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Clinical Variables and Peripheral Biomarkers Associated with Substance-Induced Psychotic Disorder: Which Differences between Alcohol, Cannabis and Psychostimulants?

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Clinical Variables and Peripheral Biomarkers Associated with Substance-Induced Psychotic Disorder: Which Differences between Alcohol, Cannabis and Psychostimulants?

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Abstract: Background: The present retrospective observational study has the objective to identify differences in clinical features and peripheral biomarkers in patients affected by Substance-induced psychotic disorder (SIPD) according to the main substance of abuse. **Methods:** A total sample of 218 patients was divided in 3 groups according to the type of consumed substance: alcohol, cannabis and psychostimulants. The 3 groups were compared for continuous variables by one-way analyses of variance (ANOVAs) and for qualitative variables by χ^2 tests. After removing alcohol-induced psychotic disorder group, the same analyses were repeated. Statistically significant variables from these latter analyses were included in a binary logistic regression model to confirm their reliability as predictors for cannabis- or psychostimulants-induced psychotic disorders. **Results:** Psychotic cannabis abusers were younger ($p<0.01$) and had an earlier age at onset ($p<0.01$). Alcohol consumers resulted to have a longer duration of illness ($p<0.01$), more previous hospitalizations ($p=0.04$), more frequent medical comorbidity ($p<0.01$), higher mean Modified Sad Person Scale scores ($p<0.01$). Finally, psychostimulant abusers had more frequently a lifetime history of poly-substance use disorders ($p<0.01$). Binary logistic regression revealed that higher mean Brief Psychiatric Rating Scale scores ($p<0.01$) higher sodium ($p=0.012$) and haemoglobin ($p=0.040$) plasma levels were predictors of cannabis misuse in SIPD patients. **Conclusions:** Different clinical factors and biochemical parameters con be associated to SIPD according to the main substance of abuse, thus requiring a specific management by clinicians.

Keywords: alcohol; cannabis; clinical variables; peripheral biomarkers; psychostimulants; substance-induced psychotic disorder:

1. Introduction

Substance-induced psychotic disorder (SPID) is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a psychiatric disorder characterized by hallucinations and/or delusions that arise during or soon after substance intoxication or withdrawal [1]. This condition occurs in the general population with a frequency that is far to be negligible (6.5 out of 100.000 people per year in accordance with the latest studies) [2]. Several agents can contribute to the onset of SIPD including alcohol, psychostimulants like cocaine, and cannabis, but the number of new substances that can be associated with this condition is constantly increasing [3,4].

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The management of this condition can be challenging for clinicians for different reasons, including the fact that SIPD does not represent a stable diagnosis: about one third of these patients are re-classified in the following years as subjects affected by schizophrenia or bipolar disorder [5]. Of note, it is not a case that one of the most important risk factors for the development of psychotic symptoms in people consuming recreational substances is represented by a family history of schizophrenia spectrum disorders [6,7].

A differential diagnosis between a primary psychotic disorder with comorbid substance misuse or a SIPD can be therefore difficult with a potential delay of the appropriate treatment of patients [8,9].

Some data of literature indicate that the different substances of abuse may confer a variable risk of SIPD [10] and may be associated with specific clinical features [11]. Of note, cannabis users with SIPD seem to have cognitive symptoms similar to those showed by subjects affected by schizophrenia [12] whereas methamphetamine users would exhibit predominantly positive symptoms [13]. Other authors observed that patients with cannabis-induced psychotic disorders were more likely to show schizophrenia-like symptoms compared to alcohol abusers [14].

The clinical differences observed according to the main substance of abuse can be related to the different impact of the various recreational drugs on biological systems. Similarly to what happens with schizophrenia, exocannabinoids favor the shift of T helper lymphocytes (Th) from subtype 1 to 2, enhancing humoral immunity [15,16]. On the contrary, alcohol would stimulate more cytokines associated with cell-mediated immunity supposed to increase susceptibility to mood symptoms than psychotic ones [17]. Finally, available data indicate that cocaine abusers show epigenetic modification of genes involved in neuroplasticity and innate immunity [18].

In this framework, the present study has the objective to identify differences in clinical features and biochemical parameters between patients affected by SIPD classified according to the prevalent substance of abuse. The findings of the present research can help clinicians in personalizing treatment strategies for patients affected by SIPD also in the light of the paucity of data in literature about this topic.

