ABSTRACT

Initially described in 1959 and followed by a variety of similar concepts, specific criteria for atypical depression were established in 1984. These criteria differentiated atypical depression from melancholia using treatment, course of illness, and family and biological studies, sufficiently validating the concept so that the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) included an atypical features modifier of Major Depression and Dysthymia, essentially adopting the 1984 criteria intact. Subsequently, problems were raised with the DSM-IV criteria, the most extensively pursued being that they produce a heterogeneous group of patients who likely have different illnesses. One suggestion for producing more homogeneous groups of patients is to limit use of depression with atypical features to patients who report very early onset (before age 20 years) and very chronic illness since onset (no spontaneous 2-month period of well-being since onset). It is suggested that these criteria be added to the DSM. [Psychiatr Ann. 2014;44(12):557-562.]

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A typical depression was added to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)\(^1\) as a features modifier of major depression and dysthymia, with criteria requiring the presence of significant mood reactivity plus 2 of 4 additional features from hyperphagia, hypersomnia, leaden paralysis, and pathologic rejection sensitivity. It was also required that during the current episode, criteria not be present for melancholia or catatonia. These criteria were retained in DSM-5.\(^2\)

What are the origins of atypical depression? Why these criteria? Are they valid? Should they be modified? How well do they define a unitary underlying illness? Should depression with atypical features be refined, redefined, or abandoned? This article will attempt to answer these questions.

THE HISTORY OF ATYPICAL DEPRESSION

The term “atypical depression” has been variably used to denote what would now be called psychotic depression,\(^3,4\) anxious depression,\(^5\) and, in DSM-III,\(^6\) unspecified depressive illness. The first use of the term to denote the DSM-IV concept was by West and Dally in 1959.\(^7\) They noted that some depressed patients did not benefit from imipramine and electroconvulsive therapy, treatments usually effective for what they called “typical” depression, but these otherwise unresponsive patients nevertheless achieved remarkable benefit when treated with iproniazid, the original monoamine oxidase inhibitor (MAOI) that was marketed as an antidepressant. To West and Dally,\(^7\) “typical” depression meant what would now be termed major depression with melancholic features. They noted that these specific MAOI-responsive patients did not have typical melancholic symptoms such as early morning wakening and marked weight loss, but instead were very emotional with marked fatigue. Because of the unusual nature of their symptoms and treatment response, West and Dally\(^7\) considered them to have “atypical depression,” meaning they did not have typical melancholic features or treatment response. This utilization of differential treatment response to infer presence of different illnesses is one of the earliest psychiatric applications of Klein’s notion of pharmacologic dissection.\(^8\)

Klein and Davis\(^9\) later described patients as having “hysteroid dysphoria.” Usually women, such patients exhibited pathologic reactions to romantic disappointments, which typically would cause them to overeat and oversleep until a new romance loomed. As with the patients described by West and Dally,\(^7\) Klein’s patients responded poorly to tricyclic antidepressants (TCAs) but did well with MAOIs. It was unclear, however, whether patients with Klein’s hysteroid dysphoria had the same disorder as those with “West and Dally’s” atypical depression.

Davidson et al.\(^10\) suggested there are two subtypes of atypical depression: an “A” type, having prominent phobic anxiety; and a “V” type, having prominent reverse vegetative symptoms. Instead of the anorexia and insomnia characteristic of melancholia, the V type of atypical depression exhibited hyperphagia and hypersomnia. The description by Davidson et al.\(^10\) of the A type bears some similarity to the phobic anxiety states described by a group of psychiatrists working at St. Thomas Hospital in London, England (ie, the St. Thomas group: West and Dally,\(^7\) Dally and Rohde,\(^11\) and Sargant\(^12\)). The reverse vegetative symptoms Davidson et al.\(^10\) describe as characteristic of the V type are reminiscent of Klein and Davis’\(^9\) hysteroid dysphoria, although Davidson et al.\(^10\) did not remark on the histrionic hyper-reactivity central to hysteroid dysphoria.

What was unclear about these various ideas was whether these authors were describing the same, overlapping, or different disorders. All authors described their patients’ presentations as usually “X” or often “Y” or sometimes “Z.” However, the allocation of value to each component (eg, how much eating constitutes hyperphagia?) or how many components must be present and whether any was paramount remained undressed. Further, even if the number and degree of symptoms were specified, how would one decide whether this symptom complex identified an illness and was not merely an arbitrary collection of signs and symptoms?

