnia, 23.88% had only hyperphagia, and 32.58% had both features.

Individuals with MDE with atypical features were significantly more likely than those without atypical features to be female, US born, younger than age 29, and never married; to live in urban areas; and to have an annual income lower than $19,000 and no insurance (Table 2).

Table 2. Prevalence and Sociodemographic Characteristics of Individuals With a Lifetime Major Depressive Episode (MDE) With and Without Atypical Features

	MDE With Atypical Features[a] (n = 4,420)		MDE Without Atypical Features (n = 2,704)			
Variable	%	95% CI	%	95% CI	OR	95% CI
Sex						
Male	30.70	28.94–32.52	39.92	37.64–42.25	0.67	0.58–0.76
Female	69.30	67.48–71.06	60.08	57.75–62.36	1.00	1.00–1.00
Race/ethnicity						
White	76.91	74.07–79.53	77.86	75.23–80.29	1.00	1.00–1.00
Black	8.46	7.27–9.81	7.68	6.56–8.97	1.11	0.95–1.31
Native American	3.47	2.72–4.40	3.10	2.29–4.18	1.13	0.77–1.67
Asian	2.44	1.59–3.70	3.16	2.27–4.39	0.78	0.49–1.25
Hispanic	8.73	6.88–11.01	8.20	6.60–10.16	1.08	0.92–1.27
Nativity						
US-born	91.93	89.75–93.68	89.68	87.14–91.76	1.31	1.09–1.58
Foreign-born	8.07	6.32–10.25	10.32	8.24–12.86	1.00	1.00–1.00
Age, y						
18–29	26.47	24.82–28.20	17.33	15.39–19.46	1.00	1.00–1.00
30–44	33.93	32.33–35.56	32.05	29.87–34.32	0.69	0.59–0.82
45–64	33.32	31.73–34.96	38.09	35.81–40.43	0.57	0.49–0.68
65+	6.28	5.52–7.13	12.52	11.06–14.15	0.33	0.26–0.41
Education						
< High school	13.64	12.26–15.14	15.53	13.76–17.48	0.84	0.70–1.02
High school	27.27	25.42–29.21	27.66	25.51–29.91	0.95	0.83–1.09
College	59.09	56.88–61.26	56.81	54.46–59.13	1.00	1.00–1.00
Individual income, $						
0–19,000	54.41	52.18–56.63	48.84	46.40–51.27	1.00	1.00–1.00
20,000–34,000	22.04	20.30–23.89	22.33	20.37–24.42	0.89	0.75–1.04
35,000–69,000	18.42	16.70–20.27	20.95	19.02–23.02	0.79	0.68–0.92
> 70,000	5.12	4.15–6.31	7.88	6.49–9.54	0.58	0.45–0.76
Family income, $						
0–19,000	25.46	23.68–27.33	24.17	22.09–26.38	1.00	1.00–1.00
20,000–34,000	21.50	20.01–23.06	20.55	18.81–22.41	0.99	0.85–1.15
35,000–69,000	31.91	30.14–33.73	31.21	29.11–33.39	0.97	0.83–1.14
> 70,000	21.13	19.23–23.17	24.07	21.72–26.59	0.83	0.70–1.00
Marital status						
Married	53.27	51.33–55.20	56.57	54.08–59.03	1.00	1.00–1.00
Widowed	22.31	21.00–23.67	26.85	24.93–28.87	0.88	0.78–1.00
Never married	24.42	22.77–26.15	16.57	14.62–18.73	1.56	1.31–1.87
Urbanicity						
Urban	79.63	76.07–82.78	77.26	73.28–80.79	1.00	1.00–1.00
Rural	20.37	17.22–23.93	22.74	19.21–26.72	0.87	0.76–0.99
Region						
Northeast	18.87	13.58–25.61	17.35	12.21–24.07	1.08	0.89–1.30
Midwest	24.68	19.16–31.18	25.20	19.68–31.67	0.97	0.82–1.14
South	32.39	26.81–38.51	33.67	28.14–39.68	0.95	0.81–1.11
West	24.06	17.94–31.47	23.78	18.01–30.70	1.00	1.00–1.00
Insurance						
Private	66.02	64.04–67.94	68.90	66.37–71.33	1.00	1.00–1.00
Public	13.77	12.42–15.25	13.52	11.88–15.36	1.06	0.88–1.28
No insurance	20.21	18.65–21.87	17.57	15.77–19.53	1.20	1.03–1.39

[a]MDE with atypical features defined as presence of *1 or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least 1 typical vegetative symptom during the MDE.

Rates of *DSM-IV* Disorders

Lifetime rates of any Axis I psychiatric disorder, except alcohol dependence, drug abuse, nicotine dependence, panic disorder, generalized anxiety disorder, and pathological gambling, were significantly higher among individuals with lifetime MDE with atypical features than among those without atypical features. Furthermore, all personality disorders, except antisocial personality disorder, were significantly more common among individuals with MDE with atypical features than among those without them (Table 3).

