Atypical Depression: A Reappraisal

Gordon Parker, M.D., Ph.D., D.Sc., F.R.A.N.Z.C.P.

Kay Roy, B.A. (Hons. Psych.)

Philip Mitchell, M.D., F.R.A.N.Z.C.P., F.R.C.Psych.

Kay Wilhelm, M.D., F.R.A.N.Z.C.P.

Gin Malhi, B.Sc., M.R.C.Psych., F.R.A.N.Z.C.P.

Dusan Hadzi-Pavlovic, B.Sc., M.Psychol.

Objective: The study evaluated the DSM-IV definition of the atypical features specifier for a major depressive episode in major depressive disorder.

Method: Nonpsychotic patients with major depressive disorder were assessed to determine if the DSM-IV model and decision rules for the atypical features specifier for a major depressive episode could be supported.

Results: The five clinical features of the DSM-IV atypical features specifier for a major depressive episode showed weak internal consistency, and the mandatory criterion A feature of mood reactivity did not show specificity in relation to any of the four criterion B accessory symptoms. The more severe the depression, the less likely the patient was to report criterion A and hence to meet criteria for the atypical features specifier. Remodeling the five features favored the personality style descriptor of interpersonal rejection sensitivity as an alternate primary feature. A reformulated model also suggested lifetime panic disorder and social phobia as higher-order determinants of atypical features in major depressive disorder. Additional analyses of criteria suggested that interpersonal rejection sensitivity and leaden paralysis had a phenomenological base in anxiety, that mood reactivity was linked with irritability, and that neither weight gain nor hypersomnia were clearly aligned with anxiety or depression, raising questions about their status as symptoms.

Conclusions: The current definition and modeling of the DSM-IV atypical features specifier for a major depressive episode in major depressive disorder appears problematic. As suggested by earlier descriptions of atypical depression, certain expressions of anxiety may have primacy, and some clinical features associated with the DSM-IV model may be adaptive homeostatic responses rather than pathological symptoms.

(Am J Psychiatry 2002; 159:1470–1479)

> The relatively high response with MAOIs [monoamine oxidase inhibitors], accompanied by the relatively poor response to tricyclic antidepressants, suggests that atypical depression may be a clinically and heuristically useful subtype of depressive illness… given its historical roots, psychopharmacological validation, and clinical utility. (1)
>
> —F.M. Quitkin, et al., 1988

> …a psychiatric colleague returning to work again in our psychiatric clinic after three years absence… pointed out that cases we had been labelling as anxiety neuroses, or anxiety hysteria before he left, were now being called atypical depression on his return. (2)
>
> —W. Sargent, 1962

The concept of "atypical depression" is unusual in its use of the qualifier of "atypical," in its combination of personality and clinical features, and in having treatment specificity implications. We review the historical development of the concept, analyze the validity of the DSM-IV definition of the atypical features specifier for a major depressive episode in major depressive disorder, and, after exploratory analyses, offer a reformulated model.

Evolution of the Construct of Atypical Depression

Definition of psychiatric syndromes most commonly emerges from clinicians' observations of a pattern of linked features—the clinical descriptor phase (3)—followed by studies pursuing diagnostic validity. However, according to one historical review (4), the process that led to the definition of atypical depression was itself atypical. In the late 1950s, West and Dally (5), from St. Thomas's Hospital in London, reported that the MAOI iproniazid was helpful in patients with "somewhat atypical states, sometimes resembling anxiety hysteria with secondary depression." They focused on the clinical features of a subgroup consisting of 58 MAOI responders and 43 MAOI nonresponders. Responders reported significantly less self-reproach, were less likely to report early morning wakening or mood worse in the morning, and had a poor response to ECT. MAOI responders were also more likely to report previous phobias and "hysterical conversions" and

to feel tremulous and were less likely to have a pattern of clinical features consistent with "the more classical endogenous depressions." West and Dally did not identify current DSM-IV criteria for the atypical features specifier, such as hypersomnia and hyperphagia, although "fatigue" was commonly reported.

West and Dally noted that some patients with an atypical pattern appeared to be "suffering from phobic anxiety states with secondary depression…[or]…'anxiety hysteria'." In identifying depressed patients highly responsive to an MAOI, they found multiple atypical depressions distinguished mainly by the presence of phobic anxiety and the absence of features of endogenous depression.

Other "London group" members developed the concept (6–8), consistently describing a preferential response to MAOIs but variably defining atypicality. Robinson and colleagues (9) built on these descriptions to develop a diagnostic index contrasting features of endogenous and nonendogenous depressions. Features underrepresented in endogenous depression, such as psychic and somatic anxiety, somatic complaints, long-standing phobias, and hysterical personality style, were more common in atypical depression. This process effectively captured features of a heterogeneous residue left after excluding endogenous depression but could not be expected to define a single entity unless only two pristine expressions of depression exist—typical and atypical.

The term atypical depression was subsequently used quite variably, with two 1982 papers identifying many applications. Paykel and colleagues (10) included patients with phobic anxiety, or reversal of classic endogeneity symptoms, among those with atypical depression. Davidson and colleagues (4) identified five principal historical classifications, describing 1) agitated, psychotic inpatients who responded to ECT; 2) mildly affected nonpsychotic outpatients with phobic anxiety, tension, and pain that responded to MAOIs; 3) patients with atypical vegetative symptoms such as increased appetite, mood lability, and irritability that responded to MAOIs; 4) patients with residual depressive conditions including depression secondary to schizophrenia; and 5) patients with bipolar depression reporting atypical vegetative symptoms that responded to MAOIs.

