Recognition and Diagnosis of Atypical Depression

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The term *atypical depression* dates to the first wave of reports describing differential response to monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). In contrast to more TCA-responsive depressions, patients with so-called atypical symptoms (e.g., hypersomnia, interpersonal sensitivity, leaden paralysis, increased appetite and/or weight, and phobic anxiety) were observed to be more responsive to MAOIs. After several decades of controversy and debate, the phrase "with atypical features" was added as an episode specifier in the DSM-IV in 1994. The 1-year prevalence of the defined atypical depression subtype is approximately 1% to 4%; around 15% to 29% of patients with major depressive disorder have atypical depression. Hardly "atypical" in contemporary contexts, atypical depression also is common in dysthymic bipolar II disorders and is notable for its early age at onset, more chronic course, and high rates of comorbidity with social phobia and panic disorder with agoraphobia. The requirement of preserved mood reactivity is arguably the most controversial of the DSM-IV criteria for atypical depression. When compared with melancholia, the neurobiological profiles of patients with atypical depression are relatively normal. The utility of the atypical depression subtype for differential therapeutics diminished substantially when the TCAs were supplanted as first-line antidepressants by the selective serotonin reuptake inhibitors. Although introduction of safer MAOIs has fostered renewed interest in atypical depression, the validity and importance of the DSM-IV definition of atypical depression for the nosology of affective illness remains an open question.

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The concept of atypical depression is nearly as old as modern psychopharmacology. In 1959, West and Dally[1] delineated a subgroup of depressed patients who were more responsive to the monoamine oxidase inhibitor (MAOI) iproniazid than the tricyclic antidepressant (TCA) imipramine. These patients were characterized by the absence of the classically endogenous neurovegetative symptoms, emotional reactivity, prominent anxiety and multiple phobias, severe fatigue, and somatization. Indeed, the roots of the concept of atypical depression may be traced even further back to the seminal work of Sir Aubrey Lewis in the 1930s, which first proposed dividing depression into endogenous and neurotic or nonendogenous subforms of depression.[2]

In the decade that followed the West and Dally publication, a number of other researchers, most notably Hordern,[3] Sargant,[4] and Klein,[5] proposed refinements of the same atypical construct. In the 1970s and early 1980s, others reported data further supporting the hypothesis that patients with atypical depression were more responsive to MAOIs than TCAs.[6–9] The fact that the TCAs were widely considered to be the first choice for antidepressant pharmacotherapy for more than 25 years, coupled with the apparent ability of the atypical subtype to predict differential treatment response to MAOIs, sustained interest in this concept into the early 1990s.

This epoch culminated in 1994, when the atypical depression subtype was formally recognized as an "episode specifier" in the DSM-IV.[10] Consistent with the approach taken by Donald F. Klein, M.D., Frederick M. Quitkin, M.D., and their colleagues at New York State Psychiatric Institute and Columbia University, the current approach requires that individuals with atypical depression have preserved mood reactivity and at least 2 associated symptoms.[5,7,9] Of note, the DSM-IV criteria do not include concomitant anxiety symptoms, which were prominently featured in the original articles on atypical depression.[1,4] The current article will provide a brief review of the relevant data published since 1994.

EPIDEMIOLOGY

Available studies that examine the prevalence of atypical depression are somewhat flawed and fall into 1 of 2 categories: (1) subanalyses of epidemiologic samples that extract subtype diagnoses on the presence of 2 or more symptoms of atypical depression, most commonly overeating and oversleeping, and (2) post hoc subtype diagnoses (i.e., "samples of convenience") among groups of patients

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with major depressive disorder (MDD) who were recruited for other types of studies.

Studies estimating the prevalence of this subtype in community samples suggest that 15% to 29% of patients with MDD have atypical depression, which translates to a 1-year prevalence of approximately 1% to 4% in the community.[11–14] Studies of clinical groups have yielded remarkably similar estimates, with 18% to 36% of patients with MDD presenting with atypical depression.[15–19] There is some tendency for the estimated proportions of patients with atypical depression to vary across settings, with higher proportions in outpatient studies of younger, female-preponderant groups. In addition to MDD, the proportion of patients presenting with atypical features has been reported to be as high as 50% in dysthymic disorder and bipolar II disorder.[8,18,20,21] Interestingly, the lowest prevalence estimate (18%) was reported in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) program dataset, which used perhaps the most restrictive criteria for atypicality and excluded patients with dysthymia and bipolar II disorder.[19]

CLINICAL PRESENTATION AND DIAGNOSIS

The DSM-IV criteria for the "with atypical features" episode modifier may be used to subtype major depressive episodes (both nonbipolar and bipolar) as well as dysthymia. The DSM-IV criteria require that an individual must exhibit mood reactivity and manifest at least 2 associated clinical features (Table 1). The criteria also exclude patients who meet criteria for 2 other severity-linked episode criteria: "with catatonic features" and "with melancholic features."