Course and Clinical Correlates

Individuals with MDE with atypical features were significantly younger at the time of their first MDE, had significantly more episodes, and reported a higher total number of criteria than those without atypical features. They were also significantly more likely than those without atypical features to use drugs or medications to help relieve symptoms of depression, to have family history of depression and early-onset anxiety, and to report subjective sensitivity to rejection. They were less likely than individuals without atypical features to report childhood parental loss or history of divorce/loss of spouse. Individuals with bipolar I (but not II) disorder were more likely than those with MDD to experience atypical features (Table 4).

Symptoms and Health Status

In addition, individuals with MDE with atypical features were significantly more likely to endorse anhedonia, fatigue, psychomotor agitation, worthlessness, guilt, indecisiveness, and irritability, and they were less likely to report motor retardation. The former group was also more likely to report thoughts of suicide and of own death, and they also reported

Table 3. Lifetime Prevalence of Comorbid Psychiatric Disorders in Individuals With a Lifetime Major Depressive Episode (MDE) With and Without Atypical Features

	MDE With Atypical Features (n = 4,420)[a]		MDE Without Atypical Features (n = 2,704)			
Variable	%	95% CI	%	95% CI	AOR[c]	95% CI
Any psychiatric disorder	83.43	82.10–84.68	77.91	75.88–79.82	1.35	1.17–1.57
Any Axis I disorder	78.88	77.28–80.40	73.81	71.55–75.96	1.30	1.13–1.49
Any substance use disorder[b]	58.81	56.90–60.70	53.92	51.46–56.37	1.22	1.07–1.39
Alcohol use disorder	45.36	43.37–47.36	40.90	38.40–43.44	1.28	1.13–1.45
Alcohol abuse	20.21	18.60–21.92	17.33	15.60–19.21	1.31	1.12–1.54
Alcohol dependence	25.15	23.44–26.93	23.57	21.33–25.96	1.09	0.94–1.27
Drug use disorder	22.46	20.69–24.35	17.95	16.14–19.92	1.28	1.07–1.52
Drug abuse	13.57	12.17–15.11	12.28	10.81–13.91	1.07	0.88–1.31
Drug dependence	8.89	7.83–10.08	5.67	4.64–6.91	1.55	1.21–1.99
Nicotine dependence	33.83	31.83–35.90	31.91	29.79–34.11	1.06	0.94–1.20
Dysthymia	16.35	15.04–17.75	13.50	11.86–15.32	1.33	1.11–1.59
Any anxiety disorder	46.94	44.87–49.02	41.82	39.28–44.42	1.16	1.01–1.33
Panic disorder	18.30	16.90–19.79	15.64	13.99–17.45	1.13	0.95–1.34
Social anxiety disorder	16.94	15.47–18.52	11.95	10.43–13.66	1.43	1.19–1.73
Specific phobia	24.23	22.52–26.02	19.38	17.38–21.55	1.20	1.02–1.41
Generalized anxiety disorder	18.26	16.79–19.82	16.09	14.33–18.03	1.18	1.00–1.40
Pathological gambling	0.83	0.59–1.16	1.14	0.70–1.85	0.83	0.48–1.45
Psychotic disorder	1.47	1.06–2.03	0.81	0.51–1.29	1.93	1.05–3.58
Any personality disorder	40.12	38.37–41.90	32.10	29.76–34.53	1.32	1.16–1.51
Avoidant personality disorder	10.56	9.52–11.69	6.52	5.35–7.93	1.52	1.20–1.93
Dependant personality disorder	2.66	2.11–3.36	0.78	0.50–1.22	3.20	1.93–5.30
Obsessive-compulsive disorder	21.55	19.90–23.29	17.27	15.61–19.07	1.29	1.11–1.50
Paranoia personality disorder	16.04	14.70–17.49	11.53	9.99–13.27	1.32	1.09–1.60
Schizoid personality disorder	10.62	9.47–11.89	7.90	6.64–9.38	1.31	1.06–1.62
Histrionic personality disorder	6.90	5.96–7.97	4.15	3.35–5.13	1.52	1.18–1.97
Antisocial personality disorder	9.42	8.32–10.64	8.29	7.00–9.79	1.12	0.88–1.43

[a]Major depressive episode with atypical features was defined as presence of *1 or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least 1 typical vegetative symptom during the MDE.
[b]Any substance use disorder, including alcohol use disorder, drug use disorder, and nicotine dependence.
[c]Adjusted for sex, US born individuals, age, annual income, marital status, region, urbanicity, and number of criteria.
Abbreviation: AOR = adjusted odds ratio.

