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Axis I comorbidity in bipolar disorder
with psychotic features

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Background  Axis I comorbidities are prevalent among patients with severe bipolar disorder but the clinical and psychopathological implications are not clear.

Aims  To investigate characteristics of four groups of patients categorised as follows: substance abuse only (group I), substance abuse associated with other Axis I disorders (group 2), non-substance-abuse Axis I comorbidity (group 3), no psychiatric comorbidity (group 4).

Method  Consecutive patients with bipolar disorder with psychotic features (n=125) were assessed using the Structured Clinical Interview for DSM–III–R – patient version, and several psychopathological scales.

Results  By comparison with group 4, group I had a higher risk of having mood-incongruent delusions, group 2 had an earlier age at onset of mood disorder, a more frequent onset with a mixed state and a higher risk of suicide, and group 3 had more severe anxiety and a better awareness of illness.

Conclusions  Substance abuse, non-substance-abuse Axis I comorbidity and their reciprocal association are associated with different characteristics of bipolar disorder.

Declaration of interest  This study was supported by funds from the Department of Psychiatry, University of Pisa.

The prevalence of psychiatric comorbidity in bipolar disorder with psychotic features ranges from 13% to 73.4%, with substance-use disorders being the most common condition, followed by anxiety and eating disorders (Black et al, 1988; Strakowsky et al, 1992; Kessler et al, 1997). Such comorbidities are associated with more severe psychotic features, longer stays in hospital, low recovery rates and earlier age at onset of mood disorder (Sonne et al, 1994; Brady & Sonne, 1995; Cassano et al, 1998; Scott et al, 1998; Strakowsky et al, 1998). However, the extent to which such clinical correlates were due to substance abuse and/or non-abuse Axis I comorbidity was not exhaustively clarified.

In this study we investigated the clinical characteristics of psychotic bipolar disorder in patients categorised into four groups according to their patterns of comorbidity: substance abuse only (group 1), substance abuse associated with other Axis I disorders (group 2), non-substance-abuse Axis I comorbidity (group 3), no psychiatric comorbidity (group 4).

METHOD

The method of this study and the characteristics of the Pisa Centre have been described in detail elsewhere (Cassano et al, 1998). Consecutively hospitalised patients with psychotic bipolar disorder (n=125) were recruited and included in this study on the basis of the following criteria: age over 16 years; presentation with psychotic symptoms (i.e. formal thought disorders, delusions, hallucinations, grossly disorganised behaviour); provision of informed written consent and approval from the local ethical committee. Patients were selected independently of previous stays in hospital and/or prior antipsychotic or mood-stabiliser treatments and independently of having had single or multiple episodes of psychosis. Patients were excluded from the study if psychotic symptoms either were secondary to acute intoxication or withdrawal from alcohol or other substances or were presenting with concomitant severe medical conditions defined according to Black et al (1998) as any serious or acute life-threatening illness such as cancer, myocardial infarction, stroke, or hepatic insufficiency. The inclusion diagnosis of psychosis was made by three senior psychiatrists who were not directly involved in the study, on the basis of their clinical judgement and reading of patient records. Then, the Structured Clinical Interview for DSM–III–R – patient version (SCID–P; Spitzer et al, 1987) was administered in the week preceding the patient’s discharge by three residents in psychiatry who had been trained in the use of the SCID–P. As recommended by Spitzer et al (1987), SCID–P interviewers were skilled clinical researchers with at least three years of clinical experience and with substantial familiarity with DSM–III–R criteria (American Psychiatric Association, 1987). In previous studies, psychiatric comorbidity has been defined as the presence of an antecedent or concurrent DSM–III–R Axis I diagnosis in addition to the principal diagnosis. Ten Axis I diagnoses were assessed in the present study (panic disorder, social phobia, simple phobia, obsessive-compulsive disorder, somatoform disorder, undifferentiated somatoform disorder, chronic pain disorder, hypochondria, anorexia and bulimia). Substance abuse (involving stimulants, sedatives, opiates, hallucinogens, cocaine, cannabis, alcohol and multiple drugs) was also assessed by the SCID–P. In completing the SCID–P, information was obtained from any source available in addition to the patient interview, including medical records, first-degree relatives and treating clinicians. Age at onset was investigated by the SCID–P. Comorbid diagnoses were defined as antecedent if patients endorsed full syndrome criteria more than one year before the onset of bipolar disorder.

Psychopathology was assessed using the 18-item version of the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). The awareness of illness was evaluated by means of the Scale for the Unawareness of Mental Disorder (SUMD; Amador et al, 1993). In this scale, scores range from 1 to 5, with higher scores indicating poorer awareness of illness. Interrater reliability for the SCID–P, BPRS, SANS and SUMD

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was assessed in a small sample study (n=8) on the basis of joint records for both principal and comorbid diagnoses. Good reliability established from joint ratings was obtained for both principal and comorbid diagnoses (κ=0.87 and κ=0.82, respectively).

