Cocaine-Induced Psychosis: A Prevalence Study of Local Cocaine Abusers

Submitted to

Beat Drug Fund Association

Submitted by

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Contents

Acknowledgements

The research team is grateful to the following agencies for their support in the recruitment of participants for this study:

Barnabas Charitable Service Association Limited;

Caritas HUGS Centre;

Caritas Wong Yiu Nam Centre;

Cheer Lutheran Centre, Hong Kong Lutheran Social Services;

Christian New Life;

Enchi Lodge;

ELCHK, Enlighten Centre;

Evergreen Lutheran Centre, Hong Kong Lutheran Social Services;

Hong Kong Christian Services PS33 – Tsim Sha Tsui Centre;

Hong Kong Children and Youth Services;

Hong Kong Sheng Kung Hui Welfare Council Neo-Horizon;

Jockey Club Lodge of Rising Sun;

Operation Dawn;

SARDA Sister Aquinas Memorial Women's Treatment Centre;

SARDA Au Tau Youth Centre;

SARDA Adult Female Rehabilitation Centre;

The Christian New Being Fellowship; and

The Hong Kong Federation of Youth groups.

Abbreviations

BDI: Beck Depression Inventory

BDNF: Brain-derived neurotrophic factor

BPRS: Brief Psychiatric Rating Scale

CI: Confidence interval

CIP: Cocaine-induced psychosis

CCPSA: Counselling Centres for Psychotropic Substance Abusers

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

HADSA: Hospital Anxiety Depression Scale

ICE: Methamphetamine

OR: Odds ratio

PANSS: Positive and Negative Syndrome Scale

PPS: Persistent psychotic symptoms

SDS: Severity of Dependence Scale

SCID: Structured Clinical Interview for DSM-IV

TPS: Transient psychotic symptoms

Background

Cocaine, as one of the most potent naturally occurring central nervous system stimulants, has a long history of use and abuse (Ellenhorn & Barceloux, 1988). It is the second most commonly abused psychotropic drug in Hong Kong (Narcotics Division, 2017). Illicit cocaine is available in both salt (hydrochloride) and base (crack) forms (Barceloux et al., 2012). Crack is the freebase form of cocaine and makes a characteristic crackling sound when smoked. Cocaine is most commonly snorted (taken via nasal inhalation) or smoked. Its effects include alertness; a sense of pleasure; reduced social inhibition and anxiety; and a heightened sense of energy, self-esteem and sexuality. The euphoric effects begin within minutes and last approximately 20–45 minutes (Barceloux et al., 2012). Chronic use of cocaine produces tolerance to its euphoric effects and physical symptoms of withdrawal, including insomnia, irritability, depression and headache (Barceloux et al., 2012). The consumption rate of cocaine varies widely amongst users. Typical doses range up to 200 mg per measure depending on the purity, with an average dose of approximately 25 mg per insufflation (Barceloux et al., 2012).

Chronic use of cocaine can result in a wide range of psychiatric symptoms, including psychosis, anxiety, depression, sexual disorders and eating disorders (Herrero et al., 2008a). Cocaine consumption can induce transient psychotic symptoms (TPS) or complete psychosis (Roncero et al., 2014(a)). Studies conducted in psychiatric settings have reported a cocaine-induced psychosis (CIP) prevalence range of 29% (Roncero et al., 2012) to 86.5% (Vorspan et al., 2012). Common psychotic symptoms resulting from cocaine use include paranoid delusions and hallucinations. Other clinical features include agitation, aggression, stereotypy, checking behaviour, self-harm and unusual sexual behaviour (Roncero et al., 2014(a)). Transient

paranoia is the most characteristic symptom, and patients with CIP most frequently report the delusion that they are surrounded by agents of the law or people who want to steal their drugs (Roncero et al., 2012). Hallucinations, especially auditory ones, are not uncommon. They are generally vivid, isolated and consistent with thought content (Roncero et al., 2012). Up to 38% of patients with CIP report tactile hallucinations such as the skin being infested with parasites, and up to 21% report formication, in which the patient believes there are parasites under their skin (Roncero et al., 2012).

CIP is characterised by the presence of delusions or hallucinations during or shortly after cocaine use, with signs or symptoms that are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance (American Psychiatric Association, 2013). The prevalence of CIP ranges from 6.9% in non-treatment-seeking young cocaine users (Herrero et al., 2008b) to 40.6% in outpatient clinics (Roncero et al., 2014(a), 2014 (b)). According to our database, of the 71 current cocaine users attending a local substance abuse clinic, 49% have psychosis, 23% have a mood disorder and 3% have an anxiety disorder (Tang, unpublished).