Some North American observers, such as Sovner (11), echoed the London reports in emphasizing a key role for anxiety. However, the current paradigm emerged in 1969 when Klein and Davis (12) stated: "So-called 'atypical depressions' consist of patients with depressive mood who reverse the usual consequences of retarded depression and have hypersomnia, hyperphagia, libidinal increase or weight gain," or who have "primary phobic-anxious trends" (p. 182). Their definition also encompassed the London group's description. They described the "hysteroid dysphoric patient," usually female, with a brittle, shallow mood who lacked "the essential characteristics of the pathological depressive mood (and were) prone to oversleep and overeat" (p. 183). Such women were held to repair their "dysphoria by exaggerating the social, seductive, exhibitionistic tactics allowable to women in our society" (p. 183). Klein and Davis proposed that such patients did not have distinctive separation anxiety nor "agoraphobia or travel phobic trends" (p. 185). It is important to note that they found that those with a hysteroid dysphoric character showed "quite specific medication response patterns" (p. 182) that could "directly change the affective reactivity" (p. 184). They found that while "the use of imipramine has negative effects…MAO inhibitors are of marked value…[so that such patients] do not become as dysphoric upon deprivation or loss of admiration" (p. 308).

Subsequently, Liebowitz and Klein (13) reported specific MAOI responsivity in "hysteroid dysphoric" and histrionic patients who were sensitive to rejection and were active and energetic, but, when depressed, were more likely to overeat, oversleep, be mood reactive, and experience extreme fatigue. This New York-based "Columbia group" thus emphasized a personality style shaping a set of atypical depressive features.

In operationalizing the Columbia criteria, researchers replaced the initial features emphasizing personality style with the feature of mood reactivity, which constitutes criterion A of the DSM-IV definition of the atypical features specifier. In the initial drug specificity studies (14), the depressed subjects were required to have a reactive mood and two or more associated features (i.e., increased appetite or weight gain, oversleeping or spending more time in bed, severe fatigue creating a sensation of leaden paralysis or extreme heaviness of arms or legs, and adulthood rejection sensitivity). Those studies were designed to determine if those with the Columbia group's atypical depression, rather than the London group's panic-phobic disorder, would selectively benefit from MAOIs and represent a distinct subgroup (15, 16). Under the Columbia approach, the atypical depressions had become a single entity, atypical depression.

In several intervention studies by the Columbia group (e.g., reference 17), varying inclusion rules were imposed, with a single associated symptom allowing a probable diagnosis and two a definite diagnosis. In light of findings demonstrating that subjects with one associated symptom were indistinguishable from those with two (1), it was argued that reactive mood and any associated atypical feature were sufficient for the diagnosis (18). Over time, individual features have been variably defined, with leaden paralysis alternatively defined as lethargy (16) or as fatigue and anergia (14). Such changes in definitions, as well as differences between studies in cutoff scores for rating the features, increased the risk that atypical depression would have chameleon status and influenced results from epidemiological, etiological, and treatment studies.

A Current Definition

The DSM-IV atypical features specifier can be applied to a current major depressive episode in nonpsychotic, nonmelancholic major depressive disorder and to dysthymic disorder. The essential criteria are mood reactivity (criterion A) and two or more of the following features (criterion B): increased appetite or weight gain, hypersomnia, leaden paralysis, and long-standing interpersonal rejection sensitivity.

Prevalence in Clinical Studies

Many studies have investigated the prevalence of atypical depression in depressed patients. A study of inpatients that used the criteria of mood reactivity and two of the associated symptoms identified a 33% rate of atypical depression (19). In outpatients with major depression, rates ranging from approximately one-third to two-thirds of patients have been reported (20–22). The high prevalence of atypical depression is not consistent with its name.

Epidemiological Studies

Kendler and colleagues (23) studied a population-based sample of female twins by using latent class analysis to identify a typology of depression. They labeled one class (3.9% of the sample) as having atypical depression. Prominent features in this class included depressed mood, loss of interest, and anhedonia, often accompanied by increased appetite, weight gain, and hypersomnia. Using a "truncated definition" of both overeating and oversleeping in an analysis of Epidemiologic Catchment Area (ECA) data, Horwath et al. (24) calculated a lifetime rate for atypical depression of 16% among those who met DSM-III criteria for major depression without psychotic features and a lifetime rate of 0.7% in the general community.

In a latent class analysis of National Comorbidity Survey data for 14 symptoms in subjects' worst episode of depression, six classes were identified, with two classes interpreted as capturing the phenomenon of atypical depression (25). Subjects in class 3 (severe atypical depression) met criteria for major depression but were likely to report appetite increase (83%), weight gain (84%), and hypersomnia (54%). Subjects in class 4 (mild atypical depression) were moderately likely to meet criteria for major depression (63%) and to have appetite increase (74%), weight increase (68%), and hypersomnia (23%). The authors suggested their analyses identified an "atypical subtype of depression…[that] exists in mild and severe variants."

Validation Data

Stewart and colleagues (26) reviewed several studies suggesting that patients with atypical depression could be distinguished by specific MAOI responsivity and also by polysomnography, tyramine excretion test patterns, and mood responsivity to dexamphetamine. Nierenberg and colleagues (27) reviewed evidence that such patients had less norepinephrine dysregulation—perhaps explaining their reduced response to tricyclic antidepressants. However, the comparison patients in such studies generally had melancholic depression, so the differences may reflect the absence of specific melancholic features in those with atypical depression rather than the presence of any sui generis positive features in atypical depression. As the current DSM-IV criteria for the atypical features specifier exclude patients with melancholia, validation studies would be more meaningful if comparison subjects had nonmelancholic depression.

Validation by MAOI Selectivity

In an overview of pre-1980 studies, Davidson and colleagues (4) reported that, while the London group found MAOIs more effective than tricyclics for atypical depression, later studies showed class equivalence, a shift perhaps reflecting overenthusiastic early claims, insufficient doses of tricyclics in the early studies, or differing side effect profiles. Difficulties in data interpretation have emerged owing to the variable definitions of atypical depression and variable comparator groups.

The first empirical test of the MAOI selectivity hypothesis was by Robinson's group (28). This and two other group studies (29) identified amitriptyline as superior for patients with higher endogeneity scores and phenelzine as superior for those with lower endogeneity scores. Columbia group study subjects (16, 26) had a DSM-III depressive disorder, some level of mood reactivity, and two of four other features (hypersomnia, leaden paralysis, hyperphagia, and rejection sensitivity). The overall data set (30) identified a superior response rate to phenelzine compared to imipramine (71% versus 50%) and a placebo response rate of 28%. Patients not responding to initial treatment were reassigned to receive the other drug in a crossover, double-blind design, and the superiority of phenelzine (67% versus 41%) was confirmed (31). These results provided strong support for MAOI selectivity in treatment of atypical depression, at least in comparison to tricyclics.

