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**Does substance use disorder affect clinical expression in first-hospitalization patients with schizophrenia? Analysis of a prospective cohort**

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(Article begins on next page)

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## **Abstract**

**Introduction.** Although several papers reported a wide range of negative outcomes among patients with both schizophrenia and SUD, only a few studies evaluated the impact of SUD on psychopathology and thus on the length of first-hospitalization.

**Objectives.** To compare clinical expression of first-episode of schizophrenia between inpatients with and without SUD, giving close attention to the length of stay.

**Methods.** 130 inpatients at first-episode of schizophrenia were assigned to SUD or not SUD group depending on SUD diagnosis and were assessed through BPRS at admission, during hospitalization and at discharge. Cross-sectional and longitudinal statistical analysis were performed to investigate differences between groups and also a linear regression was used to evaluate relationship between length of stay and BPRS scores.

**Results.** During the hospitalization there was a more marked improvement of BPRS total score in patients without SUD with a lower length of hospitalization ( $P < 0.001$ ). BPRS score during hospitalization was predictor of higher length of stay.

**Discussion.** The higher severity of psychopathology during the hospitalization suggest possible overlaps of substance induced and withdrawal symptoms. Conversely, higher levels of conceptual disorganization during the whole period of hospitalization also support a more severe and pharmacho-resistant expression of schizophrenia among SUD patients.

## **Keywords**

psychopathology, substance abuse, drug use disorder, psychotic disorders, hospitalization, length of stay, substance-induced psychoses

## **1. Introduction**

Comorbidity between Substance Use Disorders (SUD) and schizophrenia has been supported by the main epidemiological surveys. Epidemiological Catchment Area (ECA) study (Regier et al., 1990) reports a lifetime prevalence of 47.0% for some SUD in schizophrenia and it shows a 4.6 times higher risk of suffering from some SUD for schizophrenic subjects compared to general population. Similarly National Comorbidity Survey (NCS) (Kessler et al., 1994; Kendler et al., 1996) reveals 45% of comorbidity between substance abuse and schizophrenia while more recent National Comorbidity Survey Replication (NCS-R) (Kessler et al., 2005) reports 26.8% of lifetime comorbidity of non-affective psychosis with SUD. Furthermore, epidemiological investigations conducted outside United States support high prevalence of both substance abuse in psychotic

disorders (Kavanagh et al., 2004; Addington and Addington, 2007) and SUD in schizophrenia (Fowler et al., 1998).

Some authors have also closely appraised the prevalence of the use of illicit drugs among psychotic patients. The substance most commonly used is cannabis, followed by cocaine, amphetamine, hallucinogen and other drugs (Allebeck et al., 1993; Hambrecht and Häfner, 2000; Compton et al., 2009, 2011). Moreover high frequency of polysubstance abuse and misuse are reported (Wade, Harrigan, Edwards, et al., 2006; Barnett et al., 2007). A true and accurate comparison between prevalences reported by different studies is also difficult because methods used for the assessment of substances use were more diversified (scrutinizing medical records, in-depth interview, urine drug test) as well as definitions of use/abuse (lifetime vs. actual use, abuse, or dependence).

From a clinical standpoint, comparison between psychotic patients with and without SUD has consistently shown that the former have an earlier age of onset and are more frequently male. (Cantwell et al., 1999; Veen et al., 2004; Henquet et al., 2005; Mauri et al., 2006; Koskinen et al., 2010; Mazzoncini et al., 2010; Barrigón et al., 2010). Several studies on schizophrenia have reported that patients with SUD have worse premorbid social functioning (Sevy et al., 2010; Mazzoncini et al., 2010; Compton et al., 2011; Schimmelmann et al., 2011), more severe symptoms at onset (Garon and Bellack, 2000; Dawe et al., 2011), lower compliance and worse treatment response, thus more inappropriate use of mental health services, (Lambert et al., 2005; de Haan et al., 2007; Schimmelmann et al., 2011) with higher mental health costs (Bartels et al., 1993).

However these findings about course of illness would be somewhat controversial (Cantor-Graae et al., 2001; Larsen et al., 2006; Zammit et al., 2008). As a matter of fact, some authors support a shorter duration of the illness (Dubertret et al., 2006) for substance-induced psychosis compared with primary psychotic disorders, especially when associated with protracted abstinence from substances (Dawe et al., 2011) and early intervention (Archie et al., 2007; Marshall and Rathbone, 2011).

