

Psychotic and nonpsychotic bipolar mixed states: comparisons with manic and schizoaffective disorders

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Summary. We studied 259 female inpatients with bipolar spectrum disorders, of whom 26 (10%) were schizoaffective. Of the remaining 233, 61 (27%) met our conservatively set criteria for index mixed episodes (simultaneous presence of depressive and manic syndromes). These patients with rigorously defined mixed states were, in turn, about equally divided between psychotic and nonpsychotic subgroups. The psychotic mixed patients ($n = 32$) were closer to the bipolar I pattern, and more often seem to come from a familial background of psychotic mood disorders; the nonpsychotic mixed patients ($n = 29$) conformed more closely to the bipolar II pattern, and more often had a hyperthymic and cyclothymic temperament and a family background of non-psychotic disorders and substance abuse. A three-way comparison between psychotic manic ($n = 24$), psychotic mixed ($n = 32$), and schizoaffective ($n = 26$) patients revealed few significant differences in temperamental, familial and course patterns. As expected, psychotic manic patients more often arose from a hyperthymic base and pursued a predominantly manic course; psychotic mixed patients were less likely to arise from such a base and more likely to pursue a mixed course. Finally, schizoaffective had earlier age at onset and longer duration of illness, suggesting that these patients had a more severe illness. Otherwise, interepisodic social adaptation was comparable in the three psychotic groups. The findings overall suggest that the presence of psychosis had relatively little impact on mixed states, which appear more based on temperamental characteristics.

Introduction

Although a combination of opposite polarity symptoms may briefly occur in various conditions (at the beginning or at the end of a manic or depressive episode, during the switch process or during toxic-infectious psychoses), mixed states are conventionally diagnosed when manic and depressive syndromes coexist during the same epi-

sode (Berner et al. 1983). The changeable modalities of such a combination give rise to an extremely polymorphic symptomatology. Indeed, along with such typical affective features as dysphoria, hostility, emotional lability and agitation, less typical symptoms such as confusion, marked hallucinosis and even mood-incongruent delusions may be found (Akiskal and Puzantian 1979). This is why these patients are often misdiagnosed as schizophrenic.

In low-grade mixed states (Akiskal and Mallya 1987) opposite polar symptoms express themselves subclinically – sometimes with “characterologic” features – and thus a broad mélange of affective symptoms are observed: hyperactivity, generalized anxiety, somatic complaints, panic attacks, insomnia and hypersexuality (anxious hypomania), as well as irritability, explosivity, and alcohol-drug abuse (dysphoric hypomania). These low-grade, typically non-psychotic, mixed states often pursue a subchronic or even chronic evolution. In such cases they may be misdiagnosed as borderline personality disorder (Akiskal 1981).

Despite the high prevalence of mixed states, they remain poorly defined among the mood disorders in official diagnostic systems (DSM-III-R, American Psychiatric Association 1987; ICD-10, WHO 1992). Given their therapeutic implications, particularly for their response to antiepileptic agents (Post et al. 1989), mixed states must be carefully distinguished, particularly cross-sectionally, not only from schizophrenia but also from other bipolar spectrum disorders, psychotic mania, delusional depression, as well as from schizoaffective disorder.

In a previous study (Dell'Osso et al. 1991) of 108 hospitalized bipolar females, mixed states (suffering from a mixed index episode and/or a past mixed state) were compared with more classical or “straight” bipolars (manics or depressive without a history of mixed episodes ever). The comparison showed many significant findings pertaining to mixed patients such as a heavier family affective loading, particularly depressive; lower frequency of hyperthymia as a baseline temperament; a preponderantly depressive or mixed onset; and a higher frequency of prior episodes with mood-incongruent psychotic fea-

tures, yet with a general adaptive functioning score in the range for more classic mood states. Because of these characteristics, and particularly because of its tendency to recur true to type, we suggested that the mixed state refers to a bipolar form with a distinct longitudinal pattern.

In a subsequent preliminary analysis (Dell'Osso et al. 1993), bipolar patients suffering from a mixed episode with psychotic features – compared with nonpsychotic ones – showed different familial patterns for certain types of mental disorders and suicidal behaviours in first degree relatives; a higher total number of mood episodes yet with shorter length of episodes; in addition, there were hints that temperamental measures might further distinguish psychotic mixed, psychotic manic and schizoaffective disorders.

