Are atypical depression, borderline personality disorder and bipolar II disorder overlapping manifestations of a common cyclothymic diathesis?

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The constructs of atypical depression, bipolar II disorder and borderline personality disorder (BPD) overlap. We explored the relationships between these constructs and their temperamental underpinnings. We examined 107 consecutive patients who met DSM-IV criteria for major depressive episode with atypical features. Those who also met the DSM-IV criteria for BPD (BPD+), compared with those who did not (BPD-), had a significantly higher lifetime comorbidity for body dysmorphic disorder, bulimia nervosa, narcissistic, dependent and avoidant personality disorders, and cyclothymia. BPD+ also scored higher on the Atypical Depression Diagnostic Scale items of mood reactivity, interpersonal sensitivity, functional impairment, avoidance of relationships, other rejection avoidance, and on the Hopkins Symptoms Check List obsessive-compulsive, interpersonal sensitivity, anxiety, anger-hostility, paranoid ideation and psychoticism factors. Logistic regression revealed that cyclothymic temperament accounted for much of the relationship between atypical depression and BPD, predicting 6 of 9 of the defining DSM-IV attributes of the latter. Trait mood lability (among BPD patients) and interpersonal sensitivity (among atypical depressive patients) appear to be related as part of an underlying cyclothymic temperamental matrix.

Key words: Atypical depression, borderline personality disorder, bipolar II disorder, cyclothymic temperament

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The relationship between atypical depression, borderline personality disorder (BPD) and bipolar II disorder (BP-II) remains understudied. Previous work by us (1,2) and others (3-6) suggests a considerable overlap in both clinical manifestations and long-term traits of patients within this broad realm.

The rubric "atypical depression" includes a large subset (7,8) of depressive states characterized by reactive mood, a pattern of stable interpersonal sensitivity (exaggerated vulnerability to feeling hurt by criticism or rejection) and reverse vegetative symptoms such as increased appetite and hypersomnia. In its original description, atypical depression was also invariably associated with phobic-anxious symptomatology and preferential response to monoamine oxidase inhibitors (9).

The related concept of "hysteroid dysphoria" (10) has been used to describe a subgroup of depressed patients, usually women, whose hallmark is an extreme intolerance of personal rejection, with a particular vulnerability to loss of romantic relationships. The stormy lifestyle of these patients suggests a link to BP-II and related cyclothymic or "soft" bipolar conditions (11-13).

Regrettably, most clinical studies of atypical depression exclude definite bipolar disorder (9,10,14). Such exclusion appears unjustified on the basis of the observation of similar rates of atypicality in unipolar and bipolar I depressives (15) and of higher rates in BP-II compared to unipolar patients (16). Follow-up data also show a frequent bipolar outcome in atypical depressives (15,17).

In a previous study (2), we observed that 32.6% of 86 major depressive patients with DSM-IV atypical features met criteria for strictly defined BP-II and 72% met our criteria for bipolar spectrum disorder (major depression plus hypomania and/or cyclothymic or hyperthymic temperament). Family history for bipolar disorder validated these clinical observations. Lifetime comorbidity with anxiety disorders (panic disorder-agoraphobia, social phobia and obsessive-compulsive disorder) and both cluster B (dramatic, emotional or erratic) and C (anxious or fearful) personality disorders was very common. These findings suggested that the "atypicality" of depression is related to an affective temperamental dysregulation, which could explain why atypical depressive patients are often given "borderline" diagnoses (18).

In the present report, we expand our sample size and extend the aim of our analyses to compare previous course, symptomatic features, family history, and axis I and axis II comorbidity in atypical depressive patients with (BPD+) or without (BPD-) a concomitant diagnosis of BPD. Moreover, in order to better characterize this personality profile in atypical depressives, we explore its temperamental underpinnings and links with other personality disorders.