Statistical analyses
Analysis of variance (ANOVA) was performed on key demographic variables in order to determine whether there were any significant differences across groups. The ANOVA was then performed on psychopathological variables by group. Pairwise comparisons were performed on the psychopathological and clinical variables to determine which groups significantly differed from each other. All results at P<0.05 were judged to be significant. The overall error rate was also controlled for by making pairwise comparisons using the Tukey test of significant differences. Categorical variables were analysed by the χ² test. The age at onset of bipolar disorder in the four groups was assessed by means of survival analyses with the Wilcoxon (Gehan) test (Gehan, 1997) for overall and pairwise comparisons. Multiple logistic regression analysis was performed in order to estimate the strength of association between clinical variables and comorbidity after controlling for the principal psychotic diagnosis and socio-demographic variables. All analyses were performed using SPSS version 7.0 for Windows 95.

RESULTS
The total cohort of 125 bipolar patients was categorised into the four groups as follows: group 1 (patients with substance abuse disorder without any other Axis I comorbidity) consisted of nine patients (7.2%), group 2 (substance abuse plus at least one other Axis I comorbid disorder) consisted of 22 patients (17.6%), group 3 (at least one non-abuse Axis I disorder) consisted of 43 patients (34.0%), and group 4 (neither substance abuse nor other Axis I comorbidities) consisted of 49 patients (39.2%). Frequencies and mean age of onset of comorbid diagnoses and of bipolar disorder are shown in Table 1. Overall, total rates of substance-abuse and non-abuse Axis I comorbidity were 24.8% (n=31) and 36.0% (n=45), respectively.

Socio-demographic characteristics
As shown in Table 2, group 2 was significantly younger than group 4 (P<0.05). Males were significantly more represented among substance users, with or without other Axis I comorbidity, than those without any comorbidity (P<0.05). Married patients were significantly more frequent in group 4 than in the other three groups (P<0.05).

Age at onset of bipolar disorder, substance abuse and Axis I comorbidities
Mean age at onset of bipolar disorder was 22.8 years (s.d. 5.7) in group 1, 21.2 (s.d=4.6) in group 2, 25.3 (s.d=8.8) in group 3 and 26.1 (s.d=7.7) in group 4. As shown in Fig. 1, pairwise comparisons from survival analysis showed that the mean age at onset of bipolar disorder was significantly lower in group 2 than in group 4 (F=7.140, d.f.=1, P<0.01). Mean age at onset of substance abuse was 19.6 years (s.d=5.5), with stimulant abuse being earliest (15.8 years, s.d=2.9) and alcohol abuse the latest (22.9 years, s.d=8.6), while mean age at onset of non-abuse Axis I comorbidity was 22.1 years (s.d=9.5), with social phobia being earliest (8.5, s.d=2.1) and generalised anxiety disorder the latest (31.4, s.d=18.9) (see Table 1). The onset of substance abuse preceded that of mood disorder in 23 (74.9%) abusers. The onset of non-abuse Axis I comorbidity preceded the onset of psychotic disorder in 20 (44.4%) patients with Axis I comorbidity without substance abuse.

Age at onset of mood disorder was significantly earlier in subjects with cannabis abuse than in those without (20.4, s.d.=4.7 v. 25.6, s.d.=7.9; t=3.037, d.f.=123, P<0.01), but not in those with alcohol abuse (22.4, s.d.=5.2 v. 25.1, s.d.=8.0; t=1.408, d.f.=149, P<0.01). We also found a significant negative correlation between age at onset of bipolar disorder and cannabis abuse (Kendall's τb test=0.247, P<0.01) and panic disorder (Kendall's τb test=−0.187, P<0.05), but not with any of the other Axis I diagnoses.

Psychopathology
As shown in Table 3, levels of patients' awareness of illness, effects of medications and of social consequences of mental disorder showed differences between the four groups. Overall, group 3 had a better insight than both group 4 and group 1.

There were no significant differences between the four groups on BPRS scores with the exception of the anxiety/depression

Table 1: Frequency of Axis I comorbidity and age of onset in 125 consecutively hospitalised patients with bipolar disorder with psychotic features

<table>
<thead>
<tr>
<th>DSM-III-R Axis I diagnosis</th>
<th>Patients with bipolar disorder with psychotic features (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Simple phobia</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>17 (13.6)</td>
</tr>
<tr>
<td>Multiple drug abuse</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Stimulants abuse</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Cocaine use</td>
<td>7 (5.6)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Hallucinogens use</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Opiate use</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Cannabis use</td>
<td>23 (18.4)</td>
</tr>
<tr>
<td>Bulimia</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Sedative abuse</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>16 (12.8)</td>
</tr>
<tr>
<td>Somatoform disorders</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>19 (15.2)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>125 (100)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>39 (31.2)</td>
</tr>
<tr>
<td>Generalised anxiety disorder</td>
<td>5 (4.0)</td>
</tr>
</tbody>
</table>
This study aimed to investigate clinical characteristics associated with substance abuse and non-abuse Axis I comorbidity in a cohort of patients with bipolar disorder with psychotic features. Overall, 60.8% of our patients had at least one Axis I comorbid disorder. Our centre specialises in the treatment of mood and anxiety disorders; addicted patients are usually referred to other centres. This might have contributed to an under-representation of substance abuse; our figures probably do not reflect a true prevalence among bipolar patients. However, consistent with previous studies (Strakowsky et al., 1992; Kessler et al., 1997), our results indicate that a substantial proportion of subjects with psychotic bipolar disorder were complicated by additional Axis I conditions.