Alternatively, the spectrum of MDD may be conceptualized as encompassing 2 prototypes (melancholic and nonmelancholic depressions), with atypical depression comprising a subform of nonmelancholic depression. Despite the time-honored wisdom of this approach, the residual group (i.e., episodes that are neither melancholic nor atypical depressive) is populated by a large number of "mixed" or indeterminate cases.

Part of the reason for this is that the threshold for classification of atypical depression is highly dependent on the assessment of mood reactivity, which is essentially a nonpathologic descriptor (i.e., mood reactivity is a normal attribute). Specifically, if one sets the threshold quite low (i.e., only those with an autonomous or virtually unreactive mood are excluded), far more patients will meet criteria for atypical depression than melancholia. It is impossible to resist pointing out the irony that, whereas the concept of atypical depression originally was derived with the understanding that melancholia (i.e., endogenous depression) was the more common presentation of depression, the opposite is true in the 21st century.

Parker and colleagues[22] have challenged the validity of the DSM-IV criteria for atypical depression. They noted

Table 1. DSM-IV Criteria for Atypical Features in Major Depressive Disorder[a]

Mood reactivity (ie, mood brightens in response to actual or potential positive events)
Two (or more) of the following features:
Significant weight gain or increase in appetite
Hypersomnia
Leaden paralysis (ie, heavy, leaden feelings in arms or legs)
Long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment
Criteria are not meant for "with melancholic features" or "with catatonic features" during the same episode

[a]Adapted with permission from American Psychiatric Association.[10]

that the DSM-IV criteria define a heterogeneous condition and, in their hands, the internal consistency of the constituent criteria for atypical depression is low. Importantly, they found that preserved mood reactivity was not associated with increased incidence of any of the associated symptomatic criteria. Thus, leaden paralysis and reverse neurovegetative features were nearly as common in "typical" forms of MDD as in DSM-IV atypical depression.[22] Posternak and Zimmerman[23] reached similar conclusions in their study. The heterogeneity of atypical depression as defined by the DSM-IV also was evident in the STAR*D study (Figure 1).[19]

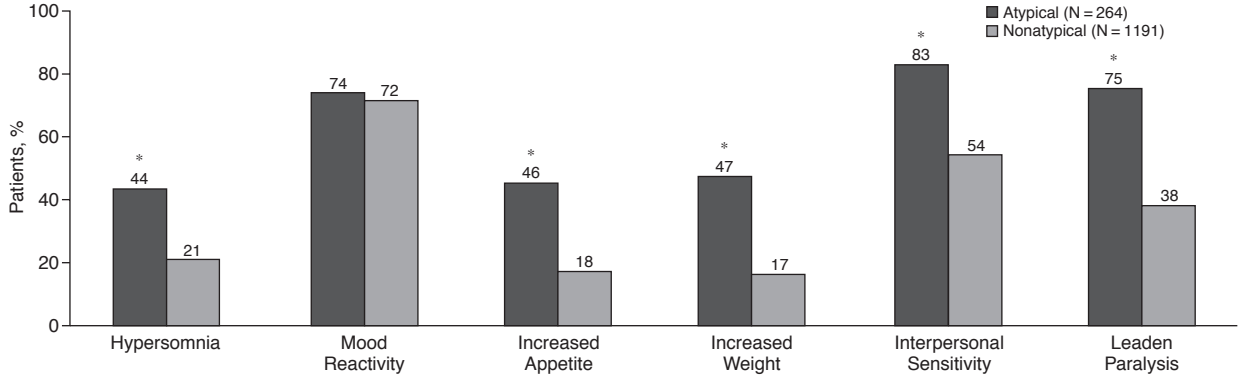
Another potential factor adversely affecting the diagnostic performance of DSM-IV MDD is that some of the criteria of atypical depression are heavily gender specific. Indeed, the early descriptions of rejection sensitivity and the closely related construct of hysteroid dysphoria could be considered sexist by 21st century standards. (The less-charged term *interpersonal sensitivity*, as studied by Davidson et al.,[24] should be considered for inclusion in the DSM-V.) Consistent with these observations, in 1 study, atypical depression was found to account for the preponderance of the overrepresentation of depression in women.[25]

In preparation for the DSM-V, further research is needed to better establish the diagnostic sensitivity and specificity of individual symptoms and features of atypical depression in order to further refine the diagnostic criteria.