Studies on the course of schizophrenia have found that substance abusers not only have an higher frequency of relapse (Linszen et al., 1994; Rosenbaum et al., 2005), higher health care cost (Bartels et al., 1993) and a worse social adaptation (Caton et al., 2007), but also present several clinical conditions such as more severe hostile attitudes (Wade, Harrigan, Edwards, et al., 2006), more frequent thought disorders (Soyka et al., 2001) and fewer severe negative symptoms (Hambrecht and Häfner, 1996; Bühler et al., 2002; Compton et al., 2004; Bersani et al., 2002).

Anyway, although SUD in schizophrenia has been associated with a wide range of negative outcomes, only a few papers have expressly investigated the different clinical expression of schizophrenia between patients with and without SUD, and thus whether the impact of substances on outcome is mediated by psychopathology. With certain exceptions (Mazzoncini et al., 2010),

most of data obtained on this topic are inconclusive and inconsistent because they arise from studies concerning others clinical or management aspects of psychosis. However, the most frequently encountered symptoms in SUD are antisocial behavior (Hambrecht and Häfner, 1996; Rabinowitz et al., 1998), delusions, unusual contents of thought, hallucinations (Hambrecht and Häfner, 1996; Mauri et al., 2006; Sevy et al., 2010; Katz et al., 2010) and mood disorders (Linszen et al., 1994; Margolese et al., 2006).

The aim of this study is to investigate the different clinical expression of early psychosis between patients with or without SUD in a prospective cohort of first-episode of schizophrenia, giving special attention to the relationship between duration of hospitalization and severity of symptoms and signs.

## **2. Methods**

### **2.1 Sample enrollment**

The study population consists of every patients aged between 18 and 65 years entering the Psychiatric Diagnosis and Care Service (*Servizio Psichiatrico di Diagnosi e Cura*) of “San Luigi Gonzaga” Hospital (Orbassano, Turin, Italy) between January 1<sup>st</sup> 2010 and January 1<sup>st</sup> 2012 at first-episode of schizophrenic-spectrum disorder (Brief Psychotic Disorder, Schizophreniform Disorder, Psychotic Disorder Not-Otherwise-Specified, according to DSM IV-TR criteria).

Initial exclusion criteria were: a) prior diagnosis of schizophrenia or other psychotic disorder; b) prior assumption of antipsychotic drugs; c) presence of severe medical and/or neurological disorders; d) prior hospitalization or contact with the public psychiatric services; e) presence of disorders linked to the use of alcohol, as per the DSM IV-TR criteria.

A posteriori exclusion criterion was diagnosis of schizophrenia not confirmed 6 months after hospitalization at scheduled outpatient psychiatric examination using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, 1997).

### **2.2 Procedures**

The study consists of three stages of observation (T0, T1 and T2). At admission to the hospital (T0) the psychiatrist collected data about patient's medical history and previous/current pattern of use/abuse of illegal substances using an in-depth clinical interview. He also assessed first appearance of psychiatric symptoms using Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and diagnosed psychiatric disorder and SUD, according to DSM IV-TR with SCID-I. After one week of hospitalization (T1) and at discharge (T2) psychiatric symptoms were assessed during psychiatric examination using BPRS. Type and dosage of every psychopharmacological treatments administered during period of hospitalization were recorded.

According to DSM IV-TR criteria, diagnosis of schizophrenia was confirmed 6 months after hospitalization at scheduled outpatient psychiatric examination using SCID-I.

### **2.3 Assessment tools**

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) is a semi-structured interview characterized by a modular structure which items are based on the criteria of the DSM-IV Axis I and it's commonly used to make diagnosis of DSM-IV Axis I Disorders with good reliability (Segal et al., 1994). In this study it was administered at admission to make sure that every patients comply with inclusion and exclusion criteria, and 6 months after discharge to confirm diagnosis of schizophrenia.

Brief Psychiatric Rating Scale (BPRS) is a clinician-based rating instrument consisting of 18 items that describe dimensions of psychopathology. Each item is rated on a 7-point scale ranging from “not present” to “very severe”. BPRS is widely used for evaluate psychiatric symptoms specially in schizophrenia research and its reliability and validity has been demonstrated repeatedly (Hedlund and Wieweg, 1980; Andersen et al., 1989; Mortimer, 2007) also in dual diagnosis patients (Lykke et al., 2008). In this study it was used to assess the severity of each psychopathological dimension at three stages of observation (T0, T1 and T2).

