Depression With Atypical Features: Diagnostic Validity, Prevalence, and Treatment

Frederic M. Quitkin, M.D.

Depression with atypical features is a treatable and relatively common disorder among depressed outpatients. A growing body of evidence suggests this is a biologically distinct subtype of depression. This assertion is supported by genetic epidemiologic studies and by a preferential response of the subtype to monoamine oxidase inhibitors compared with tricyclic antidepressants. The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) includes atypical features as a parenthetical modifier for depressive illness. According to DSM-IV diagnostic criteria ("atypical features" specifier), the disorder is primarily characterized by 2 or more of the following symptoms as predominant features in patients with major depression or dysthymic disorder: overeating, oversleeping, "leaden paralysis," and interpersonal rejection sensitivity. Patients also show mood reactivity in response to actual or potential positive events. Despite aspects of the disorder resembling a maladaptive, persistent mode of behavior, patients diagnosed with depression with atypical features demonstrate a good response to antidepressant treatment.

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Corresponding author and reprints: Frederic M. Quitkin, M.D., Department of Therapeutics, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, 1051 Riverside Dr., New York, NY 10032 (e-mail: Quitkin@PI.CPMC.Columbia.edu).

Because of the high prevalence of depression, its significant morbidity,[1–3] and the availability of effective treatment, the Agency for Health Care Policy and Research (AHCPR) convened a panel of experts to establish treatment guidelines for depressive illness.[4] A major goal of this expert panel, which represented various fields, including psychopharmacology and primary care, was to encourage primary care physicians to provide the first line of treatment for depressed patients. However, the AHCPR guidelines, published in 1993, do not widely discuss depression with atypical features.

Subsequently, the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[5] was published in 1994. DSM-IV includes atypical features as a parenthetical modifier for depressive illness. Nevertheless, it is still not widely understood that this disorder, characterized by the salient symptoms of overeating and oversleeping, is a manifestation of depressive illness that is treatable with antidepressants.[6] Some aspects of depression with atypical features—including its onset in adolescence and chronic course—do not readily suggest a mood disorder. Consequently, in the past, patients were frequently considered to have neurotic or characterologic depression, with symptoms stemming from problems in rearing. Given our current understanding of the syndrome, as well as new genetic-epidemiologic data that support the validity of this diagnostic category,[7,8] it is relevant to call clinicians' attention to depression with atypical features as a depressive subtype.

DESCRIPTION

DSM-IV lists atypical features as a "specifier" that can be applied when atypical features predominate (1) during the most recent 2 weeks of a major depressive episode in patients with major depression; (2) during a major depressive episode in patients with bipolar I or II disorder, if the major depressive episode was the most recent type of mood episode; and (3) during the most recent 2 years of dysthymic disorder. The DSM-IV criteria for major depressive episode are listed in Table 1. Diagnostic criteria for the "atypical features" specifier are shown in Table 2.

Several points about these criteria are worth clarifying. Patients should be considered hypersomnic if they sleep 10 hours per day (or 2 more hours than usual). Hyperphagia is considered to be present if the patient has gained at least 5 pounds (2 kg) or reports clear appetite increase during the current depressive illness. Leaden paralysis is identified if the patient reports feeling that his or her limbs are weighed down (many also describe fatigue). No one likes rejection, but rejection sensitivity implies that the patient frequently has an excessive response, which results in social or occupational impairment. These patients may describe stormy relationships or avoidance of situations in which they may be rejected.

Worthy of note is the fact that depression with atypical features is frequently a chronic disorder, with many patients describing onset in childhood and indicating that they have "always" felt this way. In spite of the fact that

Table 1. DSM-IV Criteria for Major Depressive Episode[a]

A. Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations

(1) depressed mood most of the day, nearly every day (in children and adolescents, can be irritable mood)
(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
(3) significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day (in children, consider failure to make weight gains)
(4) insomnia or hypersomnia nearly every day
(5) psychomotor agitation or retardation nearly every day
(6) fatigue or loss of energy nearly every day
(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day
(8) diminished ability to think or concentrate, or indecisiveness, nearly every day
(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