The present communication – which updates our previous sample of 108 to 259 patients – derives from the need to verify and extend, in a large sample, these preliminary findings. We thereby aim to contribute to a better understanding of the psychotic and non-psychotic boundaries of mixed states. Finally, we wished to test Akiskal's (1992) clinical observations suggesting that acute mixed manic (bipolar I) states might arise from a depressive temperamental base, whereas more protracted nonpsychotic depressive mixed states might arise from a cyclothymic-bipolar II and/or hyperthymic temperamental base.

Patients and methods

In a collaborative project on affective and related disorders between the Universities of Pisa (Italy) and Tennessee (USA), data on hospitalized (Dell'Osso et al. 1989) and ambulatory (Cassano et al. 1989, 1992) patients have been systematically collected. The present report concerns the inpatient sample. To date we have investigated 259 bipolar spectrum patients consecutively admitted to the female ward of the Psychiatric Clinic of the University of Pisa: 233 (90%) had bipolar disorders, and 26 (10%) were schizoaffective. Given that mixed states are more frequent in women (Himmelhoch et al. 1976), concentrating on this gender provided us with a relatively large sample suitable for subtyping. Our methodology on mixed affective states has been presented elsewhere (Dell'Osso et al. 1991). We briefly review it here, focusing on diagnostic criteria and clinical interview procedures.

Mixed state was diagnosed at index episode in 61 cases characterized by a major depressive syndrome in the context of an excited clinical picture meeting the DSM-III-R cross-sectional criteria for mania; the depressive component was assessed on the basis of the HRSD score (Hamilton 1967), more than 15 in the first 17 items; opposite affective symptoms had to coexist for at least 2 weeks; following Prien et al. (1988), the DSM-III-R criterion A of alternating manic and depressive features was not used, because of the possible overlap with rapid cycling bipolar illness; finally at least one prior unequivocal manic or hypomanic episode was required to differentiate this condition from non-affective disorders. In our previous study (Dell'Osso et al. 1991), we had combined all patients with index or past mixed episodes. In view of the difficulties of making such diagnoses on the basis of history and given that index mixed episodes were often associated with a pattern of such episodes in the past, the present sample of mixed states was chosen on the basis of the directly observed clinical mixed picture of the index episode. The underestimation of mixed states in this sample is thereby counterbalanced by more definitive and rigorous diagnosis of index patients.

The diagnosis of psychotic mania was made according to DSM-III-R (1987) criteria for mania, which permit psychotic features (both mood-congruent and -incongruent). As in our previous study (Dell'Osso et al. 1991), manic patients who had no documented past record of mixed episodes, constituted our comparison sample of "pure" bipolars.

The diagnosis of current schizoaffective disorders was made in the presence of a full depressive or manic syndrome associated with at least one Schneiderian first-rank symptom (Spitzer et al. 1978) and, on the basis of DSM-III-R, at least one prior episode characterized by psychotic symptomatology with no relevant affective symptoms for more than 2 weeks; thus, these patients had exhibited incoherence or marked loosening of associations, catatonic stupor or excitement, and bizarre behaviour, as well as delusional and hallucinatory experiences at a time when an affective syndrome was absent.

Familial, temperamental, anamnestic and clinical data were collected by means of an Italian adaptation (Dell'Osso et al. 1989) of the Mood Clinic Data Questionnaire (MCDQ) by Akiskal et al. (1978). We used a semi-structured face-to-face interview, lasting 60–120 min. Data obtained from patients were supplemented by information from family members and all other relevant sources (e.g. social workers, physicians, friends) and systematically recorded. Previous hospital records completed the collection of retrospective data. Negative life events were evaluated according to Paykel's approach (1971). Family history concerning psychiatric disturbances in first-degree biological relatives was investigated using a modified version of the Family History Research Diagnostic Criteria by Andreasen et al. (1977); only well-documented information, confirmed by several sources, were recorded, so that, although the percentages may be underestimated, the comparison is more likely to provide possible differences.

Depressive, hyperthymic and cyclothymic temperaments were assessed using Akiskal and Mallya's criteria (1987) derived in part from Schneider's descriptions (1958). All diagnoses represent consensus based on evaluation by psychiatrists with at least 7 years of post-doctoral clinical experience. Our overall clinical methodology and intercentre reliability (Pisa-Memphis) has been documented elsewhere (Cassano et al. 1992).