METHODS

A consecutive sample of 107 patients who met DSM-IV criteria for major depressive episode with atypical features (14 males and 93 females, mean age 31.5±8.8 years, range 16-55 years), was recruited in a three-year period at the Institute of Psychiatry of the University of Pisa. The subjects

came from a variety of sources, about equally divided between self-referrals, referrals from general practitioners and various medical specialists and psychiatrists. Exclusion criteria were a lifetime history of schizophrenia or other psychotic disorder, organic mental syndrome and serious or uncontrolled medical diseases. All patients provided written informed consent for participation in the study.

The Axis I diagnostic evaluation was conducted by the Structured Clinical Interview for DSM III-R (19) and the Semi-structured Interview for Depression (SID, 20). The SID, developed as part of the Pisa-San Diego Collaborative Study on Affective Disorders, has been used with 2500 patients at the time of this writing: its reliability for diagnostic assessment of patients and their temperaments has been documented elsewhere (21,22). Family history data were collected by the Family History Research Diagnostic Criteria (23). Temperaments were defined by our operational criteria, reported elsewhere (2, 24), which represent the University of Tennessee (25) modification of the Schneiderian descriptions (26). Cyclothymic temperament was defined according to Akiskal (27).

We considered two levels for the diagnosis of BP-II, based respectively on the "conservative" DSM-IV threshold of ≥ 4 days for hypomania, and the ≥ 2 days threshold embodied in the SID, which has been validated in large clinical and epidemiologic populations (28,29).

The diagnosis of atypical depression required mood reactivity (i.e., mood brightens in response to actual or potential positive events), plus two or more of the following features: significant weight gain or increase in appetite, hypersomnia, leaden paralysis, long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) resulting in significant social or occupational impairment, and absence of melancholic and catatonic features during the same episode. For the diagnosis of major depression with atypical features, we attained excellent inter-rater reliability (kappa = 0.94).

For the current and lifetime diagnosis of body dysmorphic disorder (BDD), we used a semi-structured interview (30). The diagnosis of borderline, histrionic, narcissistic, avoidant, dependent and obsessive-compulsive personality disorders was performed by the corresponding sections of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II, 31).

For symptomatological assessment, psychiatrists completed the following rating scales: the Atypical Depression Diagnostic Scale (ADDS, 32), a semi-structured interview designed to determine the presence and the severity, on a scale ranging from 1 to 6, of atypical features during the current depressive episode, the Hamilton Rating Scale for Depression (HRSD, 33) and its modified form for reverse vegetative features (34). Patients also completed the Hopkins Symptoms Check List (HSCL-90, 35).

Comparative analyses for familial, epidemiological, clini-

Table 1 Demographic and clinical features in patients with atypical depression with (BDP+) or without (BDP-) borderline personality disorder

	BDP+ (n=46)	BDP- (n=61)	t or β^2 (df=2)	p
Gender (% females)	87.0	86.7	0	0.99
Age (years, mean±SD)	30.0±7.7	32.7±9.4	-1.61	0.11
Age at onset (years, mean±SD)	22.2±7.8	23.2±8.2	-0.6	0.54
Age at first treatment (years, mean±SD)	24.6±8.9	26.3±10	-1	0.3
Age at first hospitalization (years, mean±SD)	18.2±15.0	18.3±17	0	0.98
Duration of current episode (months, mean±SD)	7.3±7.3	14.0±17.8	-2.41	0.02
Duration of illness (years, mean±SD)	7.7±6.0	9.5±7.6	-1.28	0.2
No. previous depressive episodes (mean±SD)	3.3±2.8	4.0±4.0	-1.02	0.32
No. hospitalizations (mean±SD)	1.1±1.8	1.5±2.8	-0.82	0.42
Residual (interepisodic) symptoms (%)	84.4	77.6	0.76	0.4
No. lifetime suicide attempts (mean±SD)	1.1±1.6	0.9±1.9	0.38	0.7
Suicide attempts in current episode (%)	32.6	15±24.6	0.84	0.04
Family history in first-degree relatives (%)				
Major depression	52.2	50.8	0.06	0.8
Bipolar disorder	10.9	9.9	0.22	0.73
Panic disorder-agoraphobia	8.7	16.4	1.37	0.24
Obsessive-compulsive disorder	4.3	5.0	0.55	0.46
Generalized anxiety disorder	4.3	0	2.7	0.1
Eating disorders	4.3	4.9	0.08	0.77
Alcohol abuse	2.2	5.0	0.55	0.46
Substance abuse	4.3	0	2.70	0.1