COMORBIDITY

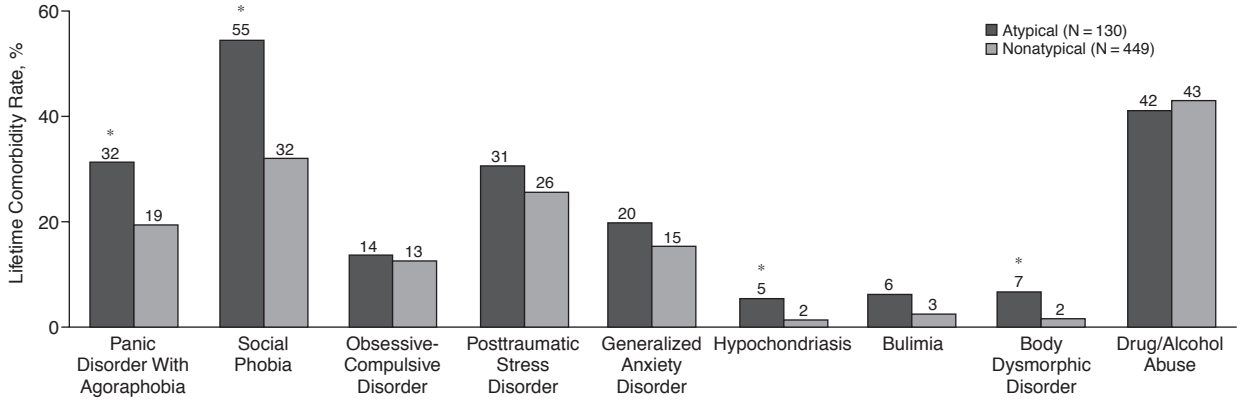
Major depressive disorder patients with atypical features have been found to have significantly higher rates of comorbidity with selected psychiatric disorders than patients with nonatypical features (Figure 2).[23] Multiple studies have reported similar patterns of increased comorbidity in MDD patients with atypical features.[13,14,21,26,27] Atypical depression has long been associated with a problematic, longstanding pattern of interpersonal difficulties characterized by intense rejection sensitivity. Studies utilizing more formal assessment of Axis II DSM-IV criteria indicate that atypical depression is associated with significantly higher

Figure 1. Percentage of Depressed Patients Reporting Specific Atypical Features[a,b]



[a]Based on Novick et al.[19]
[b]p Values were significant at the .0001 level after adjustment for illness severity, sex, age, and age at first onset.
*p < .0001.

Figure 2. Lifetime Comorbidity Rates in Depressed Patients With and Without Atypical Features[a,b]



[a]Based on Posternak and Zimmerman.[23]
[b]Bulimia was trend significant at p = .06.
*p < .05.

rates of cluster B (e.g., borderline and histrionic personality disorders) and cluster C (e.g., anxious, avoidant, dependent, obsessive-compulsive personality disorder) disorders.[25] The increased cluster C comorbidity is consistent with the increased incidence of anxiety disorders shown in Figure 2.

AGE AT ONSET AND COURSE OF ILLNESS

Patients with MDD presenting with atypical features have significantly earlier onset of depression than patients with other forms of major depression,[20,28] even when patients with early-onset comorbidity (e.g., bipolar disorder) have been excluded.[19] Compared with melancholia, which tends to have a later age at onset and is more likely to exhibit a recurrent episodic pattern, atypical depression has greater chronicity.[20,27]

There is good reason to speculate that the biological basis of atypical depression is formed by the intersection of the 2 well-replicated epidemiologic risk factors: early age at onset and female preponderance. Specifically, early-onset depressive disorders are more likely to run a chronic course and are associated with greater comorbidity (especially anxiety disorders) and a higher risk of subsequent bipolarity. Younger women—who may be the age/gender group that is the least responsive to TCAs—are more likely to manifest reverse neurovegetative symptoms and comorbid anxiety. Conversely, loss of mood reactivity is strongly associated with older age and more classical neurovegetative symptoms.

Turning full circle, the investigators of the early studies may have viewed patients who were more responsive to MAOIs as "atypical" precisely because such patients were uncommon in their hospital-based practices.

ADVANCED PSYCHOMETRIC STUDIES, GENETICS, AND FAMILY HISTORY

Data from genetic studies provide some of the most persuasive evidence for the validity of a psychiatric diagnosis. This is especially true of atypical depression, whose diagnostic boundaries, as we have seen (Figure 1), overlap extensively with nonatypical MDD.