2. Materials and Methods

In this retrospective observational study we enrolled a sample of 218 patients consecutively admitted with a diagnosis of "SIPD" according to DSM to the psychiatric inpatient clinics of Fondazione IRCCS Policlinico (Milan) and San Gerardo Hospital (Monza) from 2000 to 2022. The diagnosis of SIPD was made by an expert psychiatrist and, in case of multiple hospitalizations, only the last admission was taken into consideration. The inclusion criteria consisted of an age ≥ 18 years and the abovementioned diagnosis. The exclusion criteria were: (1) to be < 18 years old; (2) to be in treatment with pharmacological compounds that can exacerbate psychotic symptoms (e.g. corticosteroids or levetiracetam); (3) medical comorbidities that can trigger the onset of psychotic symptoms (e.g. encephalitis or dementia) or can modify significantly biochemical parameters (e.g. severe autoimmune diseases); (4) perinatal period (pregnancy and one month postpartum) as this period is characterized by specific clinical features and biological changes in new mothers [19]. Patients with psychiatric comorbidity were included if SIPD represented the main psychiatric condition defined as the disorder causing more social dysfunction. In the first day of admission clinical data were obtained by clinical charts or interviews with patients and their relatives in the case some information was not available. Biochemical data were retrieved by intranet hospital applications.

For each patient the following variables were collected:

- demographic and clinical variables: gender, age at hospitalization, age at onset, duration of hospitalization, duration of untreated illness (DUI) (years), duration of illness (years), presence and number of previous hospitalizations, presence of family history of psychiatric disorders, presence of family history of multiple psychiatric disorders, presence of family history of substance use disorders, presence of lifetime history of poly-substance use disorders, smoke habit, type and dosage of the antipsychotic drug prescribed during hospitalization (in case of multiple antipsychotic drugs we

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considered the one prescribed at the highest dosage and for the longer period of time), current prescription of benzodiazepines, current treatment with more than one psychotropic drug (including benzodiazepines), comorbidity with at least one psychiatric diagnosis, comorbidity with more than one psychiatric diagnosis, presence of comorbid personality disorders, presence and number of lifetime suicidal attempts, comorbidity with other medical conditions (including poly-comorbidity) and comorbidity with hypothyroidism, diabetes, hypercholesterolemia and obesity, lifetime psychotherapy treatment, history of obstetric complications. Global functioning and symptom severity were assessed respectively through Global Assessment of Functioning (GAF) and Positive and Negative Syndrome Scale (PANSS) together with Brief Psychiatric Rating Scale (BPRS). Suicidal risk was evaluated by Modified Sad Persons Scale (MSPS) and aggressive behavior through Modified Overt Aggression Scale (MOAS).

- biochemical parameters: sodium (Na) (mEq/L), potassium (K) (mEq/L), Na/K ratio, number of white blood cells (WBC) (10^9/L), number of lymphocytes (10^9/L), number of neutrophils (10^9/L), neutrophil to lymphocyte ratio (NLR), number of red blood cells (10^12/L), mean corpuscular volume (MCV) (fL), haemoglobin (HB) (g/dL), number of platelets (10^9/L), mean platelet volume (MPV) (fL), glycaemia (mg/dL), urea (mg/dL), creatinine (mg/dL), uric acid (mg/dL), alanine transaminase (ALT) (U/L), aspartate transaminase (AST) (U/L), gamma-glutamyl transferase (GGT) (U/L), bilirubin (mg/dL), total plasmatic proteins (g/dL), albumin (g/dL), lactate dehydrogenase (LDH) (mU/ml), creatine phosphokinase (CPK) (U/L), pseudocholinesterase (PChE) (U/L), total cholesterol (mg/dL), triglycerides (TG) (mg/dL) and thyroid-stimulating hormone (TSH) (mcU/mL).

The protocol of this study was reviewed and approved by the local Ethic Committee (approval number 1789).

DUI was defined as the time between the onset of psychotic symptoms and the administration of an antipsychotic compound [21].