Quitkin and colleagues (16) found that the presence of the associated criterion features of atypical depression predicted a selective response to MAOIs, while another study established that no single feature was more predictive than any other (32), allowing the conclusion that each feature appeared "of roughly equal importance" (26). However, selectivity could be driven by a noncriterion feature.

A key candidate is anxiety. Robinson and colleagues (9) earlier concluded that the MAOIs were preferentially efficacious in "nonendogenous depression and phobic disorders," and Joyce and Paykel (33) reported that anxious depression was more likely than nonanxious depression to respond to an MAOI. Together, these results suggested that the selective efficacy of MAOIs may result from anxiolysis. Further, a Columbia study summation noted, contrary to expectations, that superiority of both active drugs over pla-

cebo was largely confined to subsets of patients who had a history of spontaneous panic attacks and/or had hysteroid dysphoric features (30). The same group subsequently reported that the presence of panic attacks did not confer any preferential response to the MAOI phenelzine (18), a finding that did not discount the possibility that earlier preferential responses may have resulted from MAOI modulation of hysteroid dysphoric characteristics.

Empirical Assessment of Atypical Depression

Our historical review suggests that the status of atypical depression is problematic. The distinct reference to personality style and anxiety in early descriptions, and the demonstration of MAOI benefits in certain anxiety disorders and in possibly modulating "hysteroid dysphoria," suggest alternate hypotheses. We used an existing patient database to analyze properties of the DSM-IV criteria set, and we propose an alternate model in which atypical depression is shaped by personality style and/or expressions of anxiety.

Assessment Study

Study features have been described fully elsewhere (34). In brief, 270 patients meeting DSM-IV criteria for major depressive disorder (present less than 24 months) were recruited consecutively from our clinic or from two other psychiatric hospitals. The patients completed a self-report sociodemographic questionnaire and the Beck Depression Inventory (35). A research psychologist assessed current clinical features of anxiety and depression and generated lifetime anxiety disorder diagnoses from the computerized Composite International Diagnostic Interview (36). The interviewing psychiatrist completed the Hamilton Depression Rating Scale (37) and a checklist of DSM-IV clinical depressive features. On the basis of clinical questioning, they judged whether the patient had a bipolar or unipolar illness course by rating key features defining each DSM-IV personality disorder. The listing of clinical features and the precoded scoring options standardized data collection, but there were no reliability (test-retest or interrater) study components.

Symptom Ratings

The presence of mood reactivity was determined by the subject's reporting moderate to complete lifting of mood in response to a pleasant event or being with a friend or company. Weight gain was present if an increase of at least 3 kg had occurred since the onset of depression. Hypersomnia was rated categorically as present or absent. Leaden paralysis was considered present if the subject acknowledged a moderate or severe level of this feature. Interpersonal sensitivity was assessed as present or absent by the psychiatrist.

Subjects

After excluding 28 subjects with psychotic depression and 82 who met DSM-IV criteria for melancholia, the study group comprised 160 subjects (69% of whom were outpatients) with mean depression severity scores of 30.3 (SD=10.6) on the Beck Depression Inventory (completed by 151 subjects) and 20.5 (SD=6.7) on the Hamilton depression scale. Fifteen subjects (9%) had a bipolar illness pattern.

Prevalence of Atypical Depression

Adopting the recommended cutoff for probable atypical depression (17), 31.3% of the subjects (32.7% of male subjects and 30.5 % of female subjects) met the criteria. The criteria for definite atypical depression were met by 16.3% of the subjects (18.2% of the male subjects and 15.2% of the female subjects).

Interdependence and Internal Consistency

Mood reactivity and all four associated symptoms were intercorrelated in the entire study group (Pearson correlation statistic). Only weak associations existed between interpersonal rejection sensitivity and hypersomnia ($r=0.18$, $df=158$, $p=0.02$) and between weight gain and leaden paralysis ($r=0.17$, $df=158$, $p=0.03$). All other intercorrelational analyses were nonsignificant, with coefficients ranging from 0.12 to –0.09. Item intercorrelation within the subset of 50 subjects who met the criteria of reactive mood plus one or more accessory symptoms (i.e., those with probable atypical depression) failed to produce any significant associations.

The internal consistency for the total item set (Cronbach's alpha=0.21) and for the four accessory symptom set considered alone (Cronbach's alpha=0.28) was weak.

Is the DSM-IV Definition Valid?

If the DSM-IV criteria for the atypical features specifier provide a valid definition of atypical depression, then accessory features should be overrepresented in depressed patients who have a reactive mood but do not have psychotic or melancholic depression. However, as Table 1 shows, none of the DSM-IV criterion B features were significantly overrepresented in the nonmelancholic subjects who reported a reactive mood. The only significant finding was, paradoxically, that leaden paralysis was *less* common. Nonsignificant findings could theoretically reflect insufficient power. The size of the study group, however, had sufficient power (80%) to detect differences of 20% versus 42% (or larger) and thus of an order appropriate for diagnostic significance.

It is possible that mood reactivity lost its relevance as a criterion by excluding those with psychotic or melancholic depression. Thus, chi-square analyses were repeated by using data from the overall study group of 270 patients, of whom 111 had mood reactivity and 159 did not. The distribution of associated features (respectively)

TABLE 1. Symptom Criteria of the DSM-IV Atypical Features Specifier for a Major Depressive Episode Met by 160 Nonpsychotic Depressed Subjects Reporting or Not Reporting Mood Reactivity and Interpersonal Rejection Sensitivity