Risk factors for CIP include high consumption of cocaine (Floyd et al., 2006), young age at first use (Floyd et al., 2006), long duration of use (Gilder et al., 2014), intravenous use (Gilder et al., 2014), use of other substances such as cannabis (Trape et al., 2014) and low body weight (Rosse et al., 2005). Concurrent psychiatric disorders include attention-deficit/hyperactivity disorder (Roncero et al., 2012) and antisocial personality disorder (Roncero et al., 2014(b)). A few genetic studies have suggested that genes that encode dopamine transporter and dopamine beta-hydroxylase are related to CIP (Cubells et al., 2000;

Gelernter et al., 1994). Other possible biomarkers of CIP include deficits in evoked potentials (Boutros et al., 2006) and brain-derived neurotrophic factor (BDNF) (Corominas-Roso et al., 2013). The pathogenesis of CIP may include the blockade of dopamine reuptake, increased concentrations of norepinephrine and serotonin and a sensitising response (Tang et al., 2014).

The clinical picture of CIP is generally self-limiting and improves without the need to initiate treatment in the hours after the most recent consumption of cocaine. Symptom remission typically occurs during 24 hours to several days of abstinence. In a small subset of chronic users, the symptoms may persist for over a month (Barceloux et al., 2012; Tang et al., 2009).

Data are lacking on the prevalence and clinical features of and risk factors for CIP and other psychiatric disorders in local cocaine users. We conducted a large-scale study to investigate the prevalence of psychiatric comorbidity in a group of cocaine users in Hong Kong. The study's primary objective was to determine the prevalence of CIP and psychotic symptoms in local cocaine users. Secondary objectives included identification of the prevalence of mood and anxiety disorders in local cocaine users.

Methods

Design

This was a cross-sectional study to investigate the prevalence of psychosis, psychotic symptoms and other mental illnesses in local cocaine users. Data were collected through face-to-face structured interviews conducted by a trained research assistant. Each interview lasted 40–90 minutes. For their time and participation, the subjects were compensated with HK$350 supermarket shopping coupons after the interview. This study was approved by the Survey and Behavioural Research Ethics Committee of the Chinese University of Hong Kong.

Participants

Participant recruitment sites

All subjects were recruited from the following Counselling Centres for Psychotropic Substance Abusers (CCPSA) or residential treatment centres:

a. Barnabas Charitable Service Association Limited;
b. Caritas HUGS Centre;
c. Caritas Wong Yiu Nam Centre;
d. Cheer Lutheran Centre, Hong Kong Lutheran Social Services;
e. ELCHK, Ling Oi Centre;
f. Enchi Lodge;
g. Evergreen Lutheran Centre, Hong Kong Lutheran Social Services;
h. Hong Kong Christian Services PS33 – Tsim Sha Tsui Centre;

i. Hong Kong Christian Services: Yuen Long District Youth Outreaching Social Work Team;
j. Hong Kong Children and Youth Services;
k. Hong Kong Sheng Kung Hui Welfare Council Neo-Horizon;
l. Jockey Club Lodge of Rising Sun;
m. Operation Dawn;
n. SARDA Sister Aquinas Memorial Women's Treatment Centre;
o. SARDA Au Tau Youth Centre;
p. SARDA Adult Female Rehabilitation Centre;
q. The Christian New Being Fellowship; and
r. The Hong Kong Federation of Youth groups.

Inclusion criteria

a. Age between 18 and 65 years;
b. Cocaine use at least 20 times in the past year; and
c. Fulfil the criteria for cocaine use disorder in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, American Psychiatric Association, 2013).

Demographic information

The subjects' personal information was collected at the start of the interviews. The demographic information included:

a. age;

b. sex;

c. education level;

d. marital status;

e. employment status;

f. monthly income;

g. housing property;

h. smoking history; and

i. psychosis history.

Drug use patterns and severity

To establish the subjects' drug use patterns, data on their age at first cocaine use, frequency of use, duration of use and date of last use were collected. Lifetime and current use of cocaine, other illicit drugs, alcohol and cigarettes were estimated using a semi-structured interview similar to the Lifetime Drinking History interview (Skinner & Sheu, 1982). Current consumption was calculated as the average use in 1 day in the month before recruitment.

The Severity of Dependence Scale (SDS; Gossop et al., 1995) is a 5-item self-report scale used to measure the degree of drug dependence in the previous month or the month before abstinence. Each item is scored from 0 to 3, with a higher score indicating greater dependence.

Psychiatric comorbidity

The Structured Clinical Interview (SCID; Kam et al., 2003) was administered to screen for possible Axis-I psychiatric disorders. The SCID is a semi-structured interview that guides the process of DSM-V diagnosis and lasts approximately 30–45 minutes.

Psychotic disorders were further divided into primary and substance-induced (i.e., CIP). Based on the DSM-V, the criteria for a substance-induced psychotic disorder are as follows: a) onset of symptoms within 1 month of drug use, intoxication or withdrawal; b) symptoms that do not persist for more than 1 month after ceasing drug use; and c) no history of recurrent non-substance-related episodes.

