

## Comorbidity with anxiety and substance use disorders in patients with schizophrenia

*Comorbidità tra disturbi d'ansia e disturbi da uso di sostanze in pazienti con schizofrenia*

### Summary

#### Objective

Anxiety disorders and alcohol/substance use disorders (SUD) are very common in schizophrenia (SCH). Studies investigating the relationship between SUD and anxiety in patients with SCH are scanty, and virtually absent in the Mediterranean area.

The aim of the present study is to analyse the relationship between anxiety disorders and SUD in patients with SCH. We hypothesized that comorbidity with anxiety disorders would be more frequent in patients with SCH and SUD compared with those without SUD.

#### Methods

Participants were recruited in the framework of two research programs coordinated by the Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies (DPNFB) of the University of Pisa, Italy aimed to investigate the comorbidity of patients with severe mental illness using standardized interviews.

The first research program was carried out between September 2003 and March 2005 at nine Departments of Mental Health located in Tuscany, the second program included consecutive patients with schizophrenia or affective psychoses recruited from the inpatient, day-hospital and outpatient units of the Psychiatric Clinic of the DPNFB between April 2003 and March 2006. Eligible subjects were inpatients and outpatients with chronic psychotic disorders between the ages of 18-65 years in treatment for at least one year.

The diagnostic assessment was carried-out using the Structured Clinical Interview for DSM-IV Axis-I Disorders

(SCID-I). Comparisons of categorical variables between groups were carried out using the chi-square test or Fisher's exact test when appropriate. Analyses were carried out first separately in the two study groups. Logistic regression was then used to analyse in the pooled sample the association between anxiety disorders and SUD, adjusted for gender, age, and study.

#### Results

Participants included 145 patients with SCH in study 1 and 30 in study 2 (Table I). The lifetime prevalence of SUD was 18.6% vs. 50% (chi-square = 13.42,  $p < 0.01$ ). The lifetime prevalence of anxiety disorders was 32.4% in study 1 and 43.3% in study 2 (chi-square = 1.31,  $p = 0.251$ ).

In both study 1 and study 2, lifetime SUD was associated with significantly greater odds of anxiety disorders (OR = 2.8, 95% CI 1.2-6.5; OR = 8.0, 95% CI 1.5-42.0) (Table III). Logistic regression analysis carried out on the pooled sample indicated that this association continued to be significant (OR = 3.8, 95% CI 1.8-8.4,  $p < 0.001$ ) after controlling age, gender, and study.

#### Conclusion

We found a significant association between SUD and anxiety disorders in patients with SCH. In these patients, substance use could be an attempt to reduce anxiety symptoms and to improve social performance. Further studies with a longitudinal design are warranted to elucidate the reciprocal causal mechanisms underlying the comorbidity between SCH with SUD and anxiety disorders. In addition, it will be important to determine whether effective treatment of anxiety symptoms can improve treatment response in schizophrenia and SUD.

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#### Keywords

Substance use disorder • Alcohol use disorder • Schizophrenia • Anxiety disorder • Comorbidity

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## Introduction

Patients with schizophrenia (SCH) have increased levels of comorbidity with alcohol and substance use disorder (SUD), about 47%<sup>1-3</sup>, and anxiety disorders, about 60%<sup>4,5</sup>, compared with the general population, in which the lifetime prevalence for SUD is about 17%<sup>6,7</sup>, similarly to that for anxiety disorders<sup>8,9</sup>.

Studies investigating the relationship between SUD and anxiety in patients with SCH are scanty, and virtually absent in the Mediterranean area. The only study carried out in Italy reported the lifetime comorbidity of anxiety disorders and substance abuse in patients with psychotic disorders but not their relationship. Goodwin et al.<sup>10</sup> observed that patients with SCH and panic attacks are more likely to have co-occurring mental disorders, psychotic symptoms, suicidality and mental health service utilization compared to those without panic attacks. In a subsequent study, Goodwin et al.<sup>11</sup> found a positive association between panic attacks and alcohol and SUD among patients with SCH.

In the present study we analysed the relationship between anxiety disorders and SUD in patients with SCH with the aim to confirm and extend to other anxiety disorders the results of Goodwin et al.<sup>11</sup>.

## Methods

### Subjects

Participants were recruited in the framework of two research programs coordinated by the Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies (DPNFB) of the University of Pisa, Italy aimed to investigate the comorbidity of patients with severe mental illness using standardized interviews in Italian Departments of Mental Health. In Italy, with the gradual closure of mental hospital that took place in 1978<sup>12</sup>, the care for people with severe mental illness is organized through a network of community-based mental health services entirely funded by the National Health Service. The Departments of Mental Health deliver the full array of mental health care mainly through community-oriented services, including community mental health centers, day-hospitals and day-centers. Acute in-patient care is provided by a network of public facilities, including General Hospital Psychiatric Units and University Psychiatric Clinics.

