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Primary psychosis with comorbid drug abuse and drug-induced psychosis:
diagnostic and clinical evolution at follow up

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Abstract

The study reports a follow-up assessment of 48 patients with concomitant drug abuse at the first admission for psychosis. We focused on the diagnostic distinction between primary psychosis with concomitant drug abuse and drug induced psychosis, to observe whether the diagnoses are stable over time and whether the clinical course significantly differs.

The study examined 25 Primary Psychotic Disorder with comorbid Drug Abuse and 23 Drug Induced Psychotic Disorder patients. Diagnostic and psychopathological assessments were made at baseline and at follow-up.

Mean follow-up period was 4.96 years. Patients with comorbid Drug Abuse exhibited higher scores in the item Unusual Content of Thought at baseline than Drug Induced Psychotic Disorder patients: 5.48 vs 4.39 while the two patients groups did not differ in any of the BPRS items evaluated at follow-up.

The Primary Psychosis with comorbid Drug Abuse and the Substance Induced Psychosis groups were similar regarding diagnostic stability, and a diagnosis of Schizophrenia at follow-up occurred similarly. There was no evidence that Drug Induced psychotic patients' symptoms tend to improve more after cessation of drug abuse. An earlier age of onset was found in Primary Psychotic patients, particularly for patients diagnosed as affected by Schizophrenia at follow up.

These results might reflect the uncertainty of the distinction between Primary and Drug Induced Psychosis and the difficulties in applying the DSM IV-TR criteria for diagnosing comorbid drug use disorders and psychotic disorders.

Introduction

Co-occurrent drug abuse is a very frequent condition among patients presenting their first episode of psychosis, prevalence rates ranging between 25 and 60% [1].

The comorbidity of schizophrenia and substance abuse is associated with more frequent relapses, more positive symptoms and depression, cognitive impairment, and a poorer outcome and treatment response. It has been hypothesised that substance abuse could trigger psychotic symptoms in vulnerable individuals, furthermore substances might be used to self-medicate symptoms of schizophrenia [2, 3, 4, 5, 6, 7, 8, 9, 10].

Formulating a psychiatric diagnosis in patients who experience the onset of psychotic symptoms during episodes of current or recent psychoactive substance use is often challenging, even though some key predictors, such as differences in demographic, family, and clinical domains, could help emergency clinicians to correctly classify early-phase psychotic disorders that co-occur with substance use [11, 12, 13, 14, 15].

In DSM IV-TR criteria [16] so called primary or independent psychotic disorders include an exclusion criteria that "symptoms are not *due to* the direct physiological effects of a substance". Because "independent" psychotic diagnoses (eg, schizophrenia) are not to be made if symptoms are due to effects of substances, newly emerging psychotic symptoms in the presence of substance abuse are presumed to be "substance induced" until proven otherwise.

In patients who use drugs during a first episode of psychosis, evidence that psychotic symptoms are primary or independent requires persistence of the symptoms during a period of sustained abstinence from psychoactive substances (when intoxication or withdrawal effects can no longer account for psychotic symptoms). On the other hand, drug-induced psychoses are expected to resolve during a period of sustained abstinence from psychoactive substances. In other words, the substance-induced psychotic mental disorders are considered to be time limited.

When patients present with current or recent drug abuse and onset of psychosis, the key diagnostic question is whether or not the psychotic symptoms are accounted for by the drug use [14]. However, in practice, determining whether a given psychotic symptom is "due to" drug effects is far from straightforward [17].

This question is highly relevant from a clinical point of view, since antipsychotic treatment can be either seen as a short-term treatment with central emphasis placed on drug abuse treatment, or alternatively, a long-term treatment taking care of the independent psychotic disorder.

Despite the clinical significance of a differential diagnosis between a primary and a drug- induced psychosis, only few studies provide information about longitudinal diagnostic stability and change in psychotic disorders co-occurring with drug use.

A clear evidence of the uncertainty in diagnosing early phase psychosis with concomitant drug abuse is that longitudinal studies have reported high rates of diagnostic changes in psychotic disorders' diagnoses over time, most frequently associated with concomitant substance abuse [18, 19]. Witty et al. [20] found that the greatest diagnostic instability occurred in the diagnostic category of drug-induced psychosis, with a change in diagnosis, mainly to Schizophrenia, in more than 70% of the case while Caton et al. [21], in a large study with one-year follow-up, found a diagnostic change to a primary psychotic disorder in a smaller proportion of cases (25%).