Robins and Guze\(^13\) suggested an approach to validate psychiatric illness. First, a syndrome had to be identified (ie, a listing of the signs and symptoms of the proposed illness). Next, its course of illness, whether it tended to run in families, and its biology had to be elucidated. Finally, it had to be differentiated from existing illnesses using signs/symptoms, course of illness, family history, and biological abnormalities as validators.

Klein\(^8\) considered differences in treatment response as a means to infer differences in pathophysiology and proposed “pharmacologic dissection” as a validator of psychiatric illness. When a drug normalizes a patient with an illness while having no effect in the healthy, it can be inferred that the drug is acting somewhere along the pathophysologic pathway of the illness; the corollary is if one patient benefits and another patient with a superficially similar illness does not, they must have a fundamental difference in the pathophysiology of their illness and perhaps a different illness.

Following the framework created by Robins and Guze,\(^13\) Liebowitz et al.\(^14\) defined a syndrome of atypical depression as requiring significant mood reactivity plus 2 of 4 additional features, including hyperphagia, hypersomnia, leaden paralysis, and pathologic rejection sensitivity. Several in the St. Thomas group had remarked on the emotional instalb-
ity of patients having atypical depression, \textsuperscript{5,11,12} although it was Klein\textsuperscript{15} who conceptualized this as “mood reactivity” in distinction to the mood nonreactivity characteristic of endogenomorphic depression. Pitt\textsuperscript{16} remarked on the reverse vegetative signs often seen in atypical depression, specifically mentioning overeating, and Klein and Davis\textsuperscript{9} reported both hyperphagia and hypersomnia to be prominent features of hysteroïd dysphoria. The extreme fatigue and lethargy described by West and Dally\textsuperscript{7} and Sargent\textsuperscript{12} were later classified by Liebowitz et al.\textsuperscript{14,17} as “leaden paralysis.” Finally, Klein and Davis\textsuperscript{9} described pathologic rejection sensitivity as characteristic of hysteroïd dysphoria.

Applying pharmacologic dissection to their algorithm, Liebowitz et al.\textsuperscript{14,17} and Quitkin et al.\textsuperscript{18} tested whether patients with atypical depression indeed would preferentially benefit from an MAOI relative to a TCA, as might be anticipated from West and Dally’s\textsuperscript{7} earlier report. Specific threshold criteria were developed to determine whether patients had each symptom,\textsuperscript{19} and those having significant mood reactivity plus 2 of the 4 additional symptoms were recruited into two studies of definite atypical depression that randomly assigned patients meeting these criteria to phenelzine, imipramine, or placebo given for 6 weeks, including at least 2 weeks at maximal Physician’s Desk Reference doses (90 mg/day and 300 mg/day, respectively, or 6 placebo pills), if tolerated. Both the original\textsuperscript{14,17} and the replication\textsuperscript{18} studies demonstrated superiority of the MAOI phenelzine over the TCA imipramine in depressed patients meeting the Liebowitz et al.\textsuperscript{14,17} criteria.

Quitkin et al.\textsuperscript{20} later demonstrated similar preferential MAOI response in patients presenting “probable” atypical depression, defined as significant mood reactivity plus only one of the associated symptoms (hyperphagia, hypersomnia, leaden paralysis, and pathologic rejection sensitivity). A differential response to MAOI versus TCA was not demonstrated in patients having mood reactivity without any of the other four symptoms,\textsuperscript{21} suggesting that the preferential response to MAOI relative to TCA may be limited to patients presenting with definite or probable atypical depression. Thus, pharmacologic dissection suggested atypical depression exists, that it could be identified, and that it does not respond as well to TCAs as to MAOIs, whereas another group (ie, those having mood reactivity without associated atypical features) did not show this differential treatment effect. Because the series of pharmacologic dissection studies performed by the Columbia University group\textsuperscript{14,17,21} did not include patients with melancholia, the question remained whether atypical depression is distinct from melancholia.

Stewart et al.\textsuperscript{19} addressed the question of distinction by comparing melancholic and atypical depression patients. Relative to patients with melancholia, those having atypical depression had a significantly earlier onset of illness and a much more chronic course of illness. In addition, depressed patients with atypical features less frequently had an abnormal dexamethasone suppression test and failed to show the poor functioning of the right cerebral hemisphere characteristic of patients with melancholia. Finally, relative to reports of patients with melancholia, those with atypical features less frequently had family members with recurrent and severe depressive illness, but more often had chronically depressed family members. Thus, the Columbia group’s definition of atypical depression identified patients who differed from those with melancholia not only in its illness syndrome (by definition), but also in its course of illness, biology, and expected illness in its families.\textsuperscript{14} Therefore, according to the Robins and Guze\textsuperscript{13} criteria for validating psychiatric syndromes, atypical depression was valid and distinct from melancholia.