Onset of illness was defined in three ways, according to Roy-Byrne et al. (1985): first symptoms, first treatment, and first hospitalization. With regard to the course of illness, we included only the episodes that required psychiatric observation and treatment.

As for cross-sectional features, we assessed many variables, such as age, latency of hospitalization (i.e. interval between onset of episode and admission to hospital), duration of episode, and social functioning just before the index episode using the general adaptive functioning (GAF) scale (American Psychiatric Association 1987). The overall severity of the clinical picture was assessed by the Clinical Global Improvement Scale (CGI) and the Brief Psychiatric Rating scale (BPRS).

Two types of comparisons were carried out:

1. Psychotic mixed versus non-psychotic mixed patients, and
2. Psychotic mixed versus psychotic manic versus schizoaffective patients.

The data were processed at the Centre for Clinical Psychopharmacological Data Documentation (CCPDD) of the Institute of Clinical Psychiatry of Pisa University (Cassano et al. 1985), by Statistical Analysis System (SAS), with t-test, Chi-square, Fisher's exact test and analysis of variance. We conservatively used two-tailed statistics.

Results

Psychotic mixed versus nonpsychotic mixed

Sixty-one of 233 bipolar patients met criteria for index mixed episode: 32 (52.5%) with psychotic features (PM) and 29 (47.5%) without psychotic features (NPM). The

Table 1. Rates of family history for mood and related disorders

	Psychotic mixed (PM) <i>n</i> = 32 (%)	Non-psychotic mixed (NPM) <i>n</i> = 29 (%)	<i>df</i>	χ^2	<i>P</i>
Bipolar disorders	12.5	20.7	1	0.74	ns
Depressive disorders	28.1	27.6	1	0.00	ns
Unspecified mood disorders	37.5	27.6	1	0.67	ns
Hospitalized non-mood disorders	3.1	20.7	1	4.62	0.032*
Drug and alcohol abuse	12.5	27.6	1	2.19	ns
Suicide or suicide attempts	15.6	13.8	1	0.04	ns

Table 2. Course of illness: polarity and psychoticism of prior episodes

	Psychotic mixed (PM) <i>n</i> = 32 (%)	Non-psychotic mixed (NPM) <i>n</i> = 29 (%)	<i>df</i>	χ^2	<i>P</i>
Depressive	38.6	44.6	1	0.74	ns
Manic	30.7	20.5	1	2.73	ns
Mixed	30.7	34.9	1	0.40	ns
With psychotic features	65.9	31.0	1	24.38	0.0001
Without psychotic features	34.1	69.0	1	24.38	0.0001

latter group, consisting largely (80%) of mixed states with past hypomania or major depression, is more compatible with a bipolar II course; however, DSM-III-R conventions automatically classify all mixed states as bipolar I.

No significant differences were found for age (PM = 38.0 ± 14.5 vs NPM = 43.0 ± 15.8 ; $t = 1.24$, $P = 0.22$), length of hospitalization (PM = 3.3 ± 2.6 weeks vs NPM = 4.5 ± 5.6 ; $t = 1.12$, $P = 0.27$), length of episode (PM = 4.0 ± 4.3 months vs NPM = 5.2 ± 6.7 ; $t = 0.86$, $P = 0.39$) and pre-episode free interval (PM = 22.4 ± 27.1 months vs NPM = 24.5 ± 35.0 ; $t = 0.26$, $P = 0.79$). The HRSD total score was comparable (PM = 24.2 ± 7 vs NPM = 23.0 ± 7.7 , $t = 0.64$, $P = 0.52$), indicating moderate level of depressive pathology.

Yet, as expected, significant differences emerged regarding overall clinical severity assessed by the CGI item "severity of illness" (PM = 5.7 ± 0.6 vs NPM = 5.2 ± 0.8 , $t = 2.67$, $P = 0.009$), as well as BPRS total score (PM = 47.0 ± 8.5 vs NPM = 40.0 ± 6.8 , $t = 3.15$, $P = 0.003$), contributed largely by "thought disturbance" (PM = 247.6 ± 105.6 vs NPM = 152.6 ± 55.6) and "hostility-suspiciousness" (PM = 263 ± 121.1 vs NPM = 192.9 ± 123.4); it is noteworthy that "anergia", "activation" and "anxiety-depression" BPRS factor scores were comparable in the two groups.