In the present study we have observed the long-term longitudinal course of a sample of patients experiencing early phase psychosis with concomitant drug abuse. We have focused on the diagnostic distinction between the diagnosis of primary non-affective psychosis with concomitant drug abuse and drug-induced psychosis in order to observe whether the diagnoses are stable over time and whether the course of the clinical picture significantly differs.

We are also interested in focusing on those patients diagnosed at baseline with drug-induced psychoses who don't persist in drug abuse at follow up: such patients would be expected to show clinical amelioration, by DSM IV-TR definition of Drug-Induced Psychosis.

Furthermore we have looked for peculiar or distinctive clinical features that would identify patients with psychotic symptoms and comorbid drug abuse as evolving to primary disorders such as schizophrenia. Such clinical peculiarities might be represented by the severity of some clinical symptoms like delusions or hallucinations, conceptual disorganization, depressive symptoms, or hostility, which have been previously reported to be associated with progression to Schizophrenia. Other distinctive features might be psychiatric history, age of onset and pattern of drug abuse [14].

2. Materials and Methods

2.1 Study aims

The present study reports a long-term follow-up assessment of 48 patients who had concomitant drug abuse at the time of the first hospitalization for a psychotic decompensation.

The analysis included only those patients diagnosed as having a non affective Primary Psychotic disorder with comorbid Drug Abuse (PP-DA) and Drug-induced Psychotic Disorder (DIP) at the time of their first admission.

Diagnostic and psychopathological assessments made at baseline and at follow-up were compared, in order to study the diagnostic stability and clinical course over long term follow up.

2.2 Design

In order to observe the longitudinal course of the disorders, diagnostic, clinical, and demographic information were retrospectively assessed at baseline and at follow up. Baseline data were obtained through analysis of clinical charts and medical records of the Psychiatric Service of Diagnosis and Treatment of the hospital, Ospedale Maggiore Policlinico of Milan (SPDC), at the time of the first admission for psychosis. SPDC is an inpatient facility that provides community based mental health emergency care for an urban population of approximately 190.000 people residing in the centre of Milan. Follow up data were obtained through analysis of clinical charts and medical records of three Psycho-Social Centers (CPS), outpatient psychiatric facilities of reference that provide mental health care in non-acute setting after discharge from the hospital.

2.3 Subjects

The study sought to identify people experiencing psychosis at an early phase with concomitant drug abuse. The local ethical committee approved the study.

Study subjects were recruited among patients referring to the Psychiatric Services for Diagnosis and therapy (SPDC). Clinical charts of all the patients who were admitted for psychosis for the first time at the SPDC in the period 2002-2015 were reviewed. Patients were included in the analyses only if their clinical charts provided clear evidence of concomitant use of illicit substances at the time of their first admission to the psychiatric unit (urine analysis).

Patients who were discharged at that time with diagnoses other than new-onset Schizophrenia, Schizophreniform Disorder, Brief Psychotic Disorder and Drug-induced Psychotic Disorder were excluded. Patients diagnosed as having Brief Psychotic Disorder at the time of the first admission were included only if a clear evidence that their psychotic symptomatology lasted more than one month was obtained (see below in diagnoses section). Patients who did not have concomitant drug abuse or whose drug abuse at the time of admission could not be clearly assessed were also excluded by the analysis. Other exclusion criteria were: a previous diagnosis of any psychotic disorder, including schizophreniform disorder, schizophrenia, and drug-induced psychotic disorder; a previous admission to any psychiatric hospital, a steady treatment in any psychiatric service preceding admission to our SPDC, the presence of an organic brain syndrome or severe mental retardation.

Follow up assessment was obtained from medical records and clinical charts in the CPS. Only subjects whose follow up data were available for the analyses were included in the study. Not available patients at follow up have given up the CPS.

2.4 Diagnoses

The diagnoses at the time of the first hospitalization and at follow-up were formulated by a consensus of multiple expert clinicians. Diagnoses were made according to DSM IV-TR criteria.