Table 2 Diagnosis distribution and comorbidity with Axis I and II disorders in patients with (BDP+) or without (BDP-) borderline personality disorder

	BDP+ (n=46)	BDP- (n=61)	β^2 (df=2)	p
Depressive types (%)				
Bipolar I	2.2	0	1.34	0.2
Bipolar II	26.1	21.3	0.33	0.6
Bipolar III (pharmacologic hypomania)	6.2	8.2	0.15	0.7
Bipolar NOS (cyclothymic/hyperthymic temperaments)	50.0	42.6	0.57	0.4
Bipolar spectrum (total)	84.8	72.1	3.62	0.06
Major depressive disorder, recurrent	8.7	24.6	4.54	0.03
Major depressive disorder, single episode	4.4	3.3	0.83	0.8
Anxiety disorders (%)				
Panic disorder	23.9	16.4	0.94	0.3
Panic disorder with agoraphobia	50.0	42.6	0.58	0.4
Obsessive-compulsive disorder	17.3	18.0	0.01	0.9
Social phobia	9 (19.6)	18 (29.5)	1.37	0.2
Generalized anxiety disorder	4 (8.7)	4 (6.6)	0.17	0.7
Other Axis I disorders (%)				
Body dysmorphic disorder	55.8	36.1	3.99	0.05
Anorexia nervosa	0	1.7	0.76	0.3
Bulimia nervosa	26.1	9.8	4.95	0.03
Alcohol related disorders	13.0	4.9	2.25	0.1
Substance related disorders	15.2	13.1	0.10	0.8
Axis II disorders (%)				
Histrionic	33.3	19.7	2.55	0.1
Narcissistic	31.1	9.8	7.66	0.006
Obsessive-compulsive	34.8	29.5	1.29	0.6
Dependent	63.0	34.4	8.63	0.003
Avoidant	73.3	52.5	4.76	0.03
Affective temperaments (%)				
Depressive	17.4	27.9	0.23	0.2
Hyperthymic	8.7	21.3	1.37	0.08
Cyclothymic	58.7	27.9	11.72	0.001

cal and course characteristics of subgroups were conducted using the Student's t-test for dimensional variables (or the Mann-Whitney U-test, when appropriate) and the χ^2 analysis for categorical variables (or the Fisher exact-test, when appropriate). A two-tailed significance level of $p<0.05$ was set. To assess the symptomatological picture associated with BPD, a series of multivariate analyses of variance was performed with the ADDS item scores, the HRSD factor and total scores, the item scores for reverse vegetative features of the HRSD and the HSCL-90 factor scores as dependent measures and the diagnosis of BPD as independent class variable. Finally, we undertook an analysis of the explanatory power of affective temperaments and personality disorders (predictors) using a standard backward stepwise logistic regression procedure for diagnosis and each criterion of BPD.

RESULTS

The rate of definite bipolar disorders (bipolar I and II) in the entire sample was 24.3% (n=26); pharmacological hypomania raised this rate to 31.8%. Broadening the bipolar spectrum to include major depressions in association with hyperthymic or cyclothymic temperaments (which in the DSM-IV schema might be subsumed under bipolar NOS) gave a yield of 77.6% (n=83).

The comparison between BPD+ and BPD- patients did not show significant differences in sex distribution, index age, age at onset of mood disorder, age at first treatment, age at first hospitalization, number of previous depressive episodes, number of hospitalizations, presence of residual symptomatology, stressors and lifetime or current history of suicide attempts (Table 1).