Table 4. Clinical Characteristics Associated With a Lifetime Major Depressive Episode (MDE) With Atypical Features and MDE Without Atypical Features

	MDE With Atypical Features (n = 4,420)[a]		MDE Without Atypical Features (n = 2,704)			
Variable	Mean	95% CI	Mean	95% CI	Wald *F*	*P* Value
Age at onset, y	27.45	26.99–27.92	31.71	30.95–32.47	18.19	.0001
No. of episodes	6.01	5.44–6.58	4.30	3.75–4.85	18.76	.0001
Total no. of criteria	8.14	8.10–8.19	7.61	7.54–7.68	147.04	< .0001
	%		%		AOR[b]	95% CI
Use of alcohol to help relieve symptoms	21.09	19.55–22.72	20.23	18.34–22.25	1.09	0.93–1.27
Self-medication to help relieve symptoms	8.61	7.49–9.88	5.27	4.30–6.45	1.66	1.26–2.18
Family history of depression (only first-degree relatives)	66.82	64.88–68.70	60.49	58.08–62.86	1.28	1.13–1.44
Separation from a biologic parent (before age 18 years)	95.69	94.98–96.30	95.94	95.08–96.65	1.03	0.80–1.33
Childhood parental loss due to death (before age 18 years)	8.60	7.65–9.66	11.41	10.11–12.85	0.79	0.65–0.96
Conduct disorder	2.01	1.53–2.63	1.38	0.90–2.10	1.45	0.88–2.42
Early-onset anxiety (before age 18 years)[c]	46.77	44.04–49.53	40.58	37.12–44.13	1.24	1.06–1.44
History of divorce/loss of spouse	36.78	34.80–38.81	46.13	43.41–48.88	0.81	0.68–0.97
Rejection sensitivity[d]	13.92	12.72–15.21	9.58	8.19–11.17	1.41	1.15–1.72
Bipolar I disorder	13.99	12.64–15.47	8.51	7.28–9.92	1.61	1.32–1.98
Bipolar II disorder	6.56	5.77–7.45	6.77	5.55–8.23	0.85	0.66–1.09

[a]Major depressive episode with atypical features was defined as presence of *1 or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least 1 typical vegetative symptom during the MDE.
[b]Adjusted for sex, US born individuals, age, annual income, marital status, region, urbanicity, and number of criteria.
[c]Early-onset anxiety was defined as onset of any anxiety disorder before age 18.
[d]Lifetime rejection sensitivity was defined as avoiding getting involved with people unless the respondent was certain of being liked.
Abbreviation: AOR = adjusted odds ratio.

Table 5. Symptoms and Health Status Associated With a Lifetime Major Depressive Episode (MDE) With Atypical Features and MDE Without Atypical Features

	MDE With Atypical Features (n = 4,420)[a]		MDE Without Atypical Features (n = 2,704)			
Clinical Symptom	%	95% CI	%	95% CI	AOR	95% CI[b]
Lack of interest or pleasure	89.89	88.72–90.95	86.81	84.98–88.45	1.30	1.07–1.58
Fatigue	90.62	89.50–91.64	76.70	74.76–78.55	2.93	2.50–3.43
Motor retardation	49.87	47.96–51.79	63.49	60.93–65.98	0.58	0.51–0.66
Motor agitation	42.41	40.46–44.40	37.93	35.45–40.46	1.21	1.06–1.39
Worthlessness	66.82	65.00–68.60	60.28	58.13–62.38	1.32	1.16–1.50
Guilt	62.22	60.50–63.91	57.04	54.68–59.36	1.20	1.06–1.36
Trouble concentrating	85.71	84.29–87.02	86.24	84.54–87.78	0.90	0.77–1.06
Trouble making decisions	78.17	76.62–79.65	75.39	73.37–77.30	1.18	1.03–1.36
Irritability	56.51	54.84–58.16	46.66	44.20–49.13	1.32	1.18–1.48
Attempt suicide	13.29	12.13–14.53	8.78	7.52–10.24	1.45	1.17–1.81
Thoughts of suicide	42.64	40.87–44.42	34.84	32.64–37.10	1.32	1.18–1.48
Thoughts of own death	58.59	56.85–60.31	54.14	51.91–56.37	1.15	1.03–1.29
Overall health excellent to good	68.44	66.22–70.59	71.00	68.28–73.57	0.84	0.75–0.94
Overall health fair to poor	31.56	29.41–33.78	29.00	26.43–31.72	1.00	1.00–1.00
	Mean		Mean		Wald *F*	*P* Value
Physical component summary[c]	49.64	49.16–50.12	49.69	49.10–50.28	9.80	.0026
Mental component summary[c]	45.33	44.93–45.73	47.33	46.81–47.86	29.52	< .0001
Social Functioning Scale score[c]	46.74	46.29–47.19	48.24	47.67–48.80	21.83	< .0001
Role of Emotional Functioning Scale score[c]	46.08	45.63–46.53	47.73	47.16–48.30	33.51	< .0001
Mental Health Scale score[c]	44.95	44.52–45.39	46.49	45.96–47.01	16.52	.0001

[a]Major depressive episode with atypical features was defined as presence of *1 or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least 1 typical vegetative symptom during the MDE.
[b]Adjusted for sex, US born individuals, age, annual income, marital status, region, urbanicity, and number of criteria.
[c]12-Item Short Form Health Survey version 2 scores.
Abbreviation: AOR = adjusted odds ratio.