	All Subjects		Subjects Reporting Mood Reactivity (N=69)		Subjects Not Reporting Mood Reactivity (N=91)		Analysis		Subjects Reporting Interpersonal Rejection Sensitivity (N=83)		Subjects Not Reporting Interpersonal Rejection Sensitivity (N=77)		Analysis	
Symptom	N	%	N	%	N	%	χ^2 (df=1)	p	N	%	N	%	χ^2 (df=1)	p
Weight gain	34	21.3	17	24.6	17	18.7	0.8	0.36	19	22.9	15	19.5	0.3	0.60
Hypersomnia	47	29.4	25	36.2	22	24.2	2.7	0.10	31	37.3	16	20.8	5.3	<0.02
Leaden paralysis	48	30.0	15	21.7	33	36.3	3.9	<0.05	29	34.9	19	24.7	2.0	0.16
Interpersonal rejection sensitivity	83	51.9	35	50.7	48	52.7	0.1	0.80	—	—	—	—	—	—
Mood reactivity	69	43.1	—	—	—	—	—	—	35	42.2	34	44.2	0.1	0.80

for those with and without mood reactivity was 22.5% versus 18.5% (χ^2=0.8, df=1, p=0.39) for weight gain, 30.6% versus 22.6% (χ^2=2.2, df=1, p=0.14) for hypersomnia, 25.2% versus 34.6% (χ^2=2.7, df=1, p=0.10) for leaden paralysis, and 42.3% versus 37.7% (χ^2=0.6, df=1, p=0.45) for interpersonal rejection sensitivity.

Although associations between mood reactivity and individual criterion B accessory symptoms were weak, we nevertheless examined for associations between mood reactivity and salient covariates (i.e., gender, bipolar status, trichotomized age, Beck Depression Inventory and Hamilton depression scale scores) in a group of 151 subjects after excluding all subjects with missing data. Logistic regression analyses examined the impact of each covariate alone on mood reactivity, with the only significant predictors being depression severity measures. Thus, with a Hamilton depression scale score of 17 or less as the reference category, those scoring 18 to 24 were less likely to report mood reactivity (odds ratio=0.31, Wald χ^2=8.6, df=1, p=0.003), as were those scoring 25 or more (odds ratio=0.20, Wald χ^2=11.3, df=1, p=0.001). Second, with a Beck Depression Inventory score of 21 or less as the reference category, those scoring 22 to 40 were less likely to report mood reactivity (odds ratio=0.42, Wald χ^2=4.5, df=1, p=0.03), as were those scoring more than 40 (odds ratio=0.35, Wald χ^2=3.5, df=1, p=0.06). When all five covariates were included, there was a significant overall improvement in prediction (change in χ^2=20.2, df=8, p=0.01), but only the difference in Hamilton depression scale scores was significant (for Hamilton depression scale scores of 18–24: odds ratio=0.29, Wald χ^2=7.7, df=1, p=0.005; for Hamilton depression scale scores of 25 or more: odds ratio=0.19, Wald χ^2=9.4, df=1, p=0.002). Clearly, the more severe the depression the less likely it was for patients to report criterion A and thus be eligible for the diagnosis.

We then used Poisson regression to examine the effect of the five covariates and criterion A on the number of reported criterion B symptoms, which is critical to the diagnosis. All six analyses showed nonsignificant effects as did the multivariate regression analysis (χ^2=9.8, df=9, p=0.37). Thus, the number of criterion B symptoms was largely unrelated to the covariates (including depression severity) or, and more importantly, to criterion A. These several analyses argued against the intrinsic validity of the DSM-IV decision rules, perhaps because the mandatory criterion of reactive mood is nondiscriminatory and is more a marker of depression severity.

If atypical depression is a spectrum disorder (38, 39), then a personality style of interpersonal rejection sensitivity might determine overrepresented depressive symptoms. We thus compared data on the remaining atypical symptoms for subjects classified as either positive or negative for interpersonal rejection sensitivity (Table 1). Those with interpersonal rejection sensitivity were significantly more likely to report hypersomnia and nonsignificantly more likely to report leaden paralysis, but rates of weight gain and mood reactivity were similar in the two groups.

Respecting historical links between atypical features and anxiety disorders, we examined the extent to which the presence of a lifetime anxiety disorder (assessed by the Composite International Diagnostic Interview) increased the probability of DSM-IV features. Lifetime anxiety disorder included panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, agoraphobia, and social phobia, with prevalence estimates of 29%, 11%, 11%, 8%, and 36%, respectively. Table 2 shows that those experiencing any lifetime anxiety disorder differed only in being more likely to report weight gain. A separate examination of the two most prevalent anxiety disorders (panic disorder and social phobia) identified several differences. Those meeting criteria for lifetime social phobia tended to be more likely to report hypersomnia and leaden paralysis, although the differences did not reach significance. Those meeting lifetime criteria for panic disorder were significantly more likely to report weight gain, leaden paralysis, and interpersonal rejection sensitivity.

Log linear analyses examined the effects of lifetime anxiety disorder diagnosis, gender, and their interaction on the reporting of atypical depressive symptoms. For panic disorder, there were significant main effects for diagnosis on weight gain (z=2.16, p=0.03, N=156), leaden paralysis (z=2.06, p=0.04, N=156), and interpersonal rejection sensitivity rejection (z=2.68, p<0.01, N=156), indicating in-

TABLE 2. Symptom Criteria of the DSM-IV Atypical Features Specifier for a Major Depressive Episode Met by 156 Nonpsychotic Depressed Subjects With and Without a Lifetime Anxiety Disorder[a]

	All Subjects		Subjects With Any Lifetime Anxiety Disorder (N=87)		Subjects Without a Lifetime Anxiety Disorder (N=69)		Analysis		Subjects With Lifetime Social Phobia (N=57)		Subjects Without Lifetime Social Phobia (N=99)		Analysis		Subjects With Lifetime Panic Disorder (N=46)		Subjects Without Lifetime Panic Disorder (N=110)		Analysis	
Symptom	N	%	N	%	N	%	χ^2 (df=1)	p	N	%	N	%	χ^2 (df=1)	p	N	%	N	%	χ^2 (df=1)	p
Weight gain	33	21.2	25	28.7	8	11.6	6.8	<0.001	16	28.1	17	17.2	2.6	0.41	17	37.0	16	14.5	9.8	0.002
Hypersomnia	46	29.5	28	32.2	18	26.1	0.7	0.41	22	38.6	24	24.2	3.6	0.06	15	32.6	31	28.2	0.3	0.58
Leaden paralysis	47	30.1	30	34.5	17	24.6	1.8	0.18	22	38.6	25	25.3	3.6	0.08	21	45.7	26	23.6	7.5	0.006
Interpersonal rejection sensitivity	82	52.6	48	55.2	34	49.3	0.5	0.46	34	59.6	48	48.5	1.8	0.18	30	65.2	52	47.3	4.2	0.04
Mood reactivity	67	42.9	35	40.2	32	46.4	0.6	0.41	23	40.4	44	44.4	0.2	0.62	15	32.6	52	47.3	2.8	0.09