### **2.4 Data Analysis**

Data were analyzed with both cross-sectional and longitudinal methods. In the former, differences between SUD patients and not SUD patients in BPRS at T0, T1, and T2, were estimated through crude (CMD) and standardized (SMD) mean differences, with their 95% confidence intervals (95% CI) and the significance of the difference was tested using parametric or non-parametric tests, according to the distribution of the variables under study (Rothman and Greenland, 1998). In the latter, we considered decrease in BPRS total score as time-dependent variable, so we estimated Hazard Ratios (HRs) of decrease of at least 50% in T1 or T2 when compared with T0, for SUD versus not SUD patients, using a Cox regression model, adjusting for relevant baseline characteristics and testing significance of the differences through the Wilcoxon and Log rank tests. Lastly, in order to evaluate the prediction value of psychopathological dimensions on length of hospitalization, a linear regression model was performed considering days of hospitalization as dependent variable and age, gender, substance abuse and BPRS total score at T0 and T1 as independent variables.

Analysis was performed trough SAS statistical package, version 9.0 (SAS Institute Inc, Cary, NC), and all tests relied on a two-tailed  $P \leq 0.05$  as significance criterion. All data were treated in aggregate form to respect patients' anonymity.

### 3. Results

#### 3.1 Sample description

130 (95.6%) of the 136 recruited patients were diagnosed with schizophrenia on the basis of DSM IV-TR criteria and therefore they were included in the study. 60 (46.15%) of them met DSM IV-TR criteria for SUD, 76 (58.46%) were male, 73 (56.15%) were smokers, 60 (46.15%) were compulsory admitted and only a few ( $n=6$ , 4.61%) have an academic degree.

Comparing the socio-demographic characteristics of patients with SUD with those without SUD (Table 1) emerged that the former were more frequently male (76.70% vs. 42.86%,  $P<0.001$ ), smokers (83.33% vs. 32.86%,  $P=0.001$ ), unmarried (96.70% vs. 51.40%,  $P<0.001$ ), unemployed (83.33% vs. 32.86%,  $P=0.001$ ), and they were younger at onset ( $23.40\pm6.53$  years vs.  $29.40\pm9.99$ ,  $P=<0.001$ ).

The substance most frequently abused was cannabis ( $n=60$ ; 100%), followed by cocaine ( $n=13$ ; 31.70%), amphetamine-like compounds ( $n=9$ ; 15%), LSD ( $n=8$ ; 13.30%) and heroin ( $n=3$ ; 5%); 25 patients (41.70%) were polyabusers.

#### 3.2 Treatment description

During hospitalization 53.33% ( $n=62$ ) of patients with SUD and 50.00% ( $n=35$ ) of those without SUD received antipsychotic monotherapy and the remainder were treated with an association of antipsychotic drugs and mood stabilizers. Mean doses of the antipsychotic drugs in SUD and not SUD groups were respectively: haloperidol  $5.9\pm3.4$  mg/day vs.  $5.7\pm2.9$  mg/day; risperidone  $4.8\pm1.9$  mg/day vs.  $4.\pm1.5$  mg/day; olanzapine  $10.3\pm5.6$  mg/day vs.  $9.4\pm4.7$  mg/day. In cases in which an association was used, mean doses of mood stabilizers were: valproic acid  $1138.4\pm351.6$  mg/day in SUD vs.  $987.9\pm324.6$  mg/day in not SUD, and carbamazepine  $693.5\pm154.8$  mg/day in SUD vs.  $625.1\pm144.9$  mg/day in not SUD.

None of the differences between groups were statistically significant.

#### 3.3 Clinical assessment and psychopathological expression

Fig 1 presents the comparison of BPRS mean total scores between SUD and not SUD groups at three stages of assessment. At T0 no statistically significant differences were found (SMD=0.30, 95% CI=-0.05/0.65,  $P=0.09$ ). During the course of the illness, conversely, there was a trend toward a more marked improvement in patients without SUD (T1: SMD=0.76, 95% CI=0.4/1.12,  $P=0.001$ ; T2: SMD=0.20, 95% CI=-0.15/0.55,  $P=0.026$ ).