B. Symptoms do not meet criteria for a mixed episode
C. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
D. Symptoms are not caused by a substance or substance abuse or by a general medical condition
E. Symptoms are not better accounted for by bereavement (loss of a loved one)

[a]Reprinted with permission from the American Psychiatric Association.[5]

Table 2. DSM-IV Criteria for Atypical Features Specifier[a]

A. Mood reactivity (ie, mood brightens in response to actual or potential positive events)
B. Two (or more) of the following features:

(1) significant weight gain or increase in appetite
(2) hypersomnia
(3) leaden paralysis (ie, heavy, leaden feelings in arms or legs)
(4) long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment

C. Criteria are not met for With Melancholic Features or With Catatonic Features during the same episode

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this appears to be a maladaptive persistent mode of behaving, characteristic of a personality disorder, these patients do benefit from antidepressants.

Depression with atypical features may be confused with chronic fatigue syndrome, particularly if the patient presents with a chief complaint of leaden paralysis (see Table 2) and a lack of energy. Psychiatric disorders are considered a "most important source" of diagnostic confusion in chronic fatigue research.[9] In patients lacking physical signs and symptoms (tender lymph nodes, sore throat), careful history taking should help identify which patients with long-standing fatigue have atypical depression.

PREVALENCE

How often can the primary care physician anticipate seeing patients with atypical depression? It is a common disorder. Studies examining the prevalence of depression with atypical features are summarized in Table 3.[7,8,10–15] In samples of patients with major depressive disorder or dysthymia, the prevalence varies from 15% to 40%, depending on the sample studied. These are probably underestimates, since only 1 study[12] assessed all the criteria. DSM-IV criteria require the presence of 2 associated features (overeating, oversleeping, leaden paralysis, and rejection sensitivity). The most common symptom, rejection sensitivity, often was not assessed in the studies. In a study of 332 patients who met criteria for depression with atypical features, the proportions who had each of the 4 associated symptoms were as follows: pathologic rejection sensitivity, 71%; overeating, 47%; leaden paralysis, 47%; and oversleeping, 35%.[16] Estimates of prevalence not measuring rejection sensitivity must thus underestimate the true prevalence.

DIAGNOSTIC VALIDITY

Diagnosis of Depressive Subtypes: Does All Depression Exist on a Continuum?

Since Aubrey Lewis's classic study,[17] there has been debate about whether the distinction between depressive subtypes is categorical or dimensional. The dimensional view holds that there are no biological distinctions, with all differences among depressives explained by severity.[18] Recent evidence suggests that depressive subtypes are biologically distinct and, therefore, categorically distinct.[6–8] This has implications for treatment of different depressive subtypes.

A series of studies conducted by Quitkin and colleagues[6] (the Columbia group) suggest that unlike patients with all other depressive subtypes, depressed patients with atypical features who tend to overeat and oversleep are more likely to respond to monoamine oxidase inhibitors (MAOIs) than tricyclic antidepressants (TCAs). These findings are important because they suggest that the neuropathophysiology of depression with atypical features is different enough to result in a distinct antidepressant response for patients with atypical depression compared with patients with other subtypes of depression.

Historical Basis for Defining Atypical Depression

The development of the concept of depression with atypical features is linked to early attempts by psychopharmacologists to identify depressed patients who had a greater benefit from MAOIs than TCAs.[19–21] Classically, patients exhibiting melancholia as defined in DSM-IV were thought to have a depressive disorder with a biolo-

Table 3. Proportion of Depressed Patients Meeting Criteria for Atypical Depression in Different Settings

Authors	Patient Sample	Criteria for Atypical Depression	Prevalence
Horwath et al[10] (1992)	Epidemiologic Catchment Area study; N = 18,208	Overeating and oversleeping	15.7%
Levitan et al[11] (1997)	N = 8116 subjects from Ontario; 653 participants (8.0%) with major depression	Overeating and oversleeping	17.2%
Kendler et al[7] (1996)	N = 1029 population-based sample of female twins	Overeating and oversleeping	26.9%
Sullivan et al[8] (1998)	National Comorbidity Survey; N = 2836	Overeating, oversleeping, and psychomotor agitation	36.6%
Asnis et al[12] (1995)	N = 114 depressed outpatients	Overeating, oversleeping, leaden paralysis, and rejection sensitivity	29%
Robertson et al[13] (1996)	N = 109 depressed clinic patients	Overeating, oversleeping, leaden paralysis, and rejection sensitivity	28% definite; 20% probable
Zisook et al[14] (1993)	N = 1000 clinic patients; 175 major depressives and 102 dysthymics	Fatigue, overeating, and oversleeping	36% of major depressives; 43% of dysthymics
Angst et al[15] (in press)	Zurich cohort; N = 4547	Overeating and oversleeping	24% of major depression patients