[a] Data for four subjects were missing.

creased symptom rates for those with panic disorder. An effect of gender was only significant for interpersonal rejection sensitivity (z=2.49, p<0.05, N=156), which was reported by 79.3% of the female subjects and 41.2% of the male subjects. There were no significant diagnosis-by-gender interactions. For social phobia, there was a significant main effect for leaden paralysis, both for diagnosis (z=2.56, p<0.05, N=156) and for gender (z=2.65, p<0.01, N=156). Leaden paralysis was reported by 52.8% of female subjects and 14.3% of male subjects.

In a previous study (40) we refined a set of 61 clinical features of anxiety and depression to form a group of 38 clinical features (21 depression features and 17 anxiety features) and conducted cluster analyses to identify a four-cluster solution with clusters labeled anxiety, irritability, depressed mood, and residual. Here we examine the prevalence of the symptoms that constitute the DSM-IV criteria for the atypical features specifier and the prevalence of relevant lifetime anxiety disorders across the four clusters (Table 3). As might be anticipated, lifetime anxiety disorder as well as lifetime panic disorder (separately) loaded highest on the anxiety cluster, together with two of the associated atypical symptoms (interpersonal sensitivity rejection and leaden paralysis). Mood reactivity rates differed significantly across the clusters, having the lowest prevalence in the anxiety cluster and the highest in the irritability cluster. Weight gain and hypersomnia rates did not differ significantly across clusters. The analysis suggests differing levels of specificity in the phenomenological roots of the atypical features.

Poisson regression analyses were undertaken for the three anxiety disorder variables listed in Table 3 to examine the effect when the variable was entered alone and then after all other covariates. The data set comprised 147 subjects to ensure that there were no missing data. The effect of any lifetime anxiety disorder (when entered alone) corresponded to having 1.32 as many symptoms, a nonsignificant effect (χ^2=3.63, df=1, p=0.06), which remained nonsignificant (p=0.08) when the variable was entered last. When lifetime panic disorder was entered alone, the effect was equal to 1.57 times as many symptoms and was significant (χ^2=8.72, df=1, p=0.003). Panic disorder remained significant when added last, and the effect was equal to 1.60 times as many symptoms (χ^2=8.50, df=1, p=0.004). For social phobia entered alone, the effect was significant and corresponded to 1.47 times as many symptoms (χ^2=7.06, df=1, p=0.008); adding social phobia last gave a significant effect equal to 1.41 times as many symptoms (χ^2=5.21, df=1, p=0.02). These analyses indicate that elements of panic disorder/social phobia make up the key driver of the number of criterion B symptoms, which determines whether the DSM-IV atypical features specifier can be applied for depressed individuals who meet criterion A.

Discussion

Whether atypical depression is viewed as a disorder or as a symptom set, its status remains problematic. If there is more than one type of depression and at least one expression that is typical (e.g., melancholia), then atypical depression could reflect residual heterogeneous conditions. There are several problems in defining one condition by the absence of features specific to another. First is the risk of defining atypical depression on the basis of a potpourri of the features that are least characteristic of typical depression. Defining an elephant as an animal differing from a giraffe says what an elephant is not, but without defining the positive characteristics of the giraffe.

Second, previous research has emphasized a selective response to MAOIs as defining a clinical entity. While such an approach is unusual, it could be productive if the independent variable (specific intervention) and the dependent variable (clinical pattern) iteratively identified the clinical syndrome. Such iterative refinement has not occurred, nor has the utility of the criteria suggested in the English (London group) and North American (Columbia group) research been compared.

The North American approach, captured in the DSM-IV criteria set, preserved only hyperphagia and hypersomnia from the English studies. It excluded anxiety, despite earlier descriptions suggesting a distinct role for phobic anxi-

TABLE 3. Occurrence of Symptoms Constituting the Criteria of the DSM-IV Atypical Features Specifier for a Major Depressive Episode and of Lifetime Anxiety Disorders in Nonpsychotic Depressed Subjects Categorized by Dominant Symptom Cluster[a]

	Subjects Categorized by Symptom Cluster									
	Anxious (N=57)		Irritability (N=34)		Depressed (N=61)		Residual (N=33)		Analysis	
Symptom or Disorder	N	%	N	%	N	%	N	%	χ^2 (df=3)	p
Weight gain	12	21.1	6	17.6	15	24.6	4	12.1	2.2	0.52
Hypersomnia	17	29.8	9	26.5	21	34.4	6	18.2	2.9	0.41
Reactive mood	16	28.1	23	67.6	21	34.4	16	48.5	15.8	<0.001
Interpersonal rejection sensitivity	37	64.9	16	47.1	23	37.7	10	30.3	13.1	0.004
Leaden paralysis	28	49.1	3	8.8	26	42.6	1	3.0	32.3	<0.001
Lifetime panic disorder	26	45.6	4	11.8	14	23.0	4	12.1	16.8	<0.001
Lifetime social phobia	24	42.1	8	23.5	24	39.3	6	18.2	7.7	<0.06
Any lifetime anxiety disorder	40	70.2	13	38.2	32	52.5	10	30.3	14.7	0.002

[a] Symptom clusters identified in a previous cluster analysis of 38 clinical features of depression and anxiety (40).

ety. It also introduced a hysteroid dysphoric style criterion (later modified to interpersonal rejection sensitivity) as well as extreme anergia or fatigue (later labeled leaden paralysis). The DSM-IV criteria advanced the primacy of mood reactivity, but without clarifying whether this was an independent hurdle to exclude melancholic depression or a constituent feature.