As regards psychopathological expression, the sample presented high mean score of anxiety ( $4.94\pm1.32$ ), tension ( $4.68\pm1.40$ ), suspiciousness ( $4.33\pm1.64$ ), and unusual thought content ( $4.09\pm1.80$ ). At admission, SUD patients had higher mean score on each dimension of BPRS compared to not SUD ones with statistically significant differences for conceptual disorganization ( $P<0.001$ ), mannerisms and posturing ( $P<0.001$ ) and emotional withdrawal ( $P=0.001$ , Fig 2). Seven

days after admission (Fig 3), mean score comparison between two groups showed statistically significant differences with higher conceptual disorganization (SUD=3.13 vs. not SUD=1.74,  $P<0.001$ ), more hostility (SUD=2.83 vs. not SUD=1.86,  $P<0.001$ ), more grandiosity (SUD=2.00 vs. not SUD=1.34,  $P=0.002$ ) and more tension (SUD=3.53 vs. not SUD=2.91,  $P=0.009$ ) in SUD group. Moreover, it also revealed slightly significant differences in unusual thought content (SUD=3.63 vs. not SUD=2.97,  $P=0.012$ ), uncooperativeness (SUD=2.37 vs. not SUD=1.83,  $P=0.017$ ), hallucinations (SUD=1.60 vs. not SUD = 1.17,  $P=0.02$ ), emotional withdrawal (SUD= 2.97 vs. not SUD=2.49,  $P=0.035$ ), and mannerism and posturing (SUD=1.51 vs. not SUD =1.93  $P=0.035$ ) with worst clinical condition for SUD group.

Finally mean score of every BPRS psychopathological dimension at discharge decreased to mild or very mild level with significantly higher mean score of conceptual disorganization (SUD=2.07 vs. not SUD=1.40,  $P<0.001$ ), tension (SUD=2.57 vs. not SUD=2.17,  $P=0.036$ ) and grandiosity (SUD=1.46 vs. not SUD=1.22,  $P=0.021$ ) among SUD patients (Fig 4).

Longitudinal analysis estimated the hazard of BPRS score reduction of at least 50% from T0 to T2 comparing two groups. The hazard of relative reduction of 50% in SUD group was one third of not SUD one (HR=0.29, 95% CI=0.09/0.92,  $P=0.004$ ) and when it was adjusted for age at onset and smoking habit, the effect of SUD on HR was confirmed, while statistical significance was lost (HR=0.32; 95% CI=0.08/1.19,  $P=0.09$ ).

### **3.4 Duration of hospitalization**

The mean duration of hospitalization ( $17.10\pm7.12$  days vs.  $12.80\pm5.12$ ;  $P<0.001$ ) in SUD group was longer than not SUD group with statistically significance which remained after adjusting for socio-demographic characteristics.

Linear regression model with age, substance use, gender and BPRS total score at first two stages of observation could explain 56,54% of variance of length of stay ( $r^2=0.56$ ,  $F=28.53$ ,  $P<0.001$ ) and it showed that male gender ( $B=3.65$ ,  $t=-4.24$ ,  $P<0.001$ ) and the BPRS total score at T1 ( $B=0.45$ ,  $t=9.03$ ,  $P<0.001$ ) were the only significant predictors of length of stay. Adding more variables to the model did neither increase the proportion of variance explained nor founded other significant predictor.

## **4. Discussion**

The present study on patients at first episode of schizophrenia confirm growing literature results about socio-demographic differences between patients with and without SUD comorbidity. SUD patients look younger at onset of psychiatric symptoms (Modestin et al., 2001), more frequently male and smokers (Cantor-Graae et al., 2001), unmarried (Farrelly et al., 2007; Wobrock et al., 2007; Mazzoncini et al., 2010) and unemployed (Compton et al., 2009; Barrigón et al., 2010;



Schimmelmann et al., 2011).

Results about type of substance abused show that all patients with SUD are cannabis abusers and 41.7% is polyabuser according with previous studies (Hambrecht and Häfner, 1996; Wade, Harrigan, Harris, et al., 2006).

As regards clinical expression of schizophrenia, comparison of BPRS mean score between SUD and not SUD highlights a weak significant worse clinical presentation at admission, when only two BPRS dimensions are lower in not SUD patients, and it shows a strong significant worse clinical progression at T1, when a lot of BPRS items improve in not SUD patients. Therefore the present study not only confirms more severe psychopathological expression in SUD patients at admission (Mazzoncini et al., 2010) but it also reports a significant persistence of psychopathology during hospitalization among SUD patients.