The diagnoses at the time of the first hospitalization represented the baseline diagnoses in our analysis. We included all drug-abuser patients whose psychotic symptoms were lasting more than 1 month and whose disturbance was not due to the direct physiological effects of a drug of abuse or other substances in the PP-DA group. The group included only patients having their full psychiatric syndrome established before heavy substance use, or persisting more than 4 weeks after the cessation of acute intoxication or withdrawal. More specifically, the group included patients diagnosed as having new-onset Schizophrenia, Schizophreniform Disorder, and Brief Psychotic Disorder.

A different criterion was applied in case of diagnosis of Brief Psychotic Disorder (DSM IV-TR diagnostic criteria require that psychotic symptoms last less than one month): in these cases additional information about the six month follow up after discharge were obtained in order to establish whether psychotic symptomatology lasted more than one month. In these cases patients diagnosed as having Brief Psychotic Disorder at discharge were included in the PP-DA group.

The follow-up diagnoses were recoded in five different classes: Schizophrenia (S), Other Psychotic Disorders (OP), Personality Disorders (PD), Drug-Induced Psychotic Disorder (DIP), and Others. OP included Brief Psychotic Disorder, Schizophreniform Disorder, Schizoaffective Disorder, Psychotic Disorder Not Otherwise Specified.

2.5 Clinical and Demographic Assessments

Clinical evaluation was made by the Brief Psychiatric Rating Scale (BPRS) [22], a general psychopathology scale consisting in 18 items with scores ranging from 0 (absent) to 7 (most severe). Assessments were made by the same well-trained examiners, who were blind to the

diagnoses. Raters were trained before the starts of assessments regarding the use of rating scales, in order to obtain inter-rater consistency in their assessment.

Demographic information were obtained consulting medical records.

Anamnestic data and history of drug abuse were collected during a clinical interview and on the basis of the information given by the patients and their relatives. Urine toxicology was performed if clinically required.

2.6 Statistical analysis

Data were analysed by means of SPSS 15.0©.

Analyses included descriptive statistics, T-Test for independent samples, Pearson's Correlation Analysis. Moreover, Analysis of Covariance (ANCOVA) was conducted in order to test differences in age at onset and symptom variables amongst the following between-subjects factors: gender, baseline diagnoses, follow-up diagnoses, presence of drug abuse at follow-up, with adjustment for the duration of follow-up.

Pearson Chi-Square test was performed to test differences in gender distribution, diagnostic stability, and pattern of drug abuse between baseline diagnostic groups.

Multivariate Analysis of Variance (MANOVA) for Repeated Measures was used to test the effects of the cited above between-subjects factors on the improvement in BPRS symptomatology. In particular, we wanted to test the effect of the cessation of drug abuse on the change in symptoms across baseline diagnoses: therefore, time $\times$ presence of drug-abuse at follow-up $\times$ baseline diagnoses interaction was studied to test the hypothesis that DIP patients resolve their symptomatology after cessation of drug abuse.

3. Results

43 of the 48 subjects (89.6%) were males. Mean age at onset of psychotic symptoms was 26.94 ($\pm$ 6.73 SD) years. Mean duration of hospitalisation was about 12 days.

Abuse of more than one drug was found in 56.4% cases. The most common substance of abuse was cannabis in 41 cases (85.4%). Cocaine was used in 18 cases (37.5 %).

The mean duration of follow up was 4.96 years (± 3.81 SD, range 1-13). The duration of follow-up was slightly negatively correlated to the age of onset ($r = -0.28$, $p = \text{NS}$).

3.1. Primary Psychotic Disorder with concomitant drug abuse vs Drug Induced Psychosis at baseline

At time of their first hospitalization for psychosis, 25 (52.1%) and 23 (47.9%) patients were diagnosed as having PP-DA and DIP, respectively.

Baseline characteristics of the two groups are presented in Table 1.

Gender distribution was similar across the two groups.

Mean ages at onset were 25.60 (± 5.65 SD) years and 28.39 (± 7.60 SD) years for PP-DA and DIP respectively. The difference was almost statistically significant after correction for duration of follow-up. ($F = 2.7$; $p = 0.07$) (Fig.1).