Table 6. Treatment-Seeking Rates in Individuals With a Lifetime Major Depressive Episode (MDE) With Atypical Features and MDE Without Atypical Features

	MDE With Atypical Features (n = 4,420)[a]		MDE Without Atypical Features (n = 2,704)			
Variable	%	95% CI	%	95% CI	AOR[b]	95% CI
Any lifetime treatment	64.80	62.92–66.63	56.01	53.75–58.25	1.43	1.27–1.61
Lifetime outpatient treatment seeking	58.73	56.81–60.62	49.42	47.02–51.82	1.39	1.24–1.56
Lifetime emergency room/hospital	10.96	9.79–12.26	8.41	7.16–9.86	1.25	1.01–1.56
Lifetime use of medication	49.73	47.52–51.94	37.83	35.69–40.01	1.67	1.49–1.88
Treatment seeking in the past 12 months	28.65	26.82–30.57	18.27	16.42–20.27	1.68	1.44–1.96
	Mean		Mean		Wald *F*	*P* value
Age when first sought treatment, y	31.04	30.41–31.67	34.97	33.95–35.98	1.6	.211
Time to treatment seeking, y	3.68	3.37–3.99	3.55	3.09–4.01	1.5	.2253

[a]Major depressive episode with atypical features was defined as presence of *1 or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least 1 typical vegetative symptom during the MDE.
[b]Adjusted for sex, US born individuals, age, annual income, marital status, region, urbanicity, and number of criteria.
Abbreviation: AOR = adjusted odds ratio.

significantly poorer overall health than individuals without atypical features (Table 5).

Treatment Seeking

Individuals with atypical features had significantly higher rates of mental health care utilization than those without atypical features (Table 6).

Analyses of Alternative Operationalizations of MDE With Atypical Features

Across all operationalizations of MDE with atypical features shown in Table 1, only minor differences arose when comparing MDE with atypical features to MDE without atypical features across sociodemographic, comorbidity, clinical characteristics and rates of treatment-seeking. The overall pattern of results remained the same. Similarly, the pattern of results of the main analyses held true when the analyses of MDE with atypical features versus MDE without atypical features were stratified by whether the individuals had MDD or bipolar disorder (all results available upon request).

By contrast, direct comparisons between bipolar depression with atypical features and MDD with atypical features yielded several significant differences. First, the odds of any lifetime Axis I psychiatric disorder (adjusted odds ratio [AOR], 2.19; 95% CI, 1.73–2.77), except alcohol abuse (AOR, 1.04; 95% CI, 0.82–1.33), and any personality disorder (AOR, 3.40; 95% CI, 2.85–4.05) were significantly greater among bipolar depression with atypical features than among

MDD with atypical features. Secondly, bipolar depression with atypical features had a significantly stronger association than MDD with atypical features to younger age at onset ($P < .0001$), higher number of criteria for MDE ($P < .0001$), and total number of episodes ($P < .0001$). Bipolar depression with atypical features was also more strongly associated than MDD with atypical features to greater rates of alcohol and drug use to help relieve symptoms of depression (AOR, 2.03; 95% CI, 1.64–2.51), higher rates of family history of depression (AOR, 1.90; 95% CI, 1.56–2.32), early-onset anxiety (AOR, 1.69, 95% CI, 1.39–2.05), and rejection sensitivity (AOR, 2.52; 95% CI, 2.01–3.16). Third, individuals with bipolar depression with atypical features were significantly more likely to report any *DSM-IV* symptom of depression, and thoughts of suicide (AOR, 1.87; 95% CI, 1.56–2.24) and suicide attempts (AOR, 2.61; 95% CI, 2.09–3.26), than individuals with MDD with atypical features. Finally, individuals with bipolar depression with atypical features exhibited a longer time to treatment-seeking ($P < .0001$) and had higher rates of any lifetime (AOR, 1.49; 95% CI, 1.21–1.83) and 12-month treatment seeking (AOR, 1.77; 95% CI, 1.36–2.30) than the latter group (eTables 1–5, available at PSYCHIATRIST.COM).

DISCUSSION

In a large, nationally representative sample, individuals with lifetime MDE with atypical features could be distinguished from those without atypical features by the presence of either reverse vegetative symptom (hypersomnia or hyperphagia). Individuals with atypical features exhibited higher rates of psychiatric comorbidity, greater symptom severity and disability, and higher rates of treatment-seeking than those without them. Furthermore, MDE with atypical features had more severe manifestations in the context of bipolar disorder than among individuals with MDD.