gical basis.[4] The disorder was recognized as a phasic condition that causes a distinct change in a patient's mental state and appears to be uncontrollable by the patient. Patients with the melancholic symptom complex were observed to benefit from electroconvulsive therapy (ECT) and, later, after the introduction of the first-generation antidepressants, to be responsive to TCAs.[22]

In contrast to patients with melancholia, other depressed patients—whose symptoms seemed to be the antithesis of melancholic complaints—appeared to benefit from MAOIs. Anecdotal observations suggested that MAOI responders were characterized by a history of poor response to ECT, hysterical personality, hyperphagia, hypersomnia, prominent fatigue, mood worse in the evening, phobias, and anxious depression.[19–21] It appeared possible that these early investigations were describing a heterogeneous group consisting of at least 2 patient types: the V-type (vegetative), with vegetative symptoms such as hypersomnia, hyperphagia, and lethargy; and the A-type (anxious), with depressive syndromes including anxiety, panic, and phobia.[23]

Since heterogeneous samples of patients might contain, at best, only a subset of patients who would be more likely to be both MAOI responsive and TCA nonresponsive, the Columbia group focused on the V-type of atypical depression. We hypothesized that many of the A-type patients had panic disorder and, therefore, would benefit from TCAs as well as MAOIs. If both V-type and A-type patients were included in one study, the antidepressant response of A-type patients, with little difference in outcome between MAOIs versus TCAs, would make it more difficult to detect the V-type patients' superior response to MAOIs. We, therefore, chose to study V-type patients, who are characterized by overeating and oversleeping. In most previous drug trials, TCA treatment had proved consistently superior or equal to MAOI treatment.[24] Therefore, the identification of patients who preferentially improve with MAOI treatment might help delineate a depressive syndrome with a distinct neuropathophysiology.

In developing criteria for defining a patient group that might selectively benefit from MAOIs, we were also influenced by Klein and colleagues' description of a group referred to as "hysteroid dysphoric" patients.[25] When rejected, these patients develop depressive episodes characterized by lethargy, oversleeping, and overeating that preferentially respond to MAOIs. This was the basis for developing criteria for Columbia atypical depression, which, in turn, form the basis of the DSM-IV "atypical features" specifier. The prospective identification of these patients as having a superior response to MAOIs (vs. TCAs) would suggest that atypical depressives respond to antidepressants differently than other depressives, and thus support the validity of depression with atypical features as a distinct diagnostic subtype with a distinct neuropathophysiology.

ATYPICAL SYMPTOMS IN THE DEPRESSED PHASE OF BIPOLAR ILLNESS

Clinical lore suggests that the depressed phase of bipolar disorder is frequently characterized by atypical depressive symptoms. The Pittsburgh group has suggested for many years that the depressive phase of bipolar illness is hypersomnic with retarded activation.[26] There are few studies that quantify the presence of atypical symptoms in an unselected group of depressed bipolar patients. Using DSM-IV criteria, Robertson et al.[13] examined 109 patients, 79 of whom were unipolar and 30 of whom were bipolar. Criteria for definite atypical depression were met by 28% of unipolar and 30% of bipolar patients. Criteria for probable atypical depression were met by 22% of unipolar and 17% of bipolar depressed patients. Mitchell et al.[27] studied 39 bipolar and unipolar patients. These authors did not specify the proportion of patients who met DSM-IV criteria for atypical depression, but slightly

more bipolar depressed patients had hypersomnia and leaden paralysis. The study did not measure hyperphagia or rejection sensitivity.