The two groups also showed similar rates of family history for mood, anxiety and eating disorders as well as alcohol and substance abuse. Only length of the current episode (shorter in BPD+) and rate of suicide attempts (higher in BPD+, in part definitional) distinguished the two groups.

As far as diagnostic distribution for Axis I is concerned (Table 2), our data did not reveal significant differences between BPD+ and BPD-, with the exception of non-bipolar recurrent major depression, that was more represented in BPD-. It is noteworthy that bipolarity, whether narrowly or broadly defined, did not distinguish the two groups.

Regarding the lifetime comorbidity with anxiety disorders (also shown in Table 2), panic disorder and agoraphobia were the most common in both groups; obsessive-compulsive disorder, social phobia and generalized anxiety were

Table 3 Symptomatological features in patients with (BDP+) or without (BDP-) borderline personality disorder

	BDP+ (n=46)	BDP- (n=61)	t value	p
Atypical Depression Diagnostic Scale (mean±SD)				
Usual reactivity	53.3±25.5	44.4±18.3	2.09	0.04
Maximum reactivity	70.2±15.8)	65.1±12.1	1.90	0.06
Interpersonal sensitivity	4.8±0.9	4.5±0.9	1.86	0.07
Quality of relationships	4.3±1.0	3.5±0.8	2.05	0.04
Functional impairment	4.3±1.0	3.9±0.8	2.51	0.01
Avoidance of relationships	3.9±1.0	3.5±1.1	2.02	0.05
Other rejection avoidance	4.0±1.2	3.6±1.1	2.07	0.04
Leaden paralysis	4.6±1.2	4.2±1.3	1.72	0.09
Increased appetite	3.2±1.8	3.5±1.6	-0.86	0.4
Increased food intake	3.1±1.8	3.3±1.6	-0.84	0.4
Weight gain	2.4±1.6	2.8±1.4	-1.51	0.1
Weight gain-increased appetite	2.3±2.0	2.5±2.0	-0.82	0.4
Hypersomnia	3.5±3.1	2.9±2.8	1.06	0.3
Hamilton Rating Scale factors (mean±SD)				
Anxiety-somatization	0.9±0.3	0.9±0.4	-0.003	0.99
Weight	0.2±0.5	0.1±0.3	1.48	0.1
Cognitive disturbances	1.0±0.5	0.8±0.4	2.04	0.04
Diurnal variations	1.2±0.7	1.0±0.7	1.63	0.1
Retardation	1.4±0.4	1.3±0.5	1.60	0.1
Sleep disturbance	0.5±0.5	0.5±0.5	-0.02	0.98
Total	21.2±5.2	18.8±6.2	2.05	0.04
Hamilton Scale for reverse symptoms (mean±SD)				
Lack of energy	2.9±0.8	2.9±0.9	0.15	0.9
Social withdrawal	1.7±1.0	1.8±1.1	-0.67	0.5
Increased appetite	1.4±1.2	1.5±1.1	-0.28	0.8
Increased food intake	1.3±1.2	1.5±1.1	-0.55	0.6
Carbohydrate craving	1.5±1.2	1.6±1.1	-0.42	0.7
Weight gain	0.7±0.8	0.9±0.8	-1.60	0.1
Hypersomnia	1.9±1.7	1.5±1.5	1.30	0.2
Hopkins Symptoms Check List-90 (mean±SD)				
Somatization	1.7±0.9	1.4±0.8	1.5	0.15
Obsessive-compulsive	2.1±0.9	1.9±1.0	1.9	0.1
Interpersonal sensitivity	1.9±1.0	1.5±0.9	2.3	0.02
Depression	2.4±0.9	2.1±0.9	1.2	0.25
Anxiety	2.0±1.0	1.5±0.9	2.5	0.01
Anger-hostility	1.7±1.0	0.9±0.7	4.0	0.0001
Phobic anxiety	1.3±1.0	1.0±0.7	1.7	0.09
Paranoid ideation	1.9±1.0	1.4±0.9	2.9	0.005
Psychoticism	1.4±0.8	1.0±0.7	2.5	0.01