Confirming previous epidemiologic studies,[29,31] our study found that individuals with MDE with atypical features could be distinguished from those without them based on the presence of reversed vegetative symptoms. Across a broad range of operationalizations, the diagnosis of MDE with atypical features had significant associations with the prevalence of lifetime psychiatric comorbidity, the course and severity of the disorder, its degree of functional impairment, the association with bipolar I disorder, and the rates of mental health treatment seeking. Those differences held regardless of whether one or both reversed vegetative symptoms were endorsed, suggesting that there are no significant differences between individuals with 1 versus 2 atypical features. Furthermore, depressed individuals with broad versus strict atypical features had similar patterns across all dimensions examined, with even greater severity and disability in the group with broad atypical features. Our findings suggest that the presence of just 1 reversed vegetative symptom during an MDE establishes a threshold that clinically distinguishes depressed individuals with atypical features from those without them, regardless of the presence or absence of typical vegetative symptoms.

Using this new threshold, we found that, although the prevalence of individuals with both atypical features is similar to that documented in prior studies, the overall prevalence of MDE with atypical features is much higher than previously documented.[29–31] Differences in the criteria used to define atypicality (ie, one versus both reversed vegetative symptoms of hypersomnia or hyperphagia), exclusion of individuals with bipolar disorder or with typical vegetative symptoms, and changing diagnostic *DSM* criteria, may partially account for the higher prevalence estimates found in our study.[29,31] Nevertheless, these findings highlight the public health significance of a diagnostic group that, possibly due to its name, may have been assumed to be rare and, consequently, insufficiently studied.

Consistent with prior studies, MDE with atypical features was associated with female gender,[31] earlier age at onset of MDE,[29–31,51] family history of depression,[31,51] higher rates of comorbid anxiety and drug use disorders,[29–31] higher number of depressive symptoms and rates of suicidal ideation and attempts,[29,31] and greater disability and use of mental health services.[31] Our study extends previous findings by documenting the association of MDE with atypical features with (1) greater overall rates of lifetime psychiatric disorders, (2) bipolar I disorder, (3) any personality disorder except antisocial personality disorder, (4) higher total number of MDE symptoms, (5) early-onset anxiety, (6) increased use of drug or medications to help relieve depressive symptoms, (7) higher rates of rejection sensitivity, and (8) worse overall health. These findings remained significant in models adjusting for several sociodemographic covariates.

The current study also examined the relationship between reversed vegetative symptoms and bipolar disorder in a general population sample. In contrast with data from clinical samples,[52–55] individuals with MDE with atypical features had significantly higher rates of bipolar I disorder than those without atypical features. Data from clinical samples[53,55,56] may not generalize to the community. Alternatively, this discrepancy may be partially explained by the use of different definitions of MDE with atypical features across studies, or the exclusion of bipolar I patients from most clinical studies.[53,55] In our study, even after controlling for total number of criteria, individuals with bipolar depression with atypical features were more likely than individuals with MDD with atypical features to have higher rates of any Axis I and II disorders. The 2 groups also differed significantly in sociodemographic characteristics, clinical course, symptomatology, disability, and treatment-seeking behavior. These findings are consistent with previous clinical data.[56] Overall, these differences parallel those between major depression with and without atypical features and suggest that the characteristics of atypical depression, although common in both disorders, are even more accentuated in bipolar depression than in MDD with atypical features.

Some limitations of the current study should be considered in interpreting our findings. First, we identified individuals with MDE with atypical features based on the presence of reversed vegetative symptoms, rather than the

full *DSM-IV* criteria. However, our approach is consistent with that of previous epidemiologic surveys[29–31] and clinical studies,[32] which has consistently identified a clinically meaningful group of individuals characterized by greater rates of comorbidity, severity of illness, risk of suicide attempt, and overall disability similar to the group identified in clinical samples using the full *DSM-IV* criteria. Furthermore, our results were robust across multiple operationalizations of atypical depression. Indirect evidence of the validity of our approach is provided by the higher rates of rejection sensitivity among individuals with atypical features. Second, our assessment was limited to clinical features and did not any include neurobiological assessments or examination of treatment response. Third, the duration of depressive episodes may have impact on the likelihood that the individual will experience a period of atypical symptoms. However, the duration of MDEs did not differ significantly among individuals with and without atypical features, suggesting that duration of the episode is unlikely to be a major determinant of the presence of atypical symptoms. Fourth, the cross-sectional nature of this survey limits the examination of lifetime comorbidity between typical and atypical features in depressed individuals.

Despite these limitations, our data provide further evidence for the clinical significance and validity of the atypical features specifier. Based on the presence of any of the 2 reversed vegetative symptoms during an MDE, most of the commonly cited validators of atypical depression were confirmed in our study. Major depressive episode with atypical features may be, in fact, more common, severe, and impairing than MDE without atypical features. Given its prevalence, and high risk for suicide and disability, early detection, targeted interventions, and development of more effective treatments for individuals with atypical features are important.