Statistical analyses were performed through The Statistical Package for Social Sciences (SPSS) for Windows (version 27.0). Descriptive analyses on the total sample were performed. The three groups identified according to the main substance of abuse (alcohol, cannabis, psychostimulants) were compared by one-way analyses of variance (ANOVAs) for continuous variables and χ^2 tests for qualitative variables. ANOVAs were then performed to compare cannabis versus psychostimulant abusers for continuous variables. The factors that resulted to be statistically significant in this latter analysis were inserted in a binary logistic regression model as independent variables; the dependent variable was represented by cannabis versus psychostimulant abuse. The quality of the model was evaluated by the Omnibus and Hosmer-Lemeshow tests. Statistical significance was set at $p \leq 0.05$.

3. Results

3.1. Results

The total sample included 218 patients whose main substance of abuse was represented by alcohol (N=31), psychostimulants (most cocaine) (N=71) and cannabis (N=116). Clinical characteristics and biochemical parameters of the total sample and of the three groups identified by the main substance of abuse are displayed respectively in Table 1 and Table 2. The data about pharmacotherapy during hospitalization was available for 156 patients and the main pharmacological compound prescribed during hospitalization consisted of: risperidone (N=5), haloperidol (N=56), paliperidone (N=16), olanzapine (N=27), quetiapine (N=11), aripiprazole (N=14), zuclopenthixol (N=19), clozapine (N=2), levomepromazine (N=3), chlorpromazine (N=1), promazine (N=1) and clotiapine (N=1). No significant differences were found in the frequency of prescription of a specific type of antipsychotic between the three groups ($\chi2=17.90$, $p=0.71$).

Univariate analyses revealed that psychotic cannabis abusers (compared to the other two groups) were younger ($F=25.29$, $p<0.01$), had an earlier age at onset ($F=9.08$, $p<0.01$) and were more frequently tobacco smokers ($\chi2=11.26$, $p<0.01$). On the contrary, psychotic alcohol consumers resulted to have a longer duration of illness ($F= 8.43$, $p<0.01$), more previous hospitalizations ($F=3.36$, $p=0.04$), more frequent medical comorbidity ($\chi2=11.82$, $p<0.01$) and comorbidity with hypercholesterolemia

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(χ2=8.94, p=0.01), higher mean MSPS scores (F=6.19, p<0.01) as well as higher plasma levels of total cholesterol (F=3.98, p=0.02), urea (F=3.79, p=0.03) and triglycerides (F=3.69, p=0.03). Finally, psychotic psychostimulant abusers had more frequently a lifetime history of poly-substance use disorders compared to the other two groups (χ2=27.34, p<0.01). No other statistically significant differences were found between the three groups (p>0.05).

The comparison between cannabis and psychostimulant abusers showed that the first group (compared the second one) was younger (F=12.13, p<0.01), had an earlier age at onset (F=10.87, p<0.01), lower GGT plasma levels (F=4.08, p=0.04), but higher red blood cells (F=4.94, p=0.03), Na (F=3.76, p=0.05), haemoglobin (F=5.49, p=0.02) and albumin plasma levels (F=6.22, p=0.01). In addition, psychotic cannabis abusers showed a trend to have higher mean BPRS scores (F=3.21, p=0.07) and a higher number of previous hospitalizations (F=3.59, p=0.060) than the counterpart. No other statistically significant differences were found between the two groups (p>0.05).

The logistic regression model resulted to be reliable (Hosmer and Lemeshow Test: χ^2=9.011, p=0.341; Omnibus test: χ^2=31.039, p<0.001) allowing for a correct classification of 76.4% of cases. Psychotic cannabis abusers resulted to have higher mean BPRS scores (p<0.01) as well as higher Na (p=0.012) and hemoglobin (p=0.040) plasma levels than psychotic stimulant abusers (Table 3).

3.2. Figures, Tables and Schemes

Table 1. Demographic and clinical variables of the total sample and of the three groups divided according to the substance of abuse.