No significant differences emerged regarding depressive temperament: 12.5% in PM vs 13.8% in NPM ($\chi^2 = 0.07$, $P = 0.8$). Hyperthymia was found in 12.2% of PM and in 37.9% of NPM ($\chi^2 = 17.59$, $P = 0.0001$). Likewise cyclothymia was significantly less common in PM

than NPM (18.8% vs 34.5% respectively, $\chi^2 = 6.31$, $P = 0.012$).

Family history distinguished PM and NPM (Table 1): while the former had an excess, although not significant, of relatives with "unspecified mood disorders" the latter had a significant excess of relatives hospitalized for "non-mood disorders" and a higher rate of relatives with alcohol and drug abuse.

As for past course of illness (Table 2), in both groups past episodes were significantly more likely to be similar to those of index episodes, i.e. PM showed a higher percentage of previous mixed episodes with psychotic features (65.9%), whereas NPM showed mainly mixed episodes without psychotic features (69%).

The rate of psychosocial stressors preceding the index episode was nonsignificantly higher in NPM than in PM (37.3% vs 28.2%, $\chi^2 = 1.88$; $P = 0.02$). Finally, no significant differences were found in the GAF score on Axis V, indicating comparable psychosocial and occupational functioning in the year preceding the index episode (PM = 48.2 ± 23.8 , NPM = 49.7 ± 21.6 , $t = 0.25$, $P = 0.80$).

Psychotic mixed versus psychotic manic versus schizoaffective

Data on 82 psychotic bipolar and schizoaffective patients were compared: 32 (39%) met criteria for a psychotic mixed episode (PM), 24 (29%) for a psychotic manic episode (PMan), and 26 (32%) for a schizoaffective disorder, bipolar type (SA). Their index presenting age,

Table 3. Index age and presenting indices of episode severity, duration and social adaptation

	Psychotic mixed (PM) <i>n</i> = 32		Psychotic manic (NPM) <i>n</i> = 24		Schizoaffective (SA) <i>n</i> = 26		<i>F</i>	<i>P</i>
	χ	SD	χ	SD	χ	SD		
Age (years)	38.3	14.6	38.1	12.7	39.1	10.7	0.0	ns
Length of hospitalization (weeks)	3.3	2.6	2.75	1.7	3.3	2.4	0.5	ns
Length of episodes (months)	4.0	4.3	4.5	8.5	3.0	2.1	0.5	ns
Preepisode free interval (months)	22.4	27.1	18.8	26.1	28.6	29.5	0.8	ns
Severity (CGI)	5.7	0.1	5.6	0.1	5.8	0.1	0.6	ns
Axis V (GAF scale)	48.2	23.8	44.4	22.5	49.7	15.5	0.4	ns

Table 4. Rates of family history for selected psychiatric and addictive disorders and suicide

	Psychotic mixed (PM) <i>n</i> = 32 (%)	Psychotic manic (PMan) <i>n</i> = 24 (%)	Schizoaffective (SA) <i>n</i> = 26 (%)	<i>df</i>	χ	<i>P</i>
Bipolar disorders	12.5	20.0	15.4	2	0.60	ns
Depressive disorders	28.1	12.0	19.2	2	2.28	ns
Unspecified mood disorders	37.5	32.0	26.9	2	0.74	ns
Hospitalized non-mood disorder	3.1	12.0	11.5	2	1.90	ns
Schizophrenia	0.0	0.0	3.8	2	2.22	ns
Drug and alcohol abuse	12.5	8.0	7.7	2	0.49	ns
Suicide/suicide attempts	15.6	20.0	7.7	2	1.62	ns

Table 5. Past course of illness

	Psychotic mixed (PM) <i>n</i> = 32		Psychotic manic (PMan) <i>n</i> = 24		Schizoaffective (SA) <i>n</i> = 26		<i>F</i>	<i>P</i>
	χ	SD	χ	SD	χ	SD		
First symptoms (years)	27.4	11.4	27.6	12.4	22.7	7.4	1.8	ns
First treatment (years)	29.3	12.5	31.2	11.6	23.9	7.7	3.1	0.05
First hospitalization (years)	31.7	11.5	33.1	12.3	25.4	7.8	3.7	ns
First depressive episode (years)	28.7	10.6	29.4	14.1	23.7	81.0	1.6	ns
Length of illness (years) ^a	10.9	1.6	10.4	1.8	16.4	1.8	3.5	0.03
Total mood episodes	4.9	4.2	6.1	5.6	7.1	4.0	1.7	ns
N hospitalizations	3.5	3.6	3.5	3.4	5.4	3.7	2.5	ns

^a In both of these comparisons, PM = PMan, significantly different from SA

episode and interepisodic length, clinical severity and social adaptation did not differ (Table 3).