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Author contributions: Dr Grant attests that all authors had access to the study data, take responsibility for the accuracy of the analyses, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

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Supplementary Material

Article Title: Prevalence, Correlates, Comorbidity, and Treatment-Seeking Among Individuals With a Lifetime Major Depressive Episode With and Without Atypical Features: Results From the National Epidemiologic Survey on Alcohol and Related Conditions

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List of Supplementary Material for the article

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eTable 1. Prevalence and sociodemographic correlates of bipolar and unipolar major depressive episode with atypical features

	Bipolar MDE with Atypical Features [a] n=990			Unipolar MDE with Atypical Features [a] n=3,430			OR 95 % CI		
	%	95% CI		%	95% CI		OR	95% CI	
Sex									
Male	36.65	32.83	40.64	28.99	27.11	30.94	1.42	1.18	1.71
Female	63.35	59.36	67.17	71.01	69.06	72.89	1.00	1.00	1.00
Race/Ethnicity									
White	73.54	69.29	77.39	77.89	75.02	80.51	1.00	1.00	1.00
Black	11.15	8.98	13.76	7.68	6.53	9.02	1.54	1.20	1.96
Native Americans	4.21	2.86	6.14	3.25	2.45	4.31	1.37	0.86	2.19
Asian	2.07	1.04	4.07	2.54	1.64	3.91	0.86	0.44	1.67
Hispanic	9.04	6.74	12.02	8.64	6.83	10.88	1.11	0.90	1.37
Nativity									
US-Born	91.11	87.41	93.80	92.17	90.08	93.84	0.87	0.64	1.19
Foreign-born	8.89	6.20	12.59	7.83	6.16	9.92	1.00	1.00	1.00
Age									
18-29	37.28	33.49	41.24	23.36	21.68	25.12	1.00	1.00	1.00
30-44	34.09	30.59	37.76	33.88	32.01	35.80	0.63	0.51	0.78
45-64	25.92	22.67	29.46	35.45	33.49	37.48	0.46	0.36	0.58
65+	2.71	1.78	4.12	7.31	6.37	8.36	0.23	0.15	0.37
Education									
< High School	17.65	15.07	20.57	12.48	11.00	14.13	1.64	1.30	2.08
High School	29.86	26.68	33.24	26.53	24.40	28.77	1.31	1.07	1.59
College	52.49	48.57	56.38	60.99	58.58	63.35	1.00	1.00	1.00
Annual Income									
0-19K	63.85	59.91	67.61	51.70	49.10	54.29	1.00	1.00	1.00
20-34K	19.86	16.99	23.08	22.67	20.66	24.82	0.71	0.56	0.89
35-69K	13.22	10.89	15.96	19.91	17.89	22.11	0.54	0.41	0.70
>70K	3.07	1.86	5.03	5.71	4.67	6.98	0.44	0.27	0.71
Family Income									
0-19K	33.88	30.39	37.54	23.04	21.16	25.03	1.00	1.00	1.00
20-34K	23.25	20.24	26.56	20.99	19.38	22.69	0.75	0.61	0.94
35-69K	29.54	26.18	33.14	32.59	30.53	34.72	0.62	0.49	0.77
>70K	13.33	10.64	16.58	23.38	21.26	25.65	0.39	0.29	0.52
Marital Status									
Married	46.54	42.77	50.35	55.21	53.00	57.40	1.00	1.00	1.00
Widowed	21.02	18.30	24.02	22.68	21.21	24.22	1.10	0.89	1.36
Never Married	32.44	29.00	36.09	22.11	20.33	24.00	1.74	1.41	2.14
Urbanicity									
Urban	80.08	74.99	84.35	79.50	75.91	82.67	1.00	1.00	1.00
Rural	19.92	15.65	25.01	20.50	17.33	24.09	0.96	0.76	1.22
Region									
Northeast	18.92	13.09	26.55	18.86	13.50	25.72	0.94	0.69	1.28
Midwest	24.13	18.18	31.29	24.84	19.23	31.44	0.91	0.71	1.17
South	31.66	25.40	38.66	32.60	26.88	38.88	0.91	0.71	1.17
West	25.29	18.80	33.10	23.71	17.48	31.30	1.00	1.00	1.00
Insurance									
Private	56.26	52.46	59.99	68.83	66.64	70.93	1.00	1.00	1.00
Public	17.77	15.14	20.75	12.62	11.27	14.11	1.72	1.40	2.12
No insurance	25.97	22.54	29.72	18.55	16.90	20.32	1.71	1.38	2.13

[a] MDE with Atypical Features defined as presence of *one or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least one typical vegetative symptom during the MDE .

eTable 2. Psychiatric comorbidity in individuals with bipolar and unipolar major depressive episode with atypical features