Variables		**Total sample N=218**	**Alcohol induced psychosis N=31 (14.2%)**	**Psychostimulants induced psychosis N=71 (32.6%)**	**Cannabis induced psychosis N=116 (53.2%)**	**F or χ2**	**p-value**
Gender Missing=0	*Male*	191 (87.6%)	28 (90.3%)	59 (83.1%)	104 (89.7%)	1.99	0.40
	Female	27 (12.4%)	3 (9.7%)	12 (16.9%)	12 (10.3%)		
Age (years) Missing=0		33.89 (± 12.21)	45.42 (± 13.64)	35.41 (± 11.91)	29.87 (±9.63)	25.29	**<0.01**
Age at onset (years) Missing=15		28.09 (± 10.97)	33.28 (± 12.90)	30.38 (± 11.58)	25.20 (± 9.07)	9.08	**<0.01**
Duration of hospitalization (days) Missing=60		11.59 (± 9.57)	8.92 (± 6.38)	13.63 (± 12.51)	10.99 (± 7.57)	2.43	0.09
Duration of untreated illness (years) Missing=61		1.18 (± 2.74)	0.63 (± 1.61)	1.36 (± 3.19)	1.23 (± 2.68)	0.62	0.54
Duration of illness (years) Missing=15		5.83 (± 8.81)	11.83 (± 14.64)	4.97 (± 7.42)	4.74(± 6.75)	8.43	**<0.01**
Presence of previous hospitalizations Missing=8		133 (63.3%)	21 (67.8%)	39 (57.4%)	73 (65.8%)	1.59	0.45
Number of previous hospitalizations Missing=8		2.18 (± 4.73)	3.71 (± 7.05)	1.71 (± 1.48)	2.38 (± 5.13)	3.36	**0.04**

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Presence of family history of psychiatric disorders Missing=60	55 (34.8%)	10 (40.0%)	13 (23.2%)	32 (41.6%)	5.16	0.08
Presence of family history of multiple psychiatric disorders Missing=60	33 (20.9%)	5 (20.0%)	10 (17.9%)	18 (23.4%)	0.61	0.74
Presence of family history of substance use disorders Missing=60	24 (15.2%)	4 (16.0%)	12 (21.4%)	8 (10.4%)	3.08	0.20
Presence of lifetime history of poly-substance use disorders Missing=0	118 (54.1%)	7 (22.6%)	54 (76.1%)	57 (49.1%)	27.34	**<0.01**
Presence of tobacco smoke Missing=5	106 (48.6%)	15 (48.4%)	24 (34.3%)	67 (59.8%)	11.26	**<0.01**
Current prescription of benzodiazepines Missing=60	120 (75.8%)	15 (60.0%)	46 (82.1%)	59 (76.7%)	4.68	0.10
Current treatment with more than one psychotropic drug Missing=60	153 (96.8%)	23 (92.0%)	54 (96.4%)	76 (98.7%)	2.81	0.25
Comorbidity with at least one psychiatric diagnosis Missing=60	66 (41.8%)	12 (48.0%)	25 (44.6%)	29 (60.4%)	1.12	0.60
Comorbidity with more than one psychiatric diagnosis Missing=60	21 (13.2%)	5 (20.0%)	6 (10.7%)	10 (12.9%)	1.31	0.50
Presence of comorbid personality disorders Missing=60	37 (17.0%)	3 (12%)	16 (28.6%)	18 (23.4%)	2.65	0.27
Presence of lifetime suicide attempts Missing=0	29 (13.3%)	6 (19.4%)	10 (14.1%)	13 (11.2%)	1.46	0.48
Number of lifetime suicide attempts Missing=0	0.17 (± 0.56)	0.23 (± 0.50)	0.18 (± 0.66)	0.16 (± 0.50)	0.21	0.81
Comorbidity with other medical conditions Missing=60	69 (59.2%)	17 (68.0%)	28 (50.0%)	24 (31.2%)	11.82	**<0.01**
Comorbidity with multiple medical conditions Missing=60	23 (14.6%)	6 (24.0%)	8 (14.3%)	9 (11.7%)	2.31	0.32
Presence of hypothyroidism Missing=60	9 (5.7%)	0 (0.0%)	6 (10.7%)	3 (3.9%)	4.60	0.10
Presence of hypercholesterolemia Missing=0	32 (14.7%)	10 (32.3%)	8 (11.3%)	14 (12.1%)	8.94	**0.01**