less prevalent, but again, their rates were similar in BPD+ and BPD- patients. Body dysmorphic disorder and bulimia nervosa occurred more frequently in BPD+ than BPD-, while substance and alcohol related disorders were equally represented in the two groups. Personality disorders belonging to the anxious and dramatic clusters were highly represented in both groups. Narcissistic, dependent and avoidant personality disorders were significantly more common in BPD+ than BPD- patients. Of the affective temperaments, cyclothymic disposition was significantly more prevalent in the BPD+ group.

On multivariate analyses of variance, BPD+ and BPD- patients differed with respect to ADDS items scores (F=2.23, df=12/94, p=0.016) and HRCL-90 factor scores (F=2.51, df=9/97, p=0.013), but not to HRSD factor and total scores, and item scores for reverse vegetative features of the HRSD. Subsequent univariate analyses confirmed that BPD+ patients had significantly higher scores on the ADDS items covering reactivity of mood, interpersonal sensitivity, functional impairment, avoidance of relationships and other rejection avoidance, and on the HSCL-90 obsessive-compulsive, interpersonal sensitivity, anxiety, anger hostility, paranoid ideation and psychoticism factors (Table 3).

On the standard backward stepwise logistic regression, cyclothymic temperament, and dependent, avoidant and narcissistic personality disorders were predictors for BPD (Table 4). Among the BPD+ patients, cyclothymic temperament contributed significantly to 6 out of 9 DSM criteria: efforts to avoid real or imagined abandonment, unstable and intense interpersonal relationships, identity disturbance, impulsivity, recurrent suicidal behavior or self-mutilating behavior, affective instability, and marked reactivity of mood.

Dependent personality disorder was a significant variable

Table 4 Odd ratios and confidence intervals for DSM-IV diagnosis and criteria of borderline personality disorder

	Affective temperaments			Personality disorders				
	Hyperthymic	Depressive	Cyclothymic	Dependent	Avoidant	Hystrionic	Narcissistic	Obsessive-compulsive
Borderline personality disorder*****			2.02 (1.6-2.5)	1.50 (1.1-1.9)	1.62 (1.1-2.1)			1.81 (1.2-2.4)
Efforts to avoid real or imagined abandonment*****			1.64 (1.2-2.1)	2.17 (1.8-2.6)				
Unstable and intense interpersonal relationships*****			2.66 (2.2-3.2)		1.94 (1.4-2.4)	3.83 (3.1-4.5)		
Identity disturbance***			1.74 (1.3-2.2)		1.66 (1.2-2.1)			
Impulsivity*****			2.23 (1.8-2.6)				1.75 (1.2-2.3)	
Recurrent suicidal behavior, or self-mutilating behavior*			1.67 (1.3-2.1)					
Affective instability, marked reactivity of mood****			1.67 (1.2-2.1)			2.06 (1.4-2.7)		
Chronic feelings of emptiness**								
Inappropriate, intense anger or difficulty controlling anger								
Transient, stress-related paranoid ideation or severe dissociative symptoms								

*p<0.01; **p<0.007;***p<0.003; ****p<0.002; *****p<0.0001

only for efforts to avoid real or imagined abandonment; avoidant personality for unstable and intense interpersonal relationships and for identity disturbance; histrionic personality for unstable and intense interpersonal relationships, and for affective instability and marked reactivity of mood; and narcissistic personality for impulsivity.

DISCUSSION

Extending our earlier findings (2) in a much larger sample, the present study found that, when adopting "narrow criteria" based on DSM-IV, 24% of atypical depressives could be classified as bipolar. Using broader criteria, 78% could be considered to belong to the "soft" bipolar spectrum. The latter included depressions with history of hypomania shorter than four days and antidepressant-associated hypomania, as well as depressive episodes arising from cyclothymic and hyperthymic temperaments beyond the thresholds for BP-II in the DSM-IV schema. We are not the only research team reporting high rates of bipolar spectrum disorders in atypical depressives (16,36,37).