A depressive temperament was recorded in 12.5% of PM, in 15.4% of SA and in none (0%) of the PMan ($\chi^2 = 3.8$, $P = 0.149$). Hyperthymic temperament was found in 12.2% of PM, in 7.7% of SA and in 54.2% of PMan ($\chi^2 = 18.5$, $P = 0.0001$). Finally, cyclothymia was diagnosed in 18.8% of PM, 3.8% of SA and in 29.2% of PMan ($\chi^2 = 5.76$, $P = 0.056$).

Although not significant, some differences among the three groups were observed regarding the familial rates of depressive disorders (lower in PMan), schizophrenia

(only recorded in SA) and drug and alcohol abuse (higher in PMan) (Table 4).

As regards past course of illness (Table 5), PM did not significantly differ from PMan, while several differences were observed between both bipolar groups and SA, the latter showing a much earlier age at onset and a longer duration of illness. As for prior episodes, there were no differences in the total number of recurrences and hospitalizations. Regarding polarity, while the rate of depressive episodes was similar in the three groups (46.9% of all episodes in PM, 41.7% in PMan and 38.5% in SA), prior manic episodes significantly differed among

the three groups, showing a rate in PM of 12.5%, in PMan of 54.2%, and in SA of 3.8% ($\chi^2 = 80.74$; $P = 0.0001$). Mixed episodes represented 29.9% of all previous episodes in PM, 15.7% in SA, and absent by definition in PMan. In PM and SA, psychotic features were prevalently mood incongruent, while in PMan they were generally mood congruent. Finally, a high percentage of suicidal behaviour was found in the personal history of all groups: 28.4% in PM, 29.1% in PMan and 30.7% in SA.

Discussion

Depending on gender and clinical setting, 16–67% of bipolar patients have been reported to develop mixed episodes (Goodwin and Jamison 1990). In our previous study (Dell'Osso et al. 1991) deriving from a much smaller sample – and based on both index and/or past mixed episodes – we reported that 45.4% of an inpatient mood disorder population met broad criteria for mixed states. The present report deriving from a larger sample which included schizoaffective patients – but based on a more rigorous definition of directly observed mixed states – has provided a more conservative figure of 27%. We feel this more strict method for identifying index mixed states can be documented by prospective follow-up: the reverse strategy (reconstructing mixed states from past records) introduces considerable uncertainty owing to the vagaries of the past records.

In accordance with classical descriptions (Kraepelin 1921) and more recent literature (Himmelhoch and Garfinkel 1986; Himmelhoch et al. 1976, 1979; Nunn et al. 1979; Akiskal and Puzantian 1979; Keller et al. 1986; Strakowski et al. 1992) and our previous work (Dell'Osso and Placidi 1991; Dell'Osso et al. 1991, 1993), at least half of our patients with mixed states showed psychotic symptoms as associated features, both mood-congruent and -incongruent. Because of such features, mixed states have traditionally been considered among the most common “diagnostic pitfalls” causing an affective disorder to be misdiagnosed as schizophrenia (Akiskal and Puzantian 1979). Although Kraepelin (1921) had already warned about this possibility – showing how delusional ideas and hallucinations did not necessarily imply a schizophrenia diagnosis – until recent times his admonitions have been generally ignored.