The first research program was carried out between September 2003 and March 2005 at nine Departments of Mental Health located in Tuscany<sup>13</sup>. This program was aimed at carrying out an accurate diagnostic assessment of patients with chronic psychotic disorders receiving long-term treatment in community mental health services. Eligible subjects were inpatients and outpatients with chronic psychotic disorders between the ages of 18-65 years in treatment for at least one year. Exclusion criteria were inability to provide a written informed consent, and meeting criteria for the following DSM-IV diagnoses: psychotic disorder due to a general medical condition, organic mental disorder; substance use disorder active over the previous six months. Each mental health center provided a list of patients who met inclusion criteria. From the initial list, a random sample of 260 patients was selected for a standardized diagnostic assessment in the study period. The second program included consecutive patients with schizophrenia or affective psychoses recruited from the inpatient, day-hospital and outpatient units of the Psychiatric Clinic of the DPNFB<sup>14</sup>. The recruitment phase was carried out between April 2003 and March 2006. Participants were adults (age 18-65) in treatment for psychotic disorders with or without comorbid substance use disorders. Exclusion criteria were unstable neurological or medical diseases and inability to cooperate because of the severity of illness.

Study procedures for the two programs were approved by the Ethical Committee of the Azienda Ospedaliero-Universitaria of Pisa, according to the code of Ethics of the World Medical Association (Declaration of Helsinki). All participants signed a written informed consent to participate in the studies.

Eighty-six patients from the 260 participants in the first program (33.1%) were in residential facilities, the remainders were outpatients. Of these, 20 patients refused to participate and another 105 were not included in the analyses because they did not meet criteria for schizophrenia.

Six patients out of 114 (6.8%) who had consented to participate in the second protocol but did not complete the diagnostic assessment and 78 patients with psychotic depression and bipolar disorder were excluded from the analyses.

Therefore, the final sample analyzed in the present paper includes 175 patients.

### Diagnostic assessment

Participants of both studies were interviewed by residents in psychiatry using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I)<sup>15</sup>. Interviewers had clinical experience with patients suffering from psychotic symptoms and were trained (10 live interviews x rater) and certified to the use of the SCID when the percentage agreement with the trainer on the diagnosis was at least 90%. Demographic information was collected using the SCID and from clinical records.

### Statistics

Comparisons of categorical variables between subject groups were carried out using the chi-square test or Fisher exact test when appropriate. t-test was used to compare the mean age between groups. Proportions were compared between groups using Z-test. Logistic regression was used to analyze in the pooled sample the association between anxiety disorders and SUD, adjusted for gender and age and study (1 vs. 2). Statistical analyses were performed using SPSS, version 15.0 (SPSS, Inc., 2006).

## Results

### Demographic characteristics of the study 1 and 2 groups

In study 1, of 145 participants, 27 (22.8%) met DSM-IV criteria<sup>16</sup> for SCH and at least one lifetime diagnosis of SUD, exclusive of nicotine addiction. In study 2, of 30 participants, 15 (50%) met criteria for SCH and lifetime SUD. Participants were divided into two groups based on the presence/absence of lifetime SUD.

The demographic characteristics of participants in study 1 and 2 with and without SUD are shown in Table I. Lifetime SUD was significantly associated with male gender in study 1, but not in study 2. Marital status, educational level and occupation were unrelated with lifetime SUD in both studies. Only in study 1 patients with SUD had a shorter duration of illness compared to those without SUD. The frequency of the individual lifetime substance use disorders in the two study groups is provided in Table II. Alcohol and cannabis use disorders were the most frequent diagnoses in both samples. Overall, patients in study 2 had a higher lifetime prevalence of comorbid SUD compared to participants in study 1.

### Comorbid anxiety disorders in study 1 and study 2

The lifetime prevalence of SUD was 18.6% in study 1 vs. 50% in study 2 (chi-square = 13.42,  $p < 0.01$ ). The lifetime prevalence of anxiety disorders was 32.4% in study 1 and 43.3% in study 2 (chi-square = 1.31,  $p = 0.251$ ).

In study 1, the association between any anxiety disorder and SUD was significant (OR=2.8, 95% CI 1.2-6.5) (Table III). Panic disorder and social phobia were the two diagnoses associated with greater odds of SUD.