In our sample, 43% of atypical depressive patients met DSM-IV criteria for BPD. However, this was not the most common Axis II disorder: avoidant and dependent personality disorders, probably related to the presence of interpersonal sensitivity and separation anxiety, were even more prevalent.

BPD+ patients, when compared to BPD-, were characterized by a higher rate of comorbidity with Axis II disorders of the anxious and dramatic clusters, in particular narcissistic, avoidant and dependent personality disorders. The most significant association was, however, with cyclothymic temperament. These findings support the observation that borderline characterologic features are related to the mood instability of the cyclothymic type (4,6,12).

According to the logistic regression, the presence of cyclothymic attributes explains most, but not all, of the relationship between atypical depression and BPD, including avoidance of abandonment, unstable relationships, identity disturbance, impulsivity, self-injurious behavior, affective irritability and reactivity. Avoidant and dependent traits, more related to the presence of phobic-anxious attitudes, also appear relevant to the diagnosis of BPD, as well as to the prediction of several BPD criteria, such as unstable and intense interpersonal relationships, identity disturbance and efforts to avoid real or imagined abandonment. The presence of narcissistic personality appears to be related to impulsivity, while histrionic personality accounts for unstable and intense interpersonal relationships, affective instability, and marked mood reactivity. In a recent study, hypomanic symptoms have been shown to predict an increase in narcissistic and histrionic personality features in suicidal young adults: it is unclear whether "mood symptoms might impact personality" ("scar hypothesis") or vice versa (38).

According to Henry et al (39), BDP and BP-II are charac-

terized by different types of affective lability: shifts from anger and anxiety to euthymia are associated with BDP, whereas shifts from euthymia to depression and elation and vice versa are characteristic of BP-II patients. In our patients, mood lability, hostility and anxious-avoidant-sensitive traits appear to be related, within a cyclothymic temperamental matrix. Other authors interpreted the affective instability of BPD as a form of prolonged ultra-rapid cycling with extreme rapid mood switching (40), closely resembling classic descriptions of cyclothymia (1).

In a more hypothetical vein, we submit that cyclothymic disposition might represent the mediating core characteristic in this complex pattern of mood, anxiety, and impulsive disorders. Anxious-sensitive symptomatology and hostile-impulsive-addictive behavior, rather than being considered independent comorbidities, might represent core features of such cyclothymic diathesis (41,42), largely pinpointed by a common familial trait (43,44). The coexistence among mood, anxiety and impulsive disorders and BPD has been reported by Zanarini et al (45) in a large population of severe personality disorder inpatients and in a subsequent prospective follow-up of over 6 years (46). More recently, a lifetime pattern of complex Axis I comorbidity of disorders of affect (mood and anxiety disorders) and of impulse (alcohol-substance use and eating disorders) was found to have strong positive predictive power for the BPD diagnosis (47). Unfortunately these authors did not examine cyclothymic and other bipolar spectrum disorders with specific measures. This is a common omission among "borderline" researchers, possibly based on a DSM-IV convention. According to this manual, "mood lability" distinguishes BPD from BP-II. However, this can be questioned, because in a large sample of major depressive patients examined prospectively in the National Institute of Mental Health collaborative study of depression, mood lability was the most specific predictor of BP-II outcome (48).

Certainly, prospective studies with greater methodological sophistication are needed to clarify the relationship of the putative temperamental and developmental variables to the complex affective patterns we have described. However, a proper consideration of "soft" bipolarity in borderline-atypical depressive patients (50) is extremely important in order to protect them from antidepressant-induced switches or rapid cycling and make them accessible to pharmacological and psychological approaches focused on abrupt shifts in mood and consequent impulsive, hostile, and aggressive behavior.

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