PP-DA patients exhibited higher scores in the item Unusual Content of Thought at baseline than DIP: 5.48 (± 3.87 SD) vs 4.39 (± 3.75 SD) ($F = 2.19$, $p < 0.05$) while PP-DA and DIP groups did not differ in any of the BPRS items evaluated at follow-up (Table 1).

A significant difference in the pattern of drug abuse at baseline was found between the two groups: a higher prevalence of polyabusers was found in the DIP group compared to PP-DA group (78.3% vs 36% respectively, $\chi^2 = 8.69$, $p < 0.005$). Persistence of drug abuse occurred in similar percentage of cases amongst baseline diagnoses (52 % and 60.9 % for PP-DA and DIP groups, respectively) (Table 1). On the other hand, persistence of drug abuse was significantly predicted by baseline higher scores of hostility [4.22 (± 2.48 SD) vs 2.95 (± 1.88 SD), $p \leq 0.05$] and abuse than more than one drug.

Fig.2 shows the effect of drug abuse at follow up on the changes in BPRS scores: DIP patients showed no more tendency to improve their symptomatology after cessation of drug abuse, compared to PP-DA patients. In particular, DIP patients showed less improvement of hallucinations compared to PP-DA patients. No other significant time x baseline diagnosis x follow-up drug abuse interaction were observed with regard to the other symptoms, therefore there was no evidence that DIP patients had more tendency to improve their symptomatology after cessation of drug abuse, compared to PP-DA patients.

Diagnostic changes are presented in Fig.3. A shift to a diagnosis of Schizophrenia occurred in a similar percentage of cases: 40.0 % of and 34.8% of PP-DA and DIP patients respectively received a diagnosis of Schizophrenia at follow-up. Only 4 patients with a baseline diagnosis of DIP (17.4%) maintained the diagnosis at follow up. 27.1% of the patients had a diagnosis of Personality Disorder at follow-up, the 69.2 % of those were PP-DA at baseline.

3.2. *Diagnosis of Schizophrenia at follow-up*

The duration of follow-up was longer in patients who had a follow-up diagnoses of Schizophrenia, compared to patients who progressed to other disorders ($F=3.86$, $p<0.01$)

Amongst patients who shift to Schizophrenia, a baseline diagnosis of PP-DA was associated to earlier age at onset compared to a baseline diagnosis of DIP: 25 years (± 5 SD) vs 30.5 years (± 6.4 SD) respectively, $t=2.09$, $p < 0.05$ (Fig.1).

Regarding symptomatology at follow-up, those who shifted in Schizophrenia exhibited significantly higher scores in conceptual disorganization ($F=4.38$, $p<0.05$) and unusual content of thought ($F=3.83$, $p<0.01$), than any of the other diagnoses. Patients whose diagnosis changed to Schizophrenia had also higher hallucination scores than patients whose only diagnosis at follow-up was personality disorder ($F=1.64$, $p<0.05$).

With regard to baseline symptoms a diagnosis of Schizophrenia at follow-up was associated with higher baseline scores of Hostility than any other diagnosis ($F= 4.85$, $p< 0.05$) and with higher baseline scores of Conceptual Disorganization compared to the diagnosis of Personality Disorder ($F= 2.31$, $p< 0.05$).

A diagnostic change to Schizophrenia was also associated with less improvement from baseline to follow-up in Unusual Content of Thought [Schizophrenia: 5.3 (± 1.5 SD) vs 5.0 (± 1.7 SD); Other diagnoses: 5.3 (± 1.6 SD) vs 3.0 (± 2.0 SD); $F= 4.19$, $p< 0.05$] and Hallucinations [Schizophrenia: 3.7 (± 2.0 SD) vs 3.9 (± 2.2 SD); Other diagnoses: 4.4 (± 2.4 SD) vs 2.6 (± 2.2 SD); $F= 5.59$, $p< 0.05$].

The differences were still significant after adjustment for the duration of follow-up.

We did not observe any difference in the rate of drug abuse at follow-up between patients whose diagnoses shifted to Schizophrenia or other diagnoses.