Similarly in study 2 the association between anxiety disorders and SUD was significant (OR = 8.0, 95% CI 1.5-42.0) (Table III). While the odds ratios for panic disorder and social phobia were consistent with those of study 1, suggesting a positive association of these disorders with SUD, confidence intervals are wide because of the large variability and include the unity. Therefore, evidence is inconclusive in this sample.

In order to control for the possible confounding effect of the demographic characteristics and of the study group on this association, a logistic regression analysis was carried out on the pooled sample. Result indicated that lifetime SUD was significantly associated with anxiety disorders (OR = 3.8, 95% CI 1.8-8.4,  $p < 0.001$ ) after controlling for relevant variables (i.e. age, gender and study). Of note, these variables were unrelated with anxiety disorders (age: OR = 0.99, 95% CI 0.96-1.02; gender: OR = 0.6, 95% CI 0.30-1.26; study: 1.01, 95% CI 0.39-2.57).

## Discussion

The present study found a significant association between lifetime anxiety disorders and SUD. This association was consistent across two samples of patients with schizophrenia recruited from different settings. Specifically, the odds ratio of lifetime anxiety disorders in patients with SUD compared with those without SUD was 2.8 in study 1 and 8.0 in study 2. The most prominent anxiety disorders in patients with SUD were panic disorder and social phobia. Our results are in line and extend those of Goodwin et al.<sup>11</sup>, who found an association between panic attacks and increased likelihood of SUD among inpatients with SCH. Previous studies have suggested that phobias generally had onsets prior to the onset of drug dependence<sup>17,18</sup>. The relationship between social phobia and SUD

**TABLE I.**

Demographic and clinical characteristics of patients with schizophrenia (SCH) and bipolar disorder (BD) with or without substance use disorder (SUD). *Caratteristiche cliniche e demografiche dei pazienti con schizofrenia (SCH) e disturbo bipolare (BD) con o senza disturbo da uso di sostanze (SUD).*

	Study 1			Study 2		
	SCH without SUD (N = 118)	SCH with SUD (N = 27)	p-value	SCH without SUD (N = 15)	SCH with SUD (N = 15)	p-value
Mean age (SD)	44.7 (10.5)	41 (10.0)	ns	33.5 (12.9)	33.1 (7.3)	ns
	<i>n</i> (%)	<i>n</i> (%)		<i>n</i> (%)	<i>n</i> (%)	
Gender			< 0.05			ns
Male	71 (60.2)	23 (85.2)		12 (80.0)	11 (73.3)	
Female	47 (39.8)	4 (14.8)		3 (20.0)	4 (26.7)	
Marital status			ns			ns
Single	81 (69.8)	19 (76.0)		12 (80.0)	9 (60.0)	
Married	17 (14.7)	3 (12.0)		2 (13.3)	2 (13.3)	
Separated/ divorced	17 (14.6)	3 (12.0)		1 (6.7)	4 (26.7)	
Widow	1 (0.9)	0		0	0	
Educational level*			ns			ns
Primary school	27 (23.9)	19 (40)		1 (6.7)	1 (6.7)	
Secondary school	64 (56.6)	15 (60)		2 (13.3)	2 (46.7)	
High school	19 (16.9)	0		11(73.3)	6 (40)	
University degree	3 (2.7)	0		1 (6.7)	1 (6.7)	
Occupational status**			ns			ns
Student	0	1 (4.0)		2 (13.3)	0	
Not employed	38 (32.8)	9 (36.0)		7 (46.7)	4 (26.7)	
Housewife	2 (1.7)	0		()	2 (13.3)	
Unskilled/ skilled worker	8 (6.9)	1 (4.0)		2 (13.3)	2 (13.3)	
Trader/ craftsman	0	0		0	1 (6.7)	
Employee	2 (1.7)	0		1 (6.7)	4 (26.7)	
Manager	0	0		1 (6.7)	1 (6.7)	
Retired/ disability pension	66 (56.9)	14 (56.0)	ns	2 (13.3)	1 (6.7)	ns
Mean age of onset of disorder (SD)	22.2 (7.7)	22.3 (6.7)	ns	21.3 (5.8)	22.9 (8.3)	ns
Duration of illness (SD)	22.3 (10.3)	17.6 (8.5)	< 0.05	12.2 (9.8)	10.1 (8.8)	ns

\* 7 missing values; \*\* 4 missing values. ns = not significant.

even in patients with SCH might underlie a use of substances to reduce anxiety symptoms and to improve social functioning. In the two studies, patients reported frequently lifetime abuse or de-

pendence from alcohol and cannabis. Our results are consistent with studies conducted in the general population<sup>19 20</sup> that found a positive relationship between social anxiety disorder and cannabis and

alcohol dependence. On the other hand, as reported by Zvolenski et al.<sup>21</sup>, lifetime cannabis dependence is significantly associated with an increased risk of panic attacks. In addition, as suggested in another study by Zvolenski et al.<sup>22</sup> bidirectional associations are evident between panic problems and tobacco, alcohol, and marijuana use.