Our analyses failed to support the DSM-IV criteria set. First, the mandatory criterion of mood reactivity did not appear central. If it is an independent hurdle designed to exclude those with a melancholic depression, it is redundant, as criterion C for the atypical features specifier mandates that criteria are not met for the melancholic features specifier during the same episode. If mood reactivity is a higher-order descriptor of atypical depression, its presence should be associated with a higher rate of accessory symptoms. In our analyses, mood reactivity failed to predict overrepresentation of any associated symptom or the number of such symptoms. It did not appear to be discriminating other than being influenced by depression severity. Second, the accessory features were not interdependent, arguing against a syndromal construct.

Alternative Models

We tested two alternative models respecting the basic DSM-IV descriptor set. It has been argued that many nonmelancholic expressions of depression can be modeled as spectrum disorders, whereby neurobiological processes shape personality style as well as the surface symptom pattern of any depressive syndrome (38). Quitkin and colleagues (39) have suggested that atypical depression conforms to such a spectrum model. The criteria set may, however, benefit from remodeling—particularly if alternate personality traits of interpersonal rejection sensitivity and anxiety increase syndrome risk and shape the surface symptom pattern, as suggested here.

Our second reformulation respected the long-standing suggestion that atypical depression is secondary to anxiety. In pursuing this model we found limited support when *any* lifetime anxiety disorder was examined, but some support when the two commonest anxiety disorders in our subjects (panic disorder and social phobia) were examined separately. The cluster analysis supported this revisionist model. The anxiety cluster was more common in those meeting the criteria for lifetime panic disorder or lifetime social phobia, as would be anticipated. In addition, this cluster had significantly high rates of interpersonal rejection sensitivity and leaden paralysis, suggesting phenomenological association with anxiety rather than with depression. Some gender effects were identified, suggesting a greater chance of some atypical symptoms in female subjects and warranting refined study.

Anxiety Revisited

It is important to revisit the earlier suggestion that anxiety is central to atypical depression. In their London study, West and Dally (5) reported that "atypical depressive feature states…[resembled] anxiety hysteria with secondary depression." Sargant (2) noted that among rapid MAOI responders, there were subjects who "were starting to overlap and sometimes become indistinguishable from…[patients with]…anxiety states." Early North American reports clearly noted a primary contribution from anxiety, including phobic anxiety (41) and generalized anxiety (11), while commentators noted that some of their patients meeting Columbia criteria "also experienced spontaneous panic attacks" (14). Further, one ECA analysis indicated that those with atypical depression were significantly more likely to meet criteria for panic disorder and somatization disorder, but not agoraphobia, social phobia, or simple phobia (24).

As noted, the Columbia MAOI comparative studies initially observed greater responsivity in patients with panic attacks in conjunction with atypical depression (14). However, when the number of subjects was doubled, the tendency for those with lifetime panic attacks (compared to those with plain atypical depression) to respond preferentially to both tricyclics and MAOIs was no longer present, with differential responsivity restricted to the MAOIs (30). In an independent study, differential effects between MAOIs and tricyclic antidepressants were not found when atypical depression was defined as the concurrence of panic attacks and depression (42). Here, MAOI superiority was identified only in women, while men showed a prefer-

ential response to tricyclic antidepressants. Again, when atypicality was defined as depression superimposed on a diagnosis of generalized anxiety *or* panic disorder, no differences were found between the active drugs or between the active drugs and placebo.

Our data confirm the relevance of anxiety—as expressed by panic disorder and social phobia—to atypical depression symptoms. Neither were formalized diagnoses at the time of the early London studies, but several reports (43–45) have since documented more symptoms of atypical depression in those with social phobia, with one estimating that two-thirds of the subjects with major depression and social phobia met the criteria for atypical depression (44). The links between anxiety and interpersonal rejection sensitivity are conceptually strong, and anxiety is well known to respond to MAOI medication (46). We suggest that these two anxiety disorders are key candidates for further research.

Phenelzine has long been suggested as superior to tricyclic drugs in the treatment of depressed patients with anxiety (3, 47, 48), and the Columbia group has considered the contribution of panic attacks to MAOI responsivity in those with atypical depression. However, the latter studies considered panic attacks rather than lifetime panic disorder, and it remains possible that MAOIs are of more benefit for underlying panic disorder.

The preferential MAOI response may have received excessive attention in the evolution of concepts of atypical depression. The superiority of MAOIs was established against the principal antidepressants of that time (tricyclics), but there are now studies suggesting comparable efficacy of SSRIs and MAOIs (17). Furthermore, a placebo-controlled trial of cognitive therapy and phenelzine for patients with major depression and atypical features established both as superior to placebo and "comparable on all outcome measures" (21). It is possible that MAOIs are not superior, but rather that tricyclic drugs are distinctly inferior for depressed patients with atypical features or perhaps less effective than MAOIs for the overall nonmelancholic class.

Hypersomnolence and Hyperphagia

Our data suggest that hypersensitivity to rejection is a primary feature of atypical depression, whether it precedes and increases the risk of panic disorder and social phobia or is a consequence. Hypersensitivity to rejection might also increase vulnerability to developing depression in response to life stressors. Further, we speculate that such individuals respond to feeling depressed with self-consolatory strategies such as overeating and oversleeping.

Thase and colleagues (49) conjectured that hypersomnolence might be an adaptive homeostatic response that restores slow-wave sleep during stress and that hyperphagia may be a compensatory response leading to increased dietary intake of L-tryptophan, increasing brain 5-HT levels. We suggest that hyperphagia determinants should be examined in more detail. For example, it is recognized that carbohydrates (especially chocolate) have a comforting effect, triggering release of endorphins and promoting "feel-good" sensations. It is feasible that hypersensitivity to rejection is satiated by eating sugar-rich products that release multiple gut and brain peptides, including cholecystokinin and corticotrophin-releasing hormone, which are known to modify cognition. It is also recognized that antidepressants effective in treating atypical depression act on central appetite centers and modify these mechanisms through hypothalamic receptors (50, 51).

