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

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ABSTRACT

Although several papers reported a wide range of negative outcomes among patients with both schizophrenia and Substance Use Disorder (SUD), only a few studies evaluated the impact of SUD on psychopathology and thus on the length of first-hospitalization. The aim of the present study was to compare clinical expression of first-episode of schizophrenia between inpatients with and without SUD, giving close attention to the length of stay. One hundred and thirty inpatients at first-episode of schizophrenia were assigned to either 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. SUD group showed more disorganization at admission, less marked improvement of symptoms (disorganization, thought disturbance, anergia), and longer hospital stay than not SUD group. Moreover BPRS total score during hospitalization was a significant positive predictor for length of stay. Taken together, these findings suggest that SUD patients have a more severe and drug-resistant expression of schizophrenia, hence, they need longer treatment to achieve the overall symptoms improvement required for discharge.

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1. Introduction

Comorbidity between Substance Use Disorder (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 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., 2012), more severe symptoms at onset (Gearon 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., 2012) 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 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, 2010 and January 1, 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).

During the entire period of hospitalization, substances use and access to non-prescribed drugs was prevented by around-the-clock nursing care and protected environment.

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 is 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 psychiatric symptoms at three stages of observation (T0, T1 and T2). According to Schafer's meta-analysis of BPRS factor structure (Schafer, 2005) and considering the longitudinal design of the present study, the cross-validated four-factor subscale model proposed by Mueser et al. (1997) was used to assess the psychopathological dimensions. Thus, 16 of the 18 BPRS items were grouped in four subscales: thought disturbance (grandiosity, suspiciousness, hallucinations, unusual thought content); anergia (emotional withdrawal, motor retardation, uncooperativeness, and blunted affect); affect (somatic concern, anxiety, guilt, depression, and hostility); disorganization subscale (conceptual disorganization, tension, and mannerisms and posturing).

2.4. Data analysis

All computations were performed by IBM SPSS Statistics for Windows (Version 19.0. Armonk, NY: IBM Corporation).

Comparison of baseline characteristic between SUD and not SUD groups was carried out using Pearson's χ^2 test or Fisher's exact test for categorical variables, depending on expected frequencies in each group, whereas mean differences of continuous variables were evaluated either by independent-samples t test or by Mann-Whitney's U test depending on normal or not-normal distribution of variables, tested by Shapiro–Wilk test.

Two Generalized Linear Model (GLM) for repeated measures were performed to analyze the differences in longitudinal variations of symptoms between SUD and not SUD groups. The BPRS total and the BPRS subscales scores at three stages of assessment (T0, T1 and T2) were used as within-subjects variables respectively in the first and in the second model. Whereas diagnosis of SUD was employed as between-subject factor in both models. The effect size of each factor was reported as partial Eta squared (η^2p), and Huynh–Feldt correction was applied in case of violation of sphericity. Both GLMs also performed cross-sectional pairwise comparisons of mean scores at different stages of assessment which were made by repeated contrasts and were reported as mean difference (Δ) with the Sidak corrected 95% Confidence Interval (95%CI).

Moreover, 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 significant baseline characteristics, and testing significance of the differences through the Wilcoxon and Log rank tests. Lastly, in order to evaluate the prediction value of clinical presentation for length of hospitalization, a linear regression model was performed considering days of hospitalization as dependent variable, the BPRS total score at T0 and T1 as independent variables, adjusting for significant baseline characteristics. All tests relied on a two-tailed $P < =0.05$ as significance criterion. All data were treated in aggregate form to respect patients' anonymity.

3. Results

3.1. Sample description

One hundred and thirty (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. Sixty (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