Discussion

In the present study, diagnostic and clinical courses of patients who abused drugs while experiencing early-phase psychosis were examined. We focused on the initial distinction between Primary Psychosis with concomitant drug abuse and Drug-Induced Psychosis.

The two groups were substantially similar regarding diagnostic stability, and a diagnosis of Schizophrenia at follow-up occurred in a similar percentage of cases. Only a minority of DIP patients kept the diagnosis of Drug-Induced Psychosis at follow-up.

The two groups did not significantly differ in the severity of clinical symptomatology at follow-up, as measured by means of some BPRS items. There was no evidence that DIP patients had more tendency to improve their symptomatology after cessation of drug abuse, compared to PP-DA patients.

However, PP-DA patients had an earlier age of onset compared to DIP patients, particularly when only patients whose diagnosis changed to Schizophrenia were examined.

Patients initially diagnosed as having a PP-DA also presented higher scores on the Unusual Content of Thought item at baseline. On the other hand, DIP patients were more likely to abuse more than one drug at baseline and seemed to show a more resistance to Hallucination improvement also after drug abuse interruption.

In other words these results seem to be consistent with data showing that psychotic patients who use substances, including cannabis, exhibit an early onset of psychosis [23], higher baseline hostility and are at greater risk of developing a continuous illness characterized by positive symptoms [24].

The stability of Primary Psychosis with comorbid substance abuse and Substance-induced Psychosis has been previously investigated: Caton et al. [21] conducted a prospective 1-year follow-up study of 319 psychiatric emergency department admissions with diagnoses of early-phase psychosis and substance use comorbidity and found that the primary psychosis vs. substance-induced psychosis distinction was remarkably stable over time. The authors reported a change in diagnostic category from substance-induced psychosis at baseline to primary psychosis in about 25% of cases.

In our sample, the diagnostic shift from drug-induced psychosis to Schizophrenia happened in about 34% of the cases, and less than 20% of the DIP patients retained the diagnosis at follow-up.

The low prospective consistency of a diagnosis of drug-induced psychosis is of particular interest, because this finding might suggest that most people who presented in this fashion had an underlying endogenous psychotic illness or have major risks to develop a psychotic disorder.

Regarding the diagnostic stability of primary psychosis, in our study we observed that only 60% of the patients retained a diagnosis of primary psychosis (40% Schizophrenia and 20% other Primary Psychosis). In Caton's study the large majority retained the Primary Psychosis diagnosis, however the authors specify that no change in diagnostic category was applied in those cases who underwent remission of primary psychotic illness, since an illness classified as primary psychosis could have been in remission at 1 year follow-up with no change in diagnostic category [21].

The longer follow-up period and the retrospective design can further explain the differences observed in the present study. Moreover, unlike ours, in Caton's study patients with a baseline diagnosis of affective psychosis were included in the analysis. The under representation of females in our study can be explained by the inclusion of affective psychosis in the Caton's study and by the larger prevalence of substance abuse in male population.

Studies on non-selected samples of first-episode psychotic patients that weren't restricted to those having comorbid drug abuse, showed greater diagnostic consistency of primary psychotic disorders after long-term follow-up, with rates ranging between 70 and 100% [25, 26, 20]. Patients whose diagnosis changed were more likely to have a comorbid substance-related disorder at first presentation [20].

The higher rate of diagnostic inconsistency over time observed in the present study might reflect the difficulties in applying the DSM IV-TR criteria for diagnosing comorbid drug use disorders and psychotic disorders [14].

As a further result of the uncertainty of the diagnostic distinction, the primary and the drug-induced psychosis groups were also substantially similar regarding symptomatology at baseline and at follow-up, and DIP patients did not show more tendency to improve their symptomatology after cessation of drug abuse, as it was expected by definition.

In addition to the everyday practical challenges to differentiating "drug-induced" from "independent" psychotic disorders, a major issue related to the etiology of psychotic disorders is whether or not psychoactive drug use can be considered a "cause" of schizophrenia, a condition that has been traditionally thought of as "independent" of drug use. Recent evidence suggesting that drug abuse, including cannabis abuse, may have a causal role in the development of primary psychotic illness in vulnerable individuals [27] might provide an explanation to the observed uncertainty of the diagnostic distinction between primary and drug-induced psychosis. A disorder that is initially "drug induced" and "time limited" may evolve after years to an independent chronic illness due to the effect of a persistent and severe drug abuse. The finding that, among those evolving to Schizophrenia, patients initially diagnosed as having "drug-induced psychosis" exhibited an older age at onset might be compatible with that idea.