Giving special attention to each BPRS item score both higher conceptual disorganization and grandiosity at admission and higher unusual thought contents and hallucinatory behavior during the hospitalization seem to confirm previous findings that reported a more severe positive symptoms (Addington and Addington, 2007; Sevy et al., 2010) and more problematic clinical management among patients with SUD, not least due to the presence of a considerably more marked dimension of grandiosity, hostility and tension (Katz et al., 2010). Nevertheless a more rapid decrease of psychotic symptoms in patients without SUD could support, a previous found, greater pharmacoresistance in SUD patients (Hambrecht and Häfner, 2000).

Most of the psychopathological dimension found as significantly higher during hospitalization was previously reported as more prevalent in cannabis-related psychosis and cannabis abstinence (Kulhalli et al., 2007). Considering that all SUD patients in our sample are cannabis abusers we could suggest a possible overlap of cannabis induced psychosis with first episode of schizophrenia. Statistical analysis of each psychopathological dimension at T0, T1 and T2 provides new informations about the worse course of schizophrenia in SUD patients suggesting a possible role of substances in determining variability of the clinical presentation. Mannerisms and posturing, emotional withdrawal and somewhat less grandiosity are significantly higher among SUD at admission, they remain higher one week after but decrease losing statistical significance at discharge. Considering the impact of substance on psychopathological dimensions it could be suggested that higher mean scores of these BPRS items was sustained by substance abuse which would not proceed during hospitalization progress. Conversely hostility, unusual thought contents, uncooperativeness, and hallucinatory behavior became significantly higher among SUD only one week after admission and lost significance at discharge suggesting that they could be supported by several incoming conditions such as pharmacological side effects or treatment refractory as well as substance withdrawal. Tension is the only item that has become significantly higher in SUD during

hospitalization and remained higher at discharge, therefore it could be either an long-term consequence of substance withdrawal or a previous more marked feature of patient with SUD that could have induced a “self-medication” behavior (Khantzian, 1997). Otherwise conceptual disorganization defined by BPRS manual as an affection of thought processes with tangentially, circumstantially and sudden topic shifts is the BPRS dimension that most resembles the bleulerian concept of “*spaltung*” and it is higher at all three stages of observation in SUD group, regardless of substance withdrawal influences, confirming a worst clinical expression of schizophrenia in patients with SUD.

The present study shows significant longer hospitalization in patients with both SUD and schizophrenia without confirming the contradictory impact of SUD diagnosis in predicting length of stay reported by previous studies (Chang et al., 1991; Herr et al., 1991; Huntley et al., 1998). Conversely for both SUD and not SUD patients, the psychopathological condition measured by BPRS one week after admission is the only significant predictor of length of stay together with male gender (according to line slope for each 2.22-units increase in BPRS score, length of stay increases 1 unit). Unlike some authors who have investigated only clinical presentation at admission (Averill et al., 2001; Lachar et al., 2001), our analysis also compare predictive value of psychopathological severity at admission with one week after ones, finding a role in predicting length of stay only for the latter. This finding is probably explained by clinical criteria adopted by the physician to determine the length of stay during the hospitalization, therefore patients with more severe symptoms of schizophrenia, regardless of substance use, have longer hospitalization than others.

One limitation of the present study consists in the way in which we diagnosed SUD. Although SCID-I is considered a valid and consistent assessment tool for diagnose DSM-IV-TR Axis I disorders (Skre et al., 1991; Carey et al., 2001), urine drug test could be used to confirm the patient-reported abuse of illicit drugs and thus to increase the accuracy of group selection.

Future research might aim to investigate, deeply and in a wider sample, the possible relationship between several clinical manifestations of schizophrenic symptoms and each types of SUD (Mc Lellan et al., 1979; Dalmau et al., 1999). Moreover specific assessment tools may be used to investigate craving and withdrawal severity in order to better explain how substance use affects psychopathology.

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Table 1. Baseline socio-demographic and general characteristics of the sample (n=130)

Fig1. Temporal trend of BPRS total score

Fig2. BPRS item at T0

Fig3. BPRS item at T1

Fig4. BPRS item at T2