Pharmacologic dissection partially distinguishes atypical depression from melancholia because imipramine appears less effective for atypical depression than for melancholia. Ideally, a treatment for atypical depression would be ineffective for melancholia, but McGrath et al. found melancholia highly responsive to both phenelzine\textsuperscript{22} and tranylcypromine.\textsuperscript{23} Against the McGrath\textsuperscript{22,23} reports on outpatients, severely depressed inpatients have been reported not to respond to MAOIs.\textsuperscript{24,25}

On the basis of these demonstrated differences in treatment outcome, longitudinal course of illness, family history, and biology, DSM-IV\textsuperscript{1} added “atypical features” as a modifier of major depression and dysthymia, using the Columbia criteria\textsuperscript{14} but adding the presence of melancholic or catatonic features as an exclusion.

**CRITICISM OF DSM-IV DEPRESSION WITH ATYPICAL FEATURES**

Angst et al.\textsuperscript{26} followed 571 teenagers in Zurich, Switzerland, for several decades with repeated diagnostic interviews. They later estimated the presence or absence of atypical depression from information obtained in these interviews, reporting that compared with subjects not considered to have atypical depression, those meeting their criteria were more often female and had increased comorbidity with a number of other disorders, including seasonality, bipolar II, sociopathy, social phobia, binge eating, and neurasthenia. Several disorders, including social phobia, binge eating, and neurasthenia, might be considered redundant with various criteria for depression with atypical features. Those with atypical features had earlier onset and a more chronic course of illness, although neither was marked. On the basis of these differences between atypical and nonatypical depression,
these authors considered atypical depression to be valid. Further analyses, however, did not differentiate between the presence or absence of significant mood reactivity; this finding led Angst et al.\textsuperscript{26} to propose dropping mood reactivity as a criterion for atypical depression. Although Angst et al.\textsuperscript{26} addressed some validity issues in support of their ideas, they did not address differential biology or treatment response. Their suggestion to eliminate mood reactivity as a criterion for atypical depression remains to be tested in other samples.

Parker et al.\textsuperscript{27} performed sophisticated statistical analyses on 270 patients with major depressive disorder consecutively admitted to an outpatient clinic. They reported weak or insignificant associations among the criteria for atypical depression, concluding that the diagnosis is poorly defined. Because the criterion of pathologic rejection sensitivity best differentiated a group that differed from other depressed patients, they suggested that atypical depression might better be conceptualized as a personality disorder rather than as an affective disorder. Parker et al.\textsuperscript{27} can be criticized for assessing atypical features without identified criteria for presence/absence of each feature or demonstrated reliability among raters, and for not having replicated their findings or validated their proposal using other avenues of inquiry, such as biological studies or pharmacologic dissection. Also, the weak correlations Parker et al.\textsuperscript{27} cite as damning may have resulted both from limited reliability of his raters and limitations inherent in their statistical methods.

Benazzi et al.\textsuperscript{28} followed 557 patients from a large Italian private practice and found marked similarities between bipolar depression and atypical depression. Therefore, they suggested that atypical depression is a variant of bipolar disorder. Although Benazzi et al.\textsuperscript{28} have addressed some aspects of validity, other characteristics have not been reported. Perhaps most importantly, because of the private practice nature of their patient population, randomized treatment studies have not been reported. Further, it is conceptually simpler to assert that because two groups differ they may have different illnesses than to assert that because of several similarities the groups represent different manifestations of the same illness. The similarities that Benazzi et al.\textsuperscript{28} have demonstrated could be superficial.

Stewart et al.,\textsuperscript{29} in critiquing the DSM-IV criteria for depression with atypical features, pointed out that despite replicated studies demonstrating superior efficacy of MAOI relative to TCA, TCA response still separated from placebo, suggesting per pharmacologic dissection that perhaps some “melancholic-like” patients were included in the Columbia group’s studies. Reasoning that patients with misdiagnosed melancholia might have other features of melancholia, such as recurrent episodes of illness, abnormal hypothalamic-pituitary-adrenal axis, robust response to TCA, and family histories of melancholia-like illness, these authors investigated whether differences in course of illness might distinguish important differences within patients who meet cross-sectional criteria for atypical depression. Indeed, those having more melancholic-like course of illness than as demonstrated by late onset (after age 20 years) or recurrent/nonchronic illness demonstrated just as robust a response to imipramine as to phenelzine, whereas those having both early onset and very chronic illness were no more likely to improve if treated with TCA than with placebo, and phenelzine was robustly superior to both. This differential treatment finding was replicated in patients having “probable” atypical depression.