Latent class analysis has been performed on 3 separate patient samples (the National Comorbidity Survey,[29] and 2 sets of twin pairs[30,31]) in an attempt to determine whether atypical depression emerges as one of the primary empirical typologies. The results of all 3 latent class analyses yielded an atypical subtype characterized by reverse vegetative symptoms. Nevertheless, there are no studies to date that specifically examine the heritability patterns of atypical depression as defined by the DSM-IV, or whether the various genetic polymorphisms identified in melancholic depression might also occur in the atypical subtype.

In a satellite study of STAR*D, a retrospective diagnosis of atypical depression in the mother was associated with a 3.3-fold higher odds of having a child with depression (compared with mothers with no history of depression).[32] Similarly, maternal atypical depression was associated with a 2.6-fold higher risk of having a child with an anxiety disorder. Thus, for reasons that are currently unknown, maternal depression with atypical features was associated with notably higher risk of early-onset depressive and anxiety disorders. Although this was likely due to higher heritability (i.e., more heritable disorders tend to have an early age at onset), the impact of negative developmental effects of growing up with a mother who was extremely anxious, dependent, emotionally labile, and interpersonally hypersensitive cannot be ruled out.

NEUROBIOLOGY OF ATYPICAL DEPRESSION

The neurobiology of atypical depression has been examined using 4 research paradigms: (1) tests of the hypothalamic-pituitary-adrenocortical (HPA) axis, (2) studies of neurotransmitter activity, (3) polysomnographic studies of sleep neurophysiology, and (4) studies of asymmetry central nervous system activity. It should be emphasized that the studies evaluating the neurobiological correlates of atypical depression provide data indicating that atypical depression is different than melancholia, but the data are far from consistent or conclusive with respect to whether atypical depression is truly unique (i.e., different from other forms of depression and normal controls).

HPA Axis

Studies of potential differences in HPA axis activity in patients with atypical depression originate with the clinical observation that the hypercortisolism of Cushing's syndrome is associated with unusually high rates (~50%) of depression characterized by atypical symptoms such as hypersensitivity, hyperphagia, marked fatigue, and social anxiety and withdrawal.[33–36] However, several decades of research have rather conclusively established that increased HPA activity is more strongly associated with melancholia. Indeed, a growing body of recent research suggests that the atypical subtype of depression may be associated with low HPA axis activity, with abnormal responses to challenge with both corticotropin-releasing hormone and low-dose dexamethasone.[37–41] These findings are similar to what has been reported in syndromes that share many of the same symptoms as atypical depression, such as dysthymic disorder and seasonal affective disorder.[42–44]

A critical distinction needs to be made between low HPA values that are normal versus those that are abnormally low. Abnormally low values, which also have been reported in posttraumatic stress disorder, were observed in 1 study.[37] This finding is of potential interest because Levitan et al.[14] observed a significant association between the incidence of reverse neurovegetative symptoms and a history of early maltreatment in a large epidemiologic study.

Neurotransmitters

A small number of challenge tests have been reported in which patients diagnosed with atypical depression have been administered either desipramine[15,45] (a relatively selective norepinephrine reuptake inhibitor) or tyramine (a presynaptic noradrenergic stimulus).[46] In the desipramine challenge paradigm,[15,45] patients with atypical features had significantly lower cortisol levels in response to desipramine than melancholic patients. Similarly, patients with atypical features exhibited normal tyramine sulfate conjugation in response to oral tyramine, in contrast to reduced levels seen in melancholic patients.[46] When considered together, these findings indicate that depression with atypical features is not associated with the type of catecholaminergic abnormalities that have frequently been reported in melancholic depression.

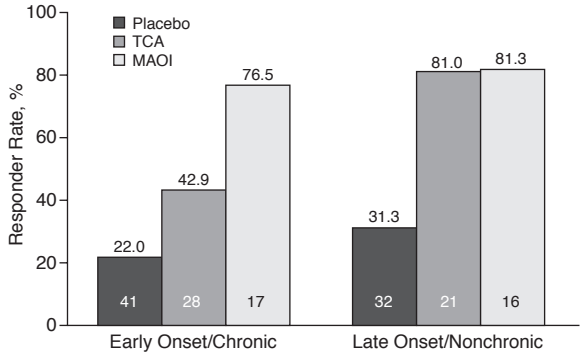
Sleep

Several studies have examined the sleep profiles of depressed patients with atypical features.[47–49] Based on the available data, the atypical subtype appears to be associated with better objective sleep continuity than other forms of depression, as well as more normal rapid eye movement (REM) sleep (i.e., REM latency is less likely to be reduced, and REM density is less likely to be increased). As one might predict on the basis of the epidemiology of atypical depression (i.e., a younger, female-predominant group), slow wave sleep also tends to be relatively normal or even increased in atypical depression.