The present study has several limitations: the retrospective design, the variable duration of follow-up, and the relatively small size of the sample. Moreover the diagnosis, although formulated by a consensus of multiple expert clinicians, was not based on structured interviews. Another limitation is that we included in the analysis only patients whose follow-up data were available. Therefore a selection bias might have excluded patients who underwent clinical remission and did not receive any more psychiatric assistance at follow-up. In a study by Caton et al. [13], the findings revealed that 50% of those with a baseline diagnosis of primary psychotic disorder were in remission at 1 year post-intake, compared to 77% of those with a baseline diagnosis of substance-induced psychosis. The authors found that clinical predictors that were reported previously in studies of schizophrenia, such as better premorbid adjustment [28], a shorter duration of untreated psychosis [29] better insight into psychotic symptoms [30], and lower severity of psychotic symptoms with improved clinical outcome [31], generalize to psychosis remission in psychotic disorders that are substance-induced.

The limits of the study consisted of low number of patients that was possible to include in the follow up and the effects size on p-value, also in comparison with Caton's study, the different gender distribution

Conclusion

Up to now, available data regarding the long-term stability of the distinction between primary psychosis with comorbid drug abuse and drug-abuse psychosis are insufficient. Despite the cited-above limitations, the present results, suggesting that such distinction tends to vanish over a long-time, are in line with other studies showing that drug-induced psychotic disorders are often followed by development of persistent psychotic conditions [32].

Further research on larger samples is needed to clarify such an important issue.

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Figure 1.

Age at onset of patients diagnosed at baseline as having Primary Psychosis with comorbid Drug Abuse (PP-DA) and Drug-Induced Psychosis (DIP) respectively between patients having diagnosis of Schizophrenia at follow-up compared to those having any other diagnosis

Fig. 2

Changes in BPRS scores from baseline to follow-up between baseline diagnoses after cessation of drug abuse. DIP patients showed less improvement of hallucinations compared to PP-DA patients.

Fig.3

Diagnostic changes at follow-up between Primary Psychosis with comorbid Drug Abuse (PP-DA) patients and Drug-Induced Psychosis (DIP) patients

Table 1

Demographic and clinical features of Primary Psychosis with comorbid Drug Abuse (PP-DA) and Drug-Induced Psychosis (DIP) patients at baseline and follow-up.

^a $p < 0.005$ vs DIP

^b $p = 0.07$ vs DIP

^c $p < 0.05$ vs DIP

		PP-DA		DIP		Total	
		<i>n</i> =25		<i>n</i> =23		<i>n</i> =48	
		<i>N</i>	%	<i>n</i>	%	<i>n</i>	%
Baseline	Males	21	84,00	22	95,65	43	89,58
	Poliabusers	9 ^a	36,00	18	78,26	27	56,25
		<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
	Age at onset	25,60 ^b	5,66	28,39	7,60	26,94	6,74
	Conceptual Disorganization	3,00	1,68	3,26	1,74	3,13	1,70
	Depressed Mood	2,60	1,71	2,26	1,21	2,44	1,49
	Hostility	3,72	2,35	3,61	2,31	3,67	2,31
	Hallucinations	4,20	2,36	4,04	2,23	4,13	2,27
	Unusual Content of Thought	5,72 ^c	1,34	4,83	1,67	5,29	1,56
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Follow-up	Drug Abusers	13	52,00	14	60,87	27	56,25
	Poliabusers	5	20,00	12	52,17	17	35,42
		<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
	Conceptual Disorganization	3,44	2,18	3,26	2,26	3,35	2,20
	Hostility	1,92	1,91	2,17	2,12	2,04	2,00
	Hallucinations	3,24	2,30	2,87	2,28	3,06	2,27
	Depressed Mood	3,24	1,98	2,61	1,80	2,94	1,91
	Unusual Content of Thought	3,64	2,25	3,91	1,95	3,77	2,10