	Bipolar MDE with Atypical Features [a] n=990			Unipolar MDE with Atypical Features [a] n=3,430			AOR [c] 95 % CI		
	%	95% CI		%	95% CI		AOR**	95% CI	
Any Psychiatric Disorder	93.22	91.24	94.78	81.34	79.77	82.82	2.98	2.19	4.04
Any Axis I Disorder	88.32	85.75	90.48	77.35	75.59	79.03	2.19	1.73	2.77
Any Substance Use Disorder [b]	70.59	66.95	73.99	55.42	53.33	57.49	1.83	1.51	2.23
Alcohol Use Disorder	57.66	53.63	61.59	41.81	39.75	43.91	1.90	1.57	2.29
Alcohol Abuse	19.55	16.32	23.25	20.40	18.67	22.24	1.04	0.82	1.33
Alcohol Dependence	38.10	34.04	42.34	21.41	19.64	23.30	2.02	1.63	2.51
Drug Use Disorder	36.19	32.33	40.23	18.51	16.78	20.38	2.11	1.73	2.57
Drug Abuse	18.37	15.35	21.84	12.19	10.75	13.80	1.37	1.06	1.77
Drug Dependence	17.81	14.73	21.37	6.32	5.33	7.48	2.65	1.97	3.57
Nicotine Dependence	45.13	40.76	49.57	30.58	28.59	32.64	1.73	1.43	2.09
Dysthymia	0.00			21.06	19.43	22.79	N/A	N/A	N/A
Any Anxiety Disorder	61.75	57.96	65.41	42.67	40.35	45.03	2.29	1.89	2.77
Panic Disorder	28.67	25.34	32.25	15.32	13.77	17.01	2.31	1.85	2.88
Social Anxiety Disorder	25.82	22.36	29.61	14.38	12.92	15.98	2.09	1.68	2.61
Specific Phobia	31.71	28.27	35.35	22.07	20.26	24.00	1.61	1.33	1.95
Generalized Anxiety Disorder	29.50	25.79	33.49	15.02	13.51	16.66	2.75	2.17	3.48
Pathological Gambling	2.23	1.35	3.66	0.43	0.28	0.67	5.11	2.48	10.50
Psychotic Disorder	3.52	2.21	5.56	0.88	0.57	1.35	3.28	1.77	6.09
Any Personality Disorder	65.18	61.71	68.50	32.91	31.00	34.87	3.40	2.85	4.05
Avoidant Personality Disorder	21.69	18.81	24.88	7.35	6.42	8.40	3.09	2.45	3.90
Dependant Personality Disorder	6.29	4.60	8.53	1.62	1.17	2.23	3.26	2.09	5.10
Obsessive-Compulsive Disorder	35.50	32.16	38.98	17.53	15.78	19.43	2.56	2.11	3.10
Paranoia Personality Disorder	33.99	30.38	37.79	10.88	9.65	12.24	3.69	2.99	4.56
Schizoid Personality Disorder	18.29	15.43	21.54	8.41	7.33	9.64	2.18	1.72	2.77
Histrionic Personality Disorder	15.72	13.18	18.64	4.36	3.46	5.48	3.39	2.40	4.78
Antisocial Personality Disorder	20.05	17.06	23.41	6.35	5.41	7.45	2.99	2.29	3.92

[a] MDE with Atypical Features defined as presence of *one or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least one typical vegetative symptom during the MDE.
[b] Any Substance Use Disorder: including alcohol use disorder, drug use disorder, and nicotine dependence.
[c] Adjusted for sex, race, US-born, age, annual income, marital status, urbanicity, and total number of criteria.

eTable 3. Clinical characteristics associated with a lifetime major depressive episode (MDE) with atypical features and MDE without atypical features

	Bipolar MDE with Atypical Features [a]			Unipolar MDE with Atypical Features [a]			AOR [b] 95 % CI		
	n=990			n=3,430					
	Mean	95% CI		Mean	95% CI		Wald F**	p-value	
Age of Onset	22.82	22.01	23.63	28.79	28.27	29.32	66.93	<0.0001	
Number of Episodes	8.38	7.26	9.50	5.35	4.72	5.98	26.79	<0.0001	
Total number of criteria	8.36	8.27	8.44	8.06	8.01	8.11	43.58	<0.0001	
	%	95% CI		%	95% CI		AOR**	95% CI	
Use of alcohol to help relieve symptoms	31.98	28.37	35.82	17.95	16.37	19.65	2.03	1.64	2.51
Self-medication to help relieve symptoms	16.64	13.56	20.27	6.29	5.34	7.40	2.50	1.89	3.31
Family History of depression (only 1st degree relatives)	75.58	72.23	78.65	64.29	62.03	66.49	1.90	1.56	2.32
Disturbed Family Environment	95.35	93.75	96.55	95.79	94.92	96.51	1.03	0.71	1.51
Childhood parental loss	9.68	7.79	11.97	8.29	7.27	9.43	1.22	0.92	1.61
Conduct Disorder	2.10	1.29	3.40	1.98	1.43	2.73	0.87	0.48	1.56
Early onset anxiety(before 18 yr-old) [c]	52.48	47.71	57.20	44.61	41.64	47.61	1.69	1.39	2.05
History of Divorce/loss of spouse	32.76	29.03	36.72	37.94	35.82	40.10	1.10	0.83	1.45
Lifetime rejection sensitivity [d]	25.97	22.69	29.55	10.44	9.31	11.69	2.52	2.01	3.16
Bipolar I	62.60	58.94	66.12	N/A					
Bipolar II	29.34	25.95	32.98	N/A					

[a] MDE with Atypical Features defined as presence of *one or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least one typical vegetative symptom during the MDE.