Any benefit from MAOIs might seem paradoxical, as hydrazines such as phenelzine are themselves associated with carbohydrate craving and weight gain. However, both depression and eating disorders alter 5-HT hypothalamic activity (52), and, as MAOIs influence serotonergic function in numerous brain regions, it is possible that they modulate appetite and weight. Theoretically, atypical depression might be expected to respond preferentially to SSRI medication as such drugs generally decrease appetite initially and do not produce weight gain (53).

Conclusions

Our data challenge the DSM-IV definition of the atypical features specifier in major depressive disorder as a valid entity and call into question the etiological, clinical, and treatment value of its diagnostic criteria. We suggest a need to reexamine rather than reify a clinically plausible but empirically weak construct. On the basis of our data, we propose a reformulation of atypical depression as a spectrum disorder and identify a number of hypotheses to be pursued in further research.

Davidson and colleagues (4) suggested that the relationship between anxiety and atypical depression requires further investigation. We suggest that that statement still holds. Our empirically based reformulation builds on both the early London work and the criteria set provided by the clinically observant Columbia group of researchers. It gives primacy to a personality style (rather than to mood reactivity) and to anxiety. The reformulation also views hyperphagia and hypersomnolence as having adaptive homeostatic potential rather than necessarily being depressive symptoms.

Progress might best occur by examining the comparative utility of the differing models. Establishing a criteria set of features is likely to be difficult for a disorder or process that appears to span symptom and personality axes and encompass expressions of anxiety and depression and that may include homeostatic features. If such a multiaxial syndrome can be redefined and validated, it would truly warrant the term "atypical depression."

Received May 30, 2001; revisions received Oct. 9 and Dec. 5, 2001, and Feb. 21, 2002; accepted March 5, 2002. From the School of Psychiatry, University of New South Wales; and the Mood Disorders Unit, Prince of Wales Hospital. Address reprint requests to Dr. Parker, Euroa Unit, Prince of Wales Hospital, Randwick, New South Wales, Australia 2031; g.parker@unsw.edu.au (e-mail).

Supported by a National Health and Medical Research Council Program Grant (993208) and an infrastructure grant from the New South Wales Department of Health.

The authors thank Kerrie Eyers, Heather Brotchie, Gemma Gladstone, Tony James, Yvonne Foy, and Christine Boyd for assistance with the study and Dr. Fred Quitkin for comments on an earlier draft.

References

1. Quitkin FM, Stewart JW, McGrath PJ, Liebowitz MR, Harrison WM, Tricamo E, Klein DF, Rabkin JG, Markowitz JS, Wager SG: Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. Am J Psychiatry 1988; 145:306–311
2. Sargant W: The treatment of anxiety states and atypical depressions by the monoamine oxidase inhibitor drugs. J Neuropsychiatry 1962; 3(suppl 1):96–103
3. Robins E, Guze SB: Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970; 126:983–987
4. Davidson JR, Miller RD, Turnbull CD, Sullivan JL: Atypical depression. Arch Gen Psychiatry 1982; 39:527–534
5. West ED, Dally PJ: Effects of iproniazid in depressive syndromes. Br Med J 1959; 1:1491–1494
6. Sargant W: Some newer drugs in the treatment of depression and their relation to other somatic treatments. Psychosomatics 1960; 1:14–17
7. Pollitt JD: Suggestions for a physiological classification of depression. Br J Psychiatry 1965; 111:489–495
8. Pare CM: Monoamine oxidase inhibitors in resistant depression. Int Pharmacopsychiatry 1979; 14:101–109
9. Robinson DS, Nies A, Ravaris CL, Ives JO, Bartlett D: Clinical pharmacology of phenelzine. Arch Gen Psychiatry 1978; 35: 629–635
10. Paykel ES, Rowan PR, Parker RR, Bhat AV: Response to phenelzine and amitriptyline in subtypes of outpatient depression. Arch Gen Psychiatry 1982; 39:1041–1049
11. Sovner RD: The clinical characteristics and treatment of atypical depression. J Clin Psychiatry 1981; 42:285–289
12. Klein DF, Davis JM: Diagnosis and Drug Treatment of Psychiatric Disorders. Baltimore, Williams & Wilkins, 1969
13. Liebowitz MR, Klein DF: Hysteroid dysphoria. Psychiatr Clin North Am 1979; 2:555–575
14. Liebowitz MR, Quitkin FM, Stewart JW, McGrath PJ, Harrison W, Rabkin J, Tricamo E, Markowitz JS, Klein DF: Phenelzine v imipramine in atypical depression: a preliminary report. Arch Gen Psychiatry 1984; 41:669–677
15. Quitkin FM, Rifkin A, Klein DF: Monoamine oxidase inhibitors: a review of antidepressant effectiveness. Arch Gen Psychiatry 1979; 36:749–760
16. Quitkin FM, Stewart JW, McGrath PJ, Tricamo E, Rabkin JG, Ocepek-Welikson K, Nunes E, Harrison W, Klein DF: Columbia atypical depression: a subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. Br J Psychiatry 1993; 163(suppl 21):30–34
17. McGrath PJ, Stewart JW, Janal MN, Petkova E, Quitkin FM, Klein DF: A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. Am J Psychiatry 2000; 157:344–350
18. Quitkin FM, McGrath PJ, Stewart JW, Harrison W, Tricamo E, Wager SG, Ocepek-Welikson K, Nunes E, Rabkin JG, Klein DF: Atypical depression, panic attacks, and response to imipramine and phenelzine: a replication. Arch Gen Psychiatry 1990; 47: 935–941
19. Derecho CN, Wetzler S, McGinn LK, Sanderson WC, Asnis GM: Atypical depression among psychiatric inpatient clinical features and personality traits. J Affect Disord 1996; 39:55–59
20. Zisook S, Schucter SR, Gallagher T, Sledge P: Atypical depression in an outpatient psychiatric population. Depression 1993; 1:268–274
21. Jarrett RB, Schaffer M, McIntyre D, Will-Browder A, Kraft D, Risser R: Treatment of atypical depression with cognitive therapy or phenelzine: a double-bind, placebo-controlled trial. Arch Gen Psychiatry 1999; 56:431–437
22. Nierenberg AA, Alpert JE, Pava J, Rosenbaum JF, Fava M: Course and treatment of atypical depression. J Clin Psychiatry 1999; 59(suppl 18):5–9
23. Kendler KS, Eaves LJ, Walters EE, Neale MC, Heath AC, Kessler RC: The identification and validation of distinct depressive syndromes in a population-based sample of female twins. Arch Gen Psychiatry 1996; 53:391–399
24. Horwath E, Johnson J, Weissman MM, Hornig CD: The validity of major depression with atypical features based on a community study. J Affect Disord 1992; 26:117–126
25. Sullivan PF, Kessler RC, Kendler KS: Latent class analysis of lifetime depressive symptoms in the National Comorbidity Survey. Am J Psychiatry 1998; 155:1398–1406
26. Stewart JW, McGrath PJ, Rabkin JG, Quitkin FM: Atypical depression: a valid clinical entity? Psychiatr Clin North Am 1993; 16: 479–495
27. Nierenberg AA, Alpert JE, Fava J, Rosenbaum JF, Fava M: Course and treatment of atypical depression. J Clin Psychiatry 1998; 59(suppl 18):5–9
28. Robinson DS, Nies A, Ravaris CL, Lamborn KR: The monoamine oxidase inhibitor, phenelzin, in the treatment of depressive-anxiety states: a controlled clinical trial. Arch Gen Psychiatry 1973; 29:407–413
29. Ravaris CL, Robinson DS, Ives JO, Nies A, Bartlett D: Phenelzine and amitriptyline in the treatment of depression: a comparison of present and past studies. Arch Gen Psychiatry 1980; 37: 1075–1080
30. Liebowitz MR, Quitkin FM, Stewart JW, McGrath PJ, Harrison WM, Rabkin JG, Tricamo E, Goetz DM, Klein DF: Antidepressant specificity in atypical depression. Arch Gen Psychiatry 1988; 45:129–137
31. Stewart JW, Quitkin FM, Liebowitz MR, McGrath PJ, Harrison WM, Klein DF: Efficacy of desipramine in depressed outpatients: response according to Research Diagnostic Criteria diagnoses and severity of illness. Arch Gen Psychiatry 1983; 40: 202–207
32. McGrath PJ, Stewart JW, Harrison WM, Ocepek-Welikson K, Rabkin JG, Nunes E, Wager S, Tricamo E, Quitkin FM, Klein DF: The predictive value of symptoms of atypical depression for differential drug treatment outcome. J Clin Psychopharmacol 1992; 12:197–202
33. Joyce PR, Paykel ES: Predictors of drug response in depression. Arch Gen Psychiatry 1989; 46:89–99
34. Parker G, Gladstone G, Wilhelm K, Hickie I, Mitchell P, Hadzi-Pavlovic D, Austin M-P, Eyers K: An aetiological model of non-melancholic depression: study design and validity of the measures. Aust NZ J Psychiatry 1998; 32:104–111
35. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561–571