Also in accordance with previous works (Dell'Osso et al. 1991, 1993), data on family history confirm in mixed states the high familial load for mood disorders, particularly depressive. Interestingly, several differences between PM and NPM emerged. PM showed a higher rate, although not significant, of “unspecified mood disorders”, a generic label used for cases of uncertain diagnoses; it is likely to include psychotic mixed states, difficult to recognize with the family history approach. Whether mixed states indeed breed true will require a direct family interview study. From the family history data, PM globally appears to be a condition with a high genetic load for mood disorders. NPM too shows high familial load of mood disorders; furthermore, the significantly

higher rate of “hospitalized non-mood disorders” (referring largely to severe anxiety disorders) together with the high rate of drug and alcohol abuse in first-degree relatives, is compatible with the high prevalence of bipolar II disorder in nonpsychotic mixed states in our and other samples (Coryell et al. 1985). These considerations suggest that the DSM-III-R convention of classifying all mixed states as bipolar I is ill-advised. Indeed, our data raise the distinct likelihood that at least two patterns of mixed states exist: psychotic mixed state arising most typically from a bipolar I base, and nonpsychotic mixed state arising largely from a bipolar II base.

The present study also shows a high percentage of suicidal behaviours in personal as well as family history of both PM and NPM. In fact, the mixed state has traditionally been considered at high risk for suicide (Kraepelin 1921; Jamison 1936; Winokur et al. 1969): the association of psychomotor agitation with impulsivity, mood lability and ideas of self-harming, typically present on a background of an extremely dysphoric mood, seems to contribute to frequent suicidal behaviour, providing the necessary motor push lacking in retarded depression. The high rate of comorbidity with drug and alcohol abuse and the presence of psychotic features, in family as well as in personal history, might further enhance the risk for suicide.

Mixed states tend to recur true to type: PM mainly shows a course characterized by episodes with predominantly depressive or mood-incongruent psychotic features, whereas NPM by episodes without psychotic features. As classically described (Kraepelin 1921), this is a general rule for bipolar illness, which seems to follow in an individual patient a relatively distinct pattern with a tendency to repeat polarity and cross-sectional features during much of its longitudinal history.

The present data extend our previous finding of mixed states – being less likely to arise from a hyperthymic background – to being, compared with pure bipolar disorders, more likely to arise from a background of a depressive temperament, as well as having a relatively good social functioning during interepisodic phases (Dell'Osso et al. 1991). No differences were found between PM and NPM in these features, which could thus be regarded as intrinsically connected with the mixed presentation of bipolar illness, not influenced by the presence of psychosis. By contrast, the significantly higher prevalence of cyclothymic and hyperthymic temperaments in the non-psychotic mixed states is compatible with the diagnosis of bipolar II disorder: this longitudinal association of temperament with depressive episodes appears to constitute a distinct form of mixed state, whereby depression is superimposed on an unstable temperament with hypomanic tendencies. Our data overall support Akiskal's (1992) clinical observation that mixed states tend to arise when temperament and episodes are opposite in polarity.

As for psychopathological aspects, by definition the presence of psychotic features clearly distinguishes PM and NPM. This involves higher severity of the episode as shown by BPRS total score, “thought disturbance” and “hostility-suspiciousness” factor scores significantly higher

in PM vs NPM. The absence of differences in other BPRS factors and in HRSD is due to the similar depressive component, based in turn on the homogeneity of the clinical population of hospitalized patients.

Familial comparisons of mixed states with schizoaffective and psychotic manic patients failed to reveal significant differences. The same was generally true for demographic comparisons, except that schizoaffectives had earlier age at onset and duration of illness. As argued by Marneros et al. (1991), bipolar, mixed and schizoaffective disorders seem to be on a continuum.

Other longitudinal data differentiated the psychotic mixed, manic, and schizoaffective groups. Psychotic mixed state is less frequently than mania preceded by hyperthymia and cyclothymia; in this regard, schizoaffective are more like psychotic mixed states. These data tend to confirm previous suggestions by Akiskal (1992). Psychosis does not seem to interfere significantly with the course of bipolar illness, which develops according to its own patterns, differing with such variables as age, polarity of onset, polarity and features of prior recurrences. Indeed cross-sectional aspects as well as duration of the index episode and of hospitalization do not show significant differences in the three psychotic groups.

To summarize, the present data demonstrate considerable heterogeneity within the large universe of mixed bipolar states, some psychotic, others nonpsychotic, each pursuing a more or less distinct course. These data overall support our previous findings (Dell'Osso et al. 1991) – as well as earlier suggestions by Berner et al. (1983) – placing mixed states within the general category of mood disorders. These data and conclusions, based on a female inpatient population, should be replicated in more representative clinical populations including males, matched by age and proportion with substance and alcohol abuse. Optimally, prospective observation and direct interview of first-degree relatives are needed to further verify the various longitudinal and familial patterns described by us.

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