An overview of the research suggests that hypersomnic and anergic symptoms are common in bipolar depressives. However, most depressed bipolar patients do not meet DSM-IV criteria for atypical depression. The proportions of unipolar and bipolar depressive episodes meeting DSM-IV criteria for atypical depression are roughly equal.

Evidence Validating Depression With Atypical Features

Validation of this syndrome gains its greatest weight from 2 distinct approaches: psychopharmacologic dissection and genetic studies of depressive syndromes in population-based samples.[6–8,28]

Psychopharmacologic dissection is based on the theory that a unique psychopharmacologic response may be a means of identifying categorically distinct diagnostic subtypes.[28] Since prior studies suggested that TCAs were always equal to or superior to MAOIs, if a group had a superior response to MAOIs (vs. TCAs), this would suggest that the group had a different pathophysiology from patients with other depressive syndromes. In a series of 6 studies,[6] patients with nonautonomous mood were randomly assigned to receive imipramine (TCA), phenelzine (MAOI), or placebo. Patients who did not respond to their first treatment were crossed over, under double-blind conditions, to an active drug. Approximately 475 patient trials were evaluated.

Depressed patients with atypical features had a poor TCA response (44% [65/147]) and a good MAOI response (72% [118/165]). A second group of patients with mood-reactive depression who were similar to atypical depressives, but lacked the vegetative symptoms, was characterized by a good response to both TCAs (80% [24/30]) and MAOIs (75% [18/24]). In both groups, placebo response was approximately 25%. Thus, the distinguishing feature of depressed patients with atypical features is their poor TCA response and good MAOI response.

We performed an aggregate chi-square analysis with the sum of natural log, using a method proposed by Fischer[29] to determine the probability that chance could account for the observations in the trials demonstrating the MAOI-TCA difference ($\chi^2 = 28.86$, df = 8, p = .0003). The likelihood of this being a chance finding is extremely small.

In the other major approach to syndrome validation, genetic-epidemiologic studies were conducted. Using epidemiologic samples of patients, Kendler et al.[7] and, independently, Sullivan et al.[8] performed a latent class analysis to identify diagnostic clusters. In these 2 independent data sets, 3 patient groups were identified: severe typical, mild typical, and atypical depressives. Each group found that depression with atypical features is genetically distinct from severe typical and mild typical depression. In the Kendler et al. study of female twins, individuals with the atypical subtype (vs. severe typical or mild typical) who had recurrent episodes tended to have the same symptoms in each episode, with higher concordance in monozygotic versus dizygotic twins. Kendler et al. also found that the atypical subtype was characterized by prominent fatigue and was not associated with anxiety (compared with other depressive subtypes). It was characterized by high body mass index, and more atypical depressives had bulimic symptoms.[7]

In an independent sample, Sullivan et al.[8] essentially replicated the findings of Kendler et al., concluding that "these convergent findings . . . constitute a compelling rationale for the existence of an atypical subtype and its inclusion in any typology of unipolar depression."[p1403] Diagnoses based on phenomenologic distinctions like hypersomnia and hyperphagia and lacking an identified pathophysiology are never completely validated. However, the fact that several independent investigations reached the conclusion that depression with atypical features is a distinct syndrome strongly supports its validity.

Thus, several lines of evidence suggest that these are categorically distinct depressive subtypes. An example of a dimensional difference is height; an example of a categorical distinction is male-female. If a dimensional view were correct, all depression would respond in a similar fashion to any treatment. Differences in treatment response between depressives would be attributable to illness severity. Perhaps more severe depressives would need higher doses of the same drug. However, acceptance of the categorical view suggests that depressive subtypes may have a superior response to different classes of drugs. With the exception of MAOIs and the atypical subtype, it has not been established that a depressive subtype has a superior response to any class of antidepressants. Obviously, MAOIs will not be widely used, even for atypical depression.