[b] Adjusted for sex, race, US-born, age, annual income, marital status, urbanicity, and total number of criteria

[c] Early onset anxiety defined as onset of any anxiety disorder before age 18.

[d] Lifetime rejection sensitivity defined as avoiding getting involved with people unless the respondent was certain of being liked.

eTable 4. Symptoms and health status associated with a lifetime major depressive episode (MDE) with atypical features and MDE without atypical features

	Bipolar MDE with Atypical Features [a] n=990			Unipolar MDE with Atypical Features [a] n=3,430			AOR [b] 95 % CI		
	%	95% CI		%	95% CI		AOR**	95% CI	
Clinical Symptoms									
Lack of interest or pleasure	93.34	91.30	94.93	88.89	87.48	90.17	1.72	1.24	2.39
Fatigue	92.14	90.00	93.85	90.18	88.92	91.32	1.44	1.08	1.93
Motor retardation	66.45	62.88	69.84	45.08	42.84	47.34	2.34	1.94	2.82
Motor agitation	51.14	47.28	55.00	39.87	37.62	42.17	1.57	1.31	1.90
Worthlessness	76.41	72.90	79.59	64.06	61.93	66.14	1.78	1.45	2.18
Guilt	72.53	68.81	75.96	59.23	57.28	61.16	1.83	1.50	2.24
Trouble concentrating	91.14	88.64	93.13	84.15	82.43	85.72	1.98	1.47	2.66
Trouble making decisions	84.55	81.83	86.93	76.33	74.51	78.06	1.88	1.52	2.34
Irritability	72.57	68.55	76.25	51.88	50.05	53.70	2.22	1.79	2.75
Attempt suicide	24.74	21.68	28.07	9.99	8.89	11.20	2.61	2.09	3.26
Thoughts of suicide	55.63	51.38	59.80	38.90	37.08	40.75	1.87	1.56	2.24
Thoughts of own death	70.37	66.39	74.06	55.20	53.29	57.10	1.85	1.51	2.25
Overall Health excellent to good	62.86	57.92	67.55	70.07	67.67	72.36	0.69	0.55	0.86
Overall health fair to poor	37.14	32.45	42.08	29.93	27.64	32.33	1.00	1.00	1.00
	Mean	**95% CI**		**Mean**	**95% CI**		**Wald F****	**p-value**	
Physical component summary [c]	49.87	48.98	50.77	49.57	49.01	50.13	0.80	0.3743	
Mental component summary [c]	41.55	40.56	42.55	46.42	46.00	46.84	66.30	<0.0001	
Social Functioning Scale Score [c]	43.76	42.61	44.92	47.59	47.08	48.11	31.29	<0.0001	
Role of Emotional Functioning Scale Score [c]	42.57	41.48	43.65	47.09	46.61	47.58	60.77	<0.0001	
Mental Health Scale Score [c]	41.94	40.99	42.89	45.82	45.36	46.28	48.78	<0.0001	

[a] MDE with Atypical Features defined as presence of *one or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least one typical vegetative symptom during the MDE.

[b] Adjusted for sex, race, US-born, age, annual income, marital status, urbanicity, and total number of criteria.

[c] SF-12 V2 Scores.

eTable 5. Treatment-seeking rates in individuals with bipolar and unipolar MDE with atypical features

	Bipolar MDE with Atypical Features [a]			Unipolar MDE with Atypical Features [a]			AOR [b] 95 % CI		
	n=990			n=3,430					
	%	95% CI		%	95% CI		AOR	95% CI	
Any Lifetime Treatment	68.74	64.67	72.54	63.66	61.60	65.68	1.49	1.21	1.83
Lifetime Outpatient treatment seeking	63.28	59.22	67.15	57.41	55.30	59.50	1.43	1.18	1.75
Lifetime Emergency Room/Hospital	18.96	16.10	22.21	8.65	7.49	9.98	2.22	1.7	2.9
Lifetime use of medication	54.45	49.98	58.85	48.36	46.05	50.68	1.56	1.29	1.89
Treatment seeking in the past 12 months	38.21	34.14	42.44	25.90	23.97	27.94	1.77	1.36	2.30
	Mean	95% CI		Mean	95% CI		Wald F*	p-value	
Age when first sought treatment (Mean)	27.88	26.66	29.09	32.03	31.33	32.73	4.34	0.0411	
Time to Treatment Seeking (Mean)(year)	4.91	4.16	5.67	3.30	2.98	3.62	26.71	<0.0001	

[a] MDE with Atypical Features defined as presence of *one or both* reversed vegetative symptoms (hyperphagia or hypersomnia), regardless of presence of at least one typical vegetative symptom during the MDE.

[b] Adjusted for sex, race, US-born, age, annual income, marital status, urbanicity, and total number of criteria.