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Presence of diabetes Missing=60	11 (7.0%)	3 (12.0%)	6 (10.7%)	2 (2.6%)	4.46	0.11
Presence of obesity Missing=0	5 (2.3%)	1 (3.2%)	1 (1.4%)	3 (2.6%)	0.41	0.81
Lifetime psychotherapy Missing=60	12 (7.6%)	1 (4.0%)	2 (3.6%)	9 (11.7%)	3.59	0.17
History of obstetric complications Missing=0	25 (11.5%)	5 (16.1%)	4 (5.6%)	16 (13.8%)	3.66	0.16
GAF score Missing=61	46.37 (± 15.20)	58.04 (± 15.83)	53.71 (± 16.66)	54.87 (±13.3)	0.73	0.49
PANSS score Missing=61	61.83 (± 15.16)	60.76 (± 15.33)	59.45 (± 16.49)	63.93 (± 13.94)	1.50	0.23
BPRS score Missing=46	43.97 (± 12.13)	46.61 (± 11.62)	41.27 (± 12.04)	44.96 (± 12.16)	2.54	0.08
MSPS score Missing=61	2.49 (± 1.09)	3.16(± 1.21)	2.29 (± 1.02)	2.42 (± 1.04)	6.19	**<0.01**
MOAS score Missing=1	4.34 (± 4.91)	4.03 (± 5.04)	4.72 (± 4.88)	4.19 (± 4.93)	0.32	0.73

Legend: BPRS=Brief Psychiatric Rating Scale; GAF=Global Assessment of Functioning; MOAS= Modified Overt Aggression Scale; MSPS= Modified Sad Persons Scale; PANSS=Positive and Negative Syndrome Scale. Means for quantitative variables and frequencies for qualitative ones are reported. Standard deviations for quantitative variables and percentages for qualitative variables are reported into brackets. In bold statistically significant p resulting from chi-square tests ($\chi 2$) or analyses of variance (F) ($p \leq 0.05$).

Table 2. Biological variables of the total sample and of the three groups divided according to the substance of abuse.

Variables	**Total sample N=218**	**Alcohol induced psychosis N=31 (14.2%)**	**Psychostimulants induced psychosis N=71 (32.6%)**	**Cannabis induced psychosis N=116 (53.2%)**	**F**	**P - value**
Sodium (Na) (mEq/L) Missing= 84	141.45 (±2.50)	142.08 (± 2.71)	140.80 (±2.90)	141.70 (±2.00)	2.66	0.07
Potassium (K) (mEq/L) Missing=84	4.23 (±0.38)	4.26 (±0.41)	4.24 (±0.34)	4.21 (±0.39)	0.22	0.81
Na/K ratio Missing=86	33.72 (±3.04)	33.69 (±3.17)	33.47 (±2.64	33.91 (±3.28)	0.29	0.75
Number of lymphocytes (10^9/L) Missing=64	2.58 (±1.59)	2.08 (±0.68)	2.55 (±0.76)	2.75 (±2.07)	1.70	0.19
Number of neutrophils (10^9/L) Missing=64	5.00 (±2.60)	4.98 (±2.51)	5.13 (±2.74)	4.93 (±2.57)	0.09	0.91