TREATMENT OF DEPRESSION WITH ATYPICAL FEATURES

MAOIs are clearly an effective treatment for atypical depressives,[6] but, as a result of associated dietary restrictions and potential side effects, are generally not considered first-line drugs. Several studies[30–34] suggest that depressed patients with atypical features have a modest response to second-generation antidepressants such as zselective serotonin reuptake inhibitors (SSRIs). However, the newer drugs represent a true advance because of their low side-effect burden and prescription ease. Certainly, these drugs should be tried first. Four studies contrast the efficacy of an SSRI in atypical depressives with

Table 4. Treatment of Depression: Diagnosis, Drugs, Dose, Duration[a]

Diagnosis
Depressed patient subgroups most frequently seen in office practice are melancholic, atypical, and major depression without a parenthetical modifier
Atypical subtype should be distinguished, because those unresponsive to the newer drugs should receive an MAOI (may require consultation)
Drugs
TCAs and MAOIs are as effective (but not as well tolerated) as the following newer drugs: SSRIs: fluoxetine, sertraline, citalopram, paroxetine venlafaxine, mirtazapine, nefazodone
Major advantages of newer drugs are as follows[35]: Fewer side effects, generally more easily tolerated Unlikely to be lethal in overdose (unlike TCAs and MAOIs)
Clinicians should become familiar with the doses of several newer drugs and use them as first-line treatment
Dose
Dose-dependent drugs include TCAs, MAOIs (good evidence)[36,37] Newer drugs? (not clear)
Before deciding that a newer drug has failed, clinicians should try to increase the dose to the recommended maximum dose
Duration
In clinical practice, antidepressant drug trials are frequently too short.[38] The full effects of MAOIs and TCAs require 6 weeks[39,40]
Patients should receive newer drugs for at least 6 weeks before response is judged inadequate; patients should then be switched to another newer drug for a second trial
About 70% to 80% of nonrefractory depressed patients should respond to the first 2 antidepressant drug trials
At any point, patients who become suicidal, whose clinical condition deteriorates, or who are unresponsive should be evaluated by a psychopharmacologist

[a]Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

various control groups. Only 1 study had a placebo control. McGrath et al.[34] reported that, in a sample of approximately 150 patients, the proportions of patients who were "much improved" were as follows: placebo 23%, fluoxetine 51%, and imipramine 53%. Outcomes with the 2 drugs were equivalent, and both were superior to placebo. In a study by Stratta et al.,[33] outcomes with fluoxetine and imipramine were similar. Lonnqvist et al.[31] reported a minimal advantage of moclobemide (71%) versus fluoxetine (60%). In a small study (fluoxetine N = 13, phenelzine N = 14), Pande et al.[32] found the efficacy of fluoxetine and phenelzine to be approximately equal. It appears that the SSRIs' efficacy is superior to that of placebo and approximately equivalent to that of TCAs in treating patients with atypical depression. The advantage of SSRIs is that they are more easily tolerated than TCAs. SSRIs' efficacy is not as robust as that of MAOIs in atypical depression. In one study of depressed patients with atypical features,[35] patient response to gepirone, an azapirone currently under review by the U.S. Food and Drug Administration, was encouraging. Further evaluation of this compound is underway.

The utility of MAOIs, especially for atypical depressives who have failed other treatments, is not as widely appreciated as it should be. Depression with atypical features is a chronic condition, with significant morbidity and high relapse rates once patients are no longer taking medication.[36] Therefore, patients unresponsive to second-generation antidepressants should be treated with MAOIs.

We are limited in predicting which patients will respond to which drugs. Therefore, careful attention to methodical treatment of patients is most important. A useful mnemonic to guide the physician in treating depressed patients consists of the "four *D*s": diagnosis, drugs, dose, and duration (Table 4).[37–42] The clinician should consider these 4 parameters when treating depressed patients.

In a study[43] utilizing a patient-completed symptom rating scale (Symptom Checklist-90), 318 outpatients, most with atypical features, had the anticipated rate of improvement (65%–70%). Worthy of note is that responder scores, which were in the pathologic range prior to treatment, were indistinguishable from the scores of a "well" community control group at study end.[43] These results suggest that the symptoms of moderately depressed patients who benefit from treatment not only decrease from baseline but are reduced to a level of symptomatology comparable to that of other community members. This suggests that these patients' symptoms are reversible and that the patients may attain a virtually asymptomatic state.

Physicians have an effective collection of antidepressants available. It can be anticipated that the majority of previously untreated patients should respond with 2 adequate trials of antidepressants. The literature suggests that depression with atypical features is a common disorder and should be recognized as a syndrome with a good response to antidepressants.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

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