36. World Health Organization: Composite International Diagnostic Interview, CIDI-A, version 1-2. Sydney, Australia, WHO Research and Training Centre, 1993
37. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
38. Parker G: Classifying depression: should paradigms lost be regained? Am J Psychiatry 2000; 157:1195–1203
39. Quitkin FM, Stewart JW, McGrath PJ, Klein DF: Classifying depression (letter). Am J Psychiatry 2001; 158:1332–1333
40. Parker G, Roy K, Wilhelm K, Mitchell P, Austin M-P, Hadzi-Pavlovic D, Little C: Sub-grouping non-melancholic depression from manifest clinical features. J Affect Disord 1999; 53:1–13
41. Ravaris CL, Nies A, Robinson DS, Ives JO, Lamborn KR, Korson L: A multiple-dose, controlled study of phenelzine in depression-anxiety states. Arch Gen Psychiatry 1976; 30:66–75
42. Davidson J, Pelton S: Forms of atypical depression and their response to antidepressant drugs. Psychiatry Res 1986; 17:87–95
43. Dilsaver SC, Qamar AB, del Medico VJ: Secondary social phobia in patients with major depression. Psychiatry Res 1992; 44:33–40
44. Mannuzza S, Schneier FR, Chapman TF, Liebowitz MR, Klein DF, Fyer AJ: Generalized social phobia. Arch Gen Psychiatry 1995; 52:230–237
45. Alpert JE, Uebelacker LA, McLean NE, Nierenberg AA, Fava JA, Worthington JJ, Tedlow JR, Rosenbaum JF, Fava M: Social phobia, avoidant personality disorder and atypical depression: co-occurrence and clinical implications. Psychol Med 1997; 27: 627–633
46. Liebowitz MR, Schneier F, Campeas R, Hollander E, Hatterer J, Fyer AJ, Gorman JM, Papp L. Davies S, Gulley R, Klein DR: Phenelzine vs atenolol in social phobia: a placebo-controlled comparison. Arch Gen Psychiatry 1992; 49:290–300
47. Sheehan DV, Ballenger J, Jacobson G: Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. Arch Gen Psychiatry 1980; 37:51–59
48. Nies A, Howard D, Robinson DS: Antianxiety effects of MAO inhibitors, in The Biology of Anxiety. Edited by Mathew RJ. New York, Brunner/Mazel, 1982, pp 123–133
49. Thase ME, Frank E, Kornstein SG, Yonkers KA: Gender differences in response to treatments of depression, in Gender and Its Effects on Psychopathology. Edited by Frank E. Washington, DC, American Psychiatric Press, 2000, pp 103–129
50. Gold PW, Chrousos GP: The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. Proc Assoc Am Physicians 1999; 111:22–34
51. Charney Y, Cusin I, Rohner-Jeanrenaud F, Muzzin P, Steimer T, Archinard M, Bouras C: Central control of food intake: new connections of interest in biological psychiatry? Schweiz Arch Neurol Psychiatr 2000; 151:236–246
52. Monteleone P, Brambilla F, Bortolotti F, Maj M: Serotonergic dysfunction across eating disorders: relationship to eating behaviour, nutritional status and general psychopathology. Psychol Med 2000; 30:1099–1110
53. Fernstrom MH, Kupfer DJ: Antidepressant-induced weight gain: a comparison study of four medications. Psychiatry Res 1998; 26:265–271