Our results should be interpreted keeping in mind several limitations. In study 2 we did not exclude patients with current SUD; this could produce confounding effects of substances upon current anxiety symptoms. Moreover, we cannot rule out that anxiety is at least partly related to the side effects of antipsychotic medications. Another potential limitation is that patients excluded from the study for inability to cooperate because of illness severity may be more likely to have both SUD and anxiety disorders. Therefore, the external validity of our results might be affected by our recruitment procedures. However, a very small percentage of subjects (< 5%) were excluded for this reason.

Also, the small sample size of study 2 does not allow drawing conclusions about the relationship between individual anxiety disorders and SUD.

Lastly, we examined the relationship between anxiety and SUD in the lifetime; therefore it was not possible to determine the sequence of onset of anxiety symptoms and substance use.

## Conclusions

We found a significant association between SUD and anxiety symptoms in patients with SCH. In these patients, substance use could be an attempt to reduce anxiety symptoms and to improve social performance. Further studies with a longitudinal design are warranted to elucidate the reciprocal causal mechanisms underlying the comorbidity between SCH with SUD and anxiety. In addition, it will be important to determine whether effective treatment of anxiety symptoms can improve response to treatment of schizophrenia and SUD.

**TABLE II.**

Distribution of substance use disorder diagnoses in patients with schizophrenia (SCH) in study 1 and study 2. *Distribuzione dei disturbi da uso di sostanze nei pazienti con schizofrenia (SCH) negli studi 1 e 2.*

	Study 1 (n = 145) n (%)	Study 2 (n = 30) n (%)
Alcohol	22 (15.2)	6 (40.0)
Cannabis	7 (4.8)	9 (60.0)
Sedatives	2 (1.4)	4 (26.7)
Cocaine	1 (0.7)	4 (26.7)
MDMA/amphetamine	1 (0.7)	2 (13.3)
Opiates	1 (0.7)	1 (6.7)
Hallucinogens	2 (1.4)	2 (13.3)
Alcohol + substances	4 (2.8)	4 (26.7)
Multiple substances without alcohol	2 (1.4)	2 (13.3)

**TABLE III.**

Comorbidity with anxiety disorders in patients with schizophrenia (SCH) with or without substance use disorder (SUD) in study 1 and study 2. *Comorbidità dei disturbi d'ansia nei pazienti con schizofrenia (SCH) con o senza disturbo da uso di sostanze (SUD) negli studi 1 e 2.*

Study 1	Without SUD	With SUD	OR (95% CI)
<b>Schizophrenia</b>	<b>n = 118</b>	<b>n = 27</b>	
Panic disorder	16 (13.6)	8 (29.6)	2.7 (1.1-7.1)
Agoraphobia	4 (3.4)	1 (3.7)	1.1 (0.1-10.2)
Social phobia	7 (5.9)	6 (22.2)	4.5 (1.4-14.8)
Obsessive-compulsive disorder	9 (7.6)	4 (14.8)	2.1 (0.6-7.4)
Generalized anxiety disorder	0	1 (3.7)	-
Simple phobia	5 (4.2)	3 (11.1)	2.8 (0.6-12.6)
<b>Any anxiety disorder</b>	<b>33 (28.0)</b>	<b>14 (51.9)</b>	<b>2.8 (1.2-6.5)</b>
Study 2	Without SUD	With SUD	OR (95% CI)
<b>Schizophrenia</b>	<b>n = 15</b>	<b>n = 15</b>	
Panic disorder	2 (13.3)	6 (40.0)	4.3 (0.7-26.5)
Agoraphobia	0	1 (6.7)	-
Social phobia	1 (6.7)	5 (33.3)	7 (0.7-69.5)
Obsessive-compulsive disorder	1 (6.7)	2 (13.3)	2.1 (0.2-26.7)
Generalized anxiety disorder	0	1 (6.7)	-
Simple phobia	1 (6.7)	5 (33.3)	7 (0.7-69.5)
<b>Any anxiety disorder</b>	<b>3 (20.0)</b>	<b>10 (66.7)</b>	<b>8.0 (1.5-42.0)</b>

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