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NLR Missing=77	2.19 (±1.32)	2.77 (± 2.03)	2.01(±1.09)	2.13(±1.17)	2.47	0.09
Number of RBC (10^12/L) Missing=25	4.86 (±0.57)	4.81 (±0.61)	4.74 (±0.57)	4.94 (±0.54)	2.52	0.08
Number of WBC (10^9/L) Missing=25	8.56 (±3.11)	8.15 (±2.56)	8.68 (±3.19)	8.60 (±3.22)	0.30	0.75
MCV (fL) Missing=86	87.61 (±6.85)	89.65 (±9.36)	87.43 (±6.27)	87.03 (±6.21)	1.22	0.30
HB (g/dL) Missing=29	14.49 (±1.55)	14.36 (± 1.68)	14.15 (±1.62)	14.73 (±1.44)	2.77	0.07
Number of PLT (10^9/L) Missing=79	254.13 (±85.54)	259.73 (±122.87)	265.23 (±71.31)	244.91 (±80.44)	0.85	0.43
MPV (fL) Missing=86	10.57 (±1.10)	10.28 (±0.90)	10.67 (±1.21)	10.60 (±1.08)	0.97	0.38
Glycaemia (mg/dL) Missing=27	90.37 (±22.79)	93.75 (±25.21)	91.21 (±25.10)	88.91 (±20.62)	0.55	0.58
Creatinine (mg/dL) Missing=32	0.90 (±0.15)	0.89 (±0.16)	0.92 (±0.16)	0.89 (± 0.15)	0.68	0.51
Urea (mg/dL) Missing=63	27.64 (±9.08)	31.56 (±11.03)	27.92 (±10.23)	26.10 (±7.03)	3.79	**0.03**
Uric acid (mg/dL) Missing=96	5.50 (±1.60)	6.06 (±1.29)	5.18 (±1.46)	5.50 (±1.76)	2.16	0.12
ALT (U/L) Missing=29	32.19 (±30.43)	31.59 (± 28.20)	36.90 (±41.76)	29.60 (±22.05)	1.08	0.34
AST (U/L) Missing=59	39.68 (±45.91)	40.81 (±54.97)	39.34 (±40.69)	39.51 (±46.07)	0.01	0.99
GGT (U/L) Missing=36	29.69 (±38.97)	33.54 (±32.40)	37.38 (±60.32)	24.12 (±18.83)	2.29	0.10
Bilirubin (mg/dL) Missing=44	0.68 (±0.42)	0.61 (±0.30)	0.61 (±0.39)	0.73 (±0.46)	1.77	0.17
Total plasmatic proteins (g/dL) Missing= 97	6.88 (±0.55)	6.91 (±0.54)	6.84 (±0.66)	6.89 (±0.49)	0.16	0.85
Albumin (g/dL) Missing=87	4.42 (±0.46)	4.38 (±0.59)	4.30 (±0.44)	4.51 (±0.40)	2.74	0.07
Total cholesterol (mg/dL) Missing=57	170.72 (±44.23)	192.92 (±49.51)	169.00 (±53.78)	165.31 (±34.16)	3.98	**0.02**
Triglycerides (mg/dL) Missing=128	112.96 (±77.20)	159.13 (±112.31)	102.55 (±65.15)	103.13 (±64.29)	3.69	**0.03**
LDH (mU/ml) Missing= 96	207.61 (±94.58)	205.02 (±102.96)	220.38 (±110.85)	199.34 (±77.81)	0.61	0.55
CPK (U/L) Missing=54	511.76 (±890.42)	292.82 (±366.90)	392.79 (±530.87)	674.59 (±1163.05)	2.11	0.13
PChE (U/L)	7523.62	8001.14	7431.03 (±1654.13)	7405.73	0.67	0.51

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Missing=104	(±2084.10)	(±2115.56)		(±2323.45)		
TSH (mcU/mL) Missing=111	1.81 (±1.35)	1.51 (±0.85)	2.03 (±1.73)	1.78 (±1.22)	0.99	0.37

Legend: ALT= alanine transaminase; AST= aspartate transaminase; CPK= creatine phosphokinase; GGT = gamma-glutamyl transferase; HB= haemoglobin; LDH= lactate dehydrogenase; MCV= mean corpuscular volume; MPV= mean platelet volume; NLR= neutrophil to lymphocyte ratio; PChE= pseudocholinesterase; PLT= platelets; RBC= red blood cells; TSH= thyroid-stimulating hormone; WBC= white blood cells. Means and standard deviations (into brackets) are reported. In bold statistically significant p resulting from ANOVA analyses (p≤0.05).

Table 3. Binary logistic regression model.

Variables	B	S.E.	Wald	P	OR	95% CI for OR
Age at hospital admission	- 0.064	0.042	2.343	0.126	0.938	0.864-1.018
Age at illness onset	0.018	0.043	0.171	0.679	1.018	0.936-1.106
Number of previous hospitalizations	0.221	0.172	1.651	0.199	1.248	0.890-1.748
BPRS score	0.082	0.028	8.8606	**0.003**	1.085	1.027-1.146
Sodium (Na)	0.343	0.137	6.308	**0.012**	1.409	1.078-1.842
Number of RBC	-0.324	0.567	0.327	0.567	0.723	0.238-2.198
Hb	0.440	0.214	4.222	**0.040**	1.553	1.021-2.362
GGT	-0.014	0.014	1.048	0.306	0.986	0.959-1.013
Albumin	0.735	0.686	1.147	0.284	2.085	0.543-7.999

Legend: B=regression coefficient; BPRS= Brief Psychiatric Rating Scale; CI=confidence interval; GGT = gamma-glutamyl transferase; Hb=haemoglobin; OR=odds ratio; RBC= red blood cells; S.E.=standard error of B; Wald=Wald statistics. In bold statistically significant p (≤ 0.05).