Pharmacologic dissection, therefore, suggested DSM-IV criteria for depression with atypical features may subsume at least two disorders, one having early onset and very chronic illness course and another with either later onset or less chronic course. This distinction was tested by comparing the biology and family histories of these two groups. Those reporting an early onset (prior to age 20 years) without spontaneous subsequent remission (nontreatment-induced well-being lasting at least 2 months) differed on several measures of the hypothalamic-pituitary-adrenal axis\textsuperscript{30} as well as in their reported family histories\textsuperscript{31} from those having either later onset or nonchronic illness. In all ways investigated, the later-onset/less-chronic patients who met symptomatic criteria for atypical depression looked more like patients with melancholia than like those having early onset and very chronic illness. This series of studies suggested that on the basis of pharmacologic dissection, biology, and family history, the group having early onset and very chronic clinical course have a different illness than patients meeting the same cross-sectional symptomatic criteria but who have a different course of illness. It was proposed, therefore, that the criteria for atypical depression be changed to better identify a truly different illness. The suggested criteria include retention of significant mood reactivity plus the presence of one associated criterion (among hyperphagia, hypersomnia, leaden paralysis, and pathologic rejection sensitivity), as well as illness onset prior to age 20 years and very chronic illness as evidenced by no 2-month period of well-being since onset.

In differentiating early-onset and very chronically depressed patients meeting criteria for atypical features from others meeting the same criteria but having later onset or less chronic illness, Stewart et al.\textsuperscript{29} appear to have answered the Parker et al.\textsuperscript{27} criticism of earlier attempts to validate atypical depression by differentiating it from melancholia.
Parker et al.27 argued that all such a differentiation demonstrates is that melancholia differs from nonmelancholia, not that nonmelancholia is a distinct illness. He implied that it remained to be demonstrated that there is a nonmelancholic depressive illness. If atypical depression is distinct from other nonmelancholic illness, pharmacologic dissection must be shown and the Robins and Guze criteria13 applied within nonmelancholic depression in comparisons of atypical and nonatypical subgroups. Stewart et al.31 appear to have made such a distinction by differentiating within DSM-IV depression with atypical features.

**FUTURE DIRECTIONS**

First, the varying conceptualizations of Angst et al.26 (irrelevancy of mood reactivity), Parker et al.27 (pre-eminence of pathologic rejection sensitivity), Benazzi et al.28 (connection with bipolarity), and Stewart et al.29-31 (privity of early onset and chronicity) require validation and comparison. Thus, do these various conceptualizations define the same, partially overlapping, or different groups of patients? In particular, do any of these conceptualizations capture the patients West and Dally7 described as preferentially responding to an MAOI relative to a TCA. Although this is a tall order at a time when MAOIs are little-used treatments, it seems important in such a debate to at least wonder whether the discussion has strayed from its roots.

Second, because the treatment implications of atypical depression seem outdated, are there treatment implications useful to today’s clinician? The selective serotonin reuptake inhibitor, fluoxetine, for example, was more effective than placebo30 but not imipramine32 or phenelzine,33 leaving moot whether a clinician might anticipate a robust response in atypical depression similar to phenelzine or a lackluster one limited to a subset such as imipramine. These two studies did not compare those having early onset and very chronic illness from others having atypical features, so we cannot address whether fluoxetine might be uniquely effective for one or the other group.

Third, assuming one or the other conceptualization of atypical depression captures a valid entity, does it have a distinctive biology? This has only been addressed in the Stewart et al.31 conceptualization, which demonstrated biology similar to melancholia in patients meeting DSM-IV criteria for depression with atypical features who also reported later onset (after age 20 years) or a less chronic course of illness (at least one spontaneous episode of well-being since onset). Depressed patients who also met DSM-IV criteria for atypical features but reported an early age of onset and very chronic illness not only differed from others having atypical features but also had hypothalamic-pituitary-adrenal hypofunction and increased right hemispheric function relative to controls, which is the opposite of both patients with melancholic features and the later-onset/less chronically depressed patients with DSM-IV atypical features. Thus, atypical depression as defined by Stewart et al.31 differs biologically not only from melancholia but also from others who in DSM-IV would be considered to have atypical features. However, the biology of atypical depression requires further delineation to define a biology that might better inform use of current treatments.

Thus, atypical depression as defined by significant mood reactivity plus 1 of 4 symptoms (hyperphagia, hypersomnia, leden paralysis, pathologic rejection sensitivity), having onset prior to age 20 years, and a very chronic course of illness appears to be a valid clinical entity worthy of further research into its pathophysiology and treatment.