Asymmetry of Central Nervous System Activity

Hemispheric asymmetry of perceptual processing has been evaluated using a standard dichotic listening task in

Figure 3. Treatment Response in Patients With Depression With Atypical Features: Comparison of Early-Onset/Chronic Versus Late-Onset/Nonchronic Illness Subtypes[a,b]



[a]Adapted with permission from Stewart et al.[28]
[b]Early onset: ≤ age 20 years; chronic: illness duration ≥ 2 years; TCA: imipramine, N = 44 (mean dose = 247 mg), desipramine, N = 4 (mean dose = 265 mg), amitriptyline, N = 1 (mean dose = 150 mg); MAOI: phenelzine, N = 23 (mean dose = 73 mg), deprenyl, N = 10 (mean dose = 38 mg).
Abbreviations: MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant.

which different sounds or words are presented simultaneously to each ear. In normal controls, the right hemisphere is dominant in processing verbal and nonverbal sounds. In melancholic depression, the dominance of the right hemisphere relative to the left hemisphere is significantly reduced; this profile has been associated with favorable response to TCAs and poorer response to placebo. In contrast, patients with atypical depression are more likely to show a normal response (i.e., preservation of right hemispheric processing).[50,51]

ATYPICAL DEPRESSION AND TREATMENT RESPONSE

The differentially higher response to MAOIs relative to tricyclic antidepressants has been one of the more consistent and robust validators of the atypical depression subtype.[52–54] However, as with all clinical and biological variables hypothesized to be characteristics of the atypical subtype, the specificity of treatment response is good, but not high. Across available comparator studies, the odds of responding to an MAOI relative to a TCA are generally about 1.5:1. For example, in the important early study by Liebowitz and colleagues,[52] antidepressant response rates were 71% on phenelzine, 50% on imipramine, and 28% on placebo. Several analyses have attempted to identify predictors of increased MAOI response (e.g., anxiety or panic attacks, individual atypical symptoms), but none have yielded consistently significant predictors.[54] In fact, McGrath et al.[55] found that, among patients with atypical depression, one of the associated symptoms was as predictive of MAOI response as another. Even higher levels of platelet MAO inhibition on phenelzine (i.e., an indirect biological measure of drug effect) have been reported to account for only a modest amount of the variance in treatment outcome.[54]

The relatively high rate of nonspecific response to TCAs in MDD with atypical features has led some investigators to propose using treatment responsivity itself as a method to "pharmacologically dissect" depression into biologically discrete and clinically homogenous subtypes.[56] This approach has never been fully implemented, because ideally it requires applying a multivariate regression model to a large dataset in which MAOI response is the dependent variable, and candidate predictor variables include a full array of clinical, demographic, course of illness, and biological variables. An initial step in the direction of this approach has been taken in a study reported by Stewart and colleagues[28] that evaluated the differential antidepressant responsivity of patients with atypical depression criteria who also had an age at onset (prior to age 20 years) and course of illness (chronicity ≥ 2 years) that have been reported to be more frequent in the atypical subtype. As can be seen in Figure 3, application of early-onset/high-chronicity criteria reduced the TCA response rate from 81% to 43%. It is important to note that the analysis was post hoc, and the sample sizes were small, but this approach appears to be promising. Specifically, if replicated, this approach would suggest that the diagnostic validity of atypical depression would be strengthened by requiring an early onset and a chronic course as secondary characteristics.

Finally, there have been surprisingly few controlled trials that evaluate the efficacy of SSRI antidepressants in atypical depression[57–59] and none that evaluate the efficacy of serotonin-norepinephrine reuptake inhibitor antidepressants. Results from available studies[57–59] suggest that SSRIs are efficacious treatments of atypical depression, but that they may not have the same magnitude of advantage over TCAs as do older MAOIs such as phenelzine. The extent to which the SSRI-responsive atypical subtype is coextensive with the MAOI-responsive atypical subtype is uncertain.

CONCLUSION

Atypical depression has been a useful construct, but its syndromic boundary with melancholic depression is more blurred than initially hypothesized, and it is likely that the current DSM-IV criteria warrant revision. The clinical, biological, and treatment response indicator parameters associated with the respective subtypes are not discretely bimodal. Atypical depression has existed for almost 50 years in a tantalizing but speculative limbo. Perhaps the time will soon come when rigorous biological and treatment research will either empirically establish the validity of the syndrome, or relegate it to the status of an interesting footnote in the evolving history of psychiatry.

Drug names: bupropion (Wellbutrin and others), desipramine (Norpramin and others), imipramine (Tofranil and others), phenelzine (Nardil).

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