4. Discussion

This is one of the few studies comparing the clinical and biochemical features of subjects affected by SIPD in relation to the main substance of abuse. Several results have clinical implications and will be discussed in detail the following paragraphs.

Among the three groups identified by the main substance of abuse, the alcohol consumers resulted to be more prone to dyslipidaemia and suicidal risk, as showed by higher MSPS scores. Hyperlipidaemia in alcohol abusers is explained by the specific metabolism of alcohol that produces accumulation of lactic acid and block of Krebs' cycle which, in turn, is associated with the transformation of Acetyl-CoA excess in fat acids [21]. The detrimental physical effects of alcohol [22] also justify the higher frequency of medical comorbidity in alcohol abusers than the other two groups. Of note, the mean plasma triglyceride value in our group of patients with alcohol misuse overcomes the recommend figure of 150 mg/dL [23]. The similar elevation of urea in alcohol chronic abusers can be explained by a metabolic counter response to the downregulation of urea cycle during alcohol intoxication [24]. In addition, the higher risk of self-harm in this group is supported by the evidence that alcohol use disorders are associated with a 94% increase of death by suicide [25]. Additionally, alcohol abusers frequently suffer from concomitant anxiety and depressive disorders [26] and they often live under conditions of social exclusion [27].

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Regarding patients with SIPD and cannabis misuse, this group showed a more severe clinical presentation (higher BPRS scores) than the patients with cocaine abuse in agreement with previous literature [28]. Cannabis-induced psychotic disorders are often the result of early consumption of forms of substance with high tetrahydrocannibinol (THC) content [29] and this aspect can explain the young age and early age at onset of patients with SIPD and cannabis abuse. Furthermore, psychotic cannabis abusers resulted to be more likely tobacco smokers than the other two groups: this may be due to the fact that smoking is one of the most popular ways to consume cannabis, but cannabis is also able to potentiate the reward effects of nicotine [30]. Of note, lack of CB1 cannabinoid receptors in mice resulted in reduced reward after acute nicotine administration [31]. Regarding biochemical parameters, psychotic cannabis abusers showed higher haemoglobin levels compared to psychostimulant ones: a recent article reported that cannabis can increase haemoglobin plasma levels as a result of haemolysis [32]. Similarly, higher albumin plasma levels were found in cannabis versus psychostimulant abusers. Albumin has antioxidant properties [33] and previous research reported that higher levels of this molecule are associated with a better prognosis of psychiatric disorders [34,35].

Finally, psychotic psychostimulant abusers presented more frequently poly-substance use disorders than the other two groups. This finding agrees with available literature reporting that the cocaine or other psychostimulant abusers frequently counterbalance the effects of these substances by recurring to Central Nervous Systems depressants such as alcohol or opioids [36]. Sodium was in the physiological range for both psychotic cannabis and psychostimulant abusers, but the significant differences between the two groups could be interpreted by the fact that psychostimulants cause excessive water intake and inappropriately elevated antidiuretic hormone (ADH) levels [37]. In addition, the elevation of GGT plasma levels in psychostimulant abusers is the result of liver metabolism by cytochrome P450 and the production of pro-oxidant compounds [38].

The findings of the present article indicate that patients with SIPD may require a different management according to the main type of abused substance. In patients with alcohol-induced psychotic disorder, careful monitoring of the lipid profile would be useful for the early identification of medical complications and to propose supportive interventions to reduce the suicidal risk. In subjects with cannabis-induced psychotic disorder, the management of psychiatric symptoms may be more challenging and blood counts should be monitored. In case of comorbidity with smoking, interventions finalized at reducing cigarette smoking could be useful (e.g. nicotine patch or varenicline) [39]. In patients with psychostimulant-induced psychotic disorder, the concomitant use of other substances should be investigated and access to therapeutic programs focused on these aspects should be encouraged.

Our study has different limitations including: (1) the retrospective design; (2) the use of routinely investigated biochemical parameters during hospital admissions, without a preliminary selection; (3) data for some variables are missing either because this information is not routinely collected in one of the two inpatient clinics or because it cannot be derived from medical records.

The findings of the present study suggest that patients with SIPD can require a specific management according to the main substance of abuse. Future studies with larger samples are necessary to confirm the present findings and identify the optimal management of these patients.

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