### DISCUSSION

This study aimed to investigate clinical characteristics associated with substance abuse and non-abuse Axis I comorbidity in a cohort of patients with bipolar disorder with psychotic features. Overall, 60.8% of our patients had at least one Axis I comorbid disorder. Our centre specialises in the treatment of mood and anxiety disorders; addicted patients are usually referred to other centres. This might have contributed to an under-representation of substance abuse; our figures probably do not reflect a true prevalence among bipolar patients. However, consistent with previous studies (Strakowsky et al., 1992; Kessler et al., 1997), our results indicate that a substantial proportion of subjects with psychotic bipolar disorder were complicated by additional Axis I conditions.

### Results of logistic regression analyses

The association of each of the four comorbidity groups with a series of clinical variables was analysed by composite logistic regression models. Delusions and hallucinations, formal thought disturbances, affective flattening, polarity of first affective episode, suicide attempts, and good insight were used as dependent variables. Group, gender, age and principal diagnosis of bipolar disorder were used as independent variables.

As shown in Table 4, mood-incongruent delusions were significantly associated with group 1, an onset with a mixed episode and a history of previous suicide attempts with group 2. An onset with a manic episode was negatively and good awareness of illness positively associated with group 3.

### Substance abuse without other Axis I comorbidity (group 1)

In group 1, onset of substance abuse preceded onset of affective illness in the majority (64%) of cases. Logistic regression analysis showed that this group had a higher risk of having mood-incongruent delusions than the rest of the subjects. The reason for this last association not being found in group 2 is difficult to define. It is possible that these abusers, who were also
The co-occurrence of substance abuse and mental disorder is well established. However, larger samples are needed to support such a hypothesis empirically.

Suicide attempts onsets with a mixed episode appeared to be more pronounced than that of alcohol abuse. This finding is consistent with a recent study by Brook et al. (1998), which reports a significant relationship between earlier adolescent drug use and later depressive and disruptive disorders in young adulthood, controlling for earlier psychiatric disorders. Strakowski et al. (1996) found that patients with bipolar disorder and antecedent alcohol abuse had a later onset of affective illness, arguing that this represented a subgroup of patients in whom previous alcohol abuse was only necessary to precipitate an affective episode. Furthermore, given the remarkably earlier age at onset of cannabis abuse than that of bipolar illness or alcohol abuse, our data give support to the hypotheses that soft-drug abuse is likely to anticipate the onset of psychosis, while alcohol is more likely to complicate it. However, the fact that the onset of mood disorder was earlier in group 2 than in group 1 also suggests that non-abuse Axis I comorbidity may play an important role in anticipating the onset of psychosis.

### Non-abuse Axis I comorbidity (group 3)

By comparison with the group without comorbidity, the group with non-abuse Axis I comorbidity had higher levels of anxiety and depression, more anhedonia/asociality and a greater likelihood of having an onset of illness with a mixed or depressive affective episode. Overall, the onset of Axis I comorbidity preceded that of bipolar disorder in 43% of cases. This group appeared to have fewer psychotic symptoms and a lower risk of serious suicide attempts than the other groups. These features, and the more negative self-experience of psychopathology -- reflected by a better insight of illness and a higher level of anxiety -- that characterises these patients, suggest that the boundaries between psychosis and neurosis are likely to be less marked in this cluster than in the others. These findings seem to support the hypothesis of Black et al. (1988) that manic patients with non-abuse comorbidity resemble in many respects the ‘neurotic’ secondary depressive described by Winokur et al. (1988).

### Limitations

It is important to acknowledge several limitations of this study. We investigated only hospitalised patients, limiting the applicability of these results in relation to patients with bipolar disorder in general. Rates of lifetime substance abuse and Axis I comorbidity, as well as of psychopathology...
and age at onset, could have been distorted by patients' or relatives' recall bias. Analyses were performed independently of whether bipolar patients had prevalently manic or depressive episodes. The small size of the cohort examined did not allow us to investigate the effect of each single comorbid Axis I disorder on psychotic phenomenology.

Implications and future directions

Our results support the importance of detecting specific patterns of comorbidity in patients with severe bipolar disorder (Casamento et al., 1998, 1999; Schatzberg, 1998). Either substance abuse or non-abuse Axis I comorbidity may have an impact on phenomenology of bipolar disorder. These associations in various forms should be investigated further because of potential implications on age of onset of affective illness and risk of suicide. Clarification of the relationships between bipolar disorder and other Axis I conditions, which are traditionally situated at a lower hierarchical level, may be of great value in better understanding the course of bipolar illness and the phenomenology of acute and interepisodic phases, and in describing subsets of patients whose symptoms are not entirely accounted for by mood disorder. Furthermore, comorbidity may have clear implications for treatment. Different forms of bipolar disorder, for example, could have different treatment responses, and it would be interesting to see whether comorbidity predicts treatment outcome.

REFERENCES