Based on the pattern of psychotic symptoms, the participants were also divided into the following groups:

a) no psychotic symptoms;

b) TPS, in which the subjects experienced psychotic symptoms for at least 1 month when they were using cocaine, but not in any months when they were not using cocaine;

c) persistent psychotic symptoms (PPS), in which the subjects experienced psychotic symptoms for at least 1 month when they were using cocaine and also in at least 1 month when they were not using cocaine;

d) current psychotic symptoms, i.e., not yet in the detoxification stage;

e) psychotic symptoms only in the months of cocaine abstinence;

f) psychotic symptoms followed by flashbacks, representing a spontaneous recurrence of psychosis, even without further use of cocaine.

The Brief Psychiatric Rating Scale (BPRS: Lukoff et al., 1986), which measures the positive, negative and affective symptoms of an individual with psychotic disorders, schizophrenia in particular, was used to measure the subjects' severity of currently (during the interview) occurring psychotic symptoms and mood conditions (if any). The score ranges from 0 (not assessed) to 7 (extremely severe). The Positive and Negative Syndrome Scale (PANSS: Bell et al., 1992) was used to measure the subjects' severity of currently occurring positive and negative symptoms. The score for each item ranges from 1 (absent) to 7 (extreme).

A 21-item version of the Beck Depression Inventory (BDI: Shek, 1990) was used to measure depressive symptoms in the past week. The BDI was previously applied in a group of ecstasy users in Hong Kong (Chen et al., 2005). The total BDI scores range from 0 to 63. The sensitivity and specificity of the BDI are 100% and 82%, respectively (Lee et al., 2001)

The Hospital Anxiety Depression Scale for Anxiety (HADSA: Leung et al., 1993; Spinhoven et al., 1997) was used to measure anxiety symptoms in the past week. The HADSA has seven items, each scored from 0 to 3. The total scores range from 0 to 21, with a higher score indicating a greater severity of symptoms (Bunevicius et al., 2007).

Statistical analysis

Data analyses were performed using SPSS 17.0. The independent variables were socio-demographic and drug-use parameters; the primary dependent variables were CIP, psychotic, mood and anxiety symptoms; and the secondary dependent variable was other psychiatric comorbidity. The frequency distribution of all variables was calculated, and descriptive statistics are used to summarise the variables.

The prevalence of CIP and other psychiatric comorbidity was calculated. Potential associations with CIP were first evaluated using the chi-square test or *t*-test, as appropriate. Significant associations were subsequently examined using multivariate regression analysis to identify independent predictors of CIP. Statistical significance was set at 0.5 in two-sided tests. The analysis was repeated for the other dependent variables.

Results

Demographic characteristics and basic information

Two hundred and sixty cocaine users participated in this study. Most of the subjects were male (68%) and unemployed (85%), with a mean age of 28 years (range, 18–63 years) and an average of 10 years of education (range, 2–17 years). More than three fourths of the sample were single (80%), and more than half of them were current smokers (58%). All subjects were recruited from residential centres (77%) or CCPSA (23%). Fifty-five percent of the subjects lived in public housing, 13% had a family history of psychiatric diseases and 44% had religious beliefs (Table 1).

Table 1. Descriptive statistics of the demographic characteristics of the entire sample (n = 260).

Age, mean ± SD	27.5 ± 7.6
Gender (male), n (%)	176 (67.7)
Education (year), mean ± SD	9.6 ± 1.9
Marital status, n (%)	
Single	207 (79.6)
Married	46 (17.7)
Separated	6 (2.3)
Widowed	1 (0.4)
Occupation, *n (%)*	
Unemployed	222 (85.4)
Employed	38 (14.6)
Source of referral, *n (%)*	
Residential	201 (77.3)
Non-residential	59 (22.7)
Family psychiatric history, n (%)	34 (13.1)
Has a religious belief, n (%)*	113 (43.5)
Accommodation, *n (%)*	
Public housing	144 (55.4)
Private housing	91 (35.0)
Home Owner Scheme housing	22 (8.5)
Others	3 (1.2)
Smoking history, *n (%)*	
Current	151 (58.1)
Previous	105 (40.4)
Non-smoker	4 (1.5)
Onset age, mean ± SD	13.6 ± 2.4

SD: standard deviation

Patterns of cocaine use

The mean age at initiation of cocaine use and the duration of cocaine use were 20 and 5 years, respectively. Ninety-seven percent of the subjects had lifetime cocaine dependence, whereas only 12% had current cocaine dependence. The average number of days of cocaine use in lifetime, the past 2 years, the past 1 year and the previous month were 1,010, 309, 154 and 2, respectively. Forty (15%) subjects had used cocaine in the previous month. The subjects' average total cocaine consumption in lifetime, the past 2 years, the past 1 year and the previous month were 1,728, 679, 340 and 2.4 grams, respectively. The average cocaine consumption in 1 day in the past year was 1.8 gram (Tables 2 and 3).

Table 2. Descriptive statistics of cocaine use patterns of the entire sample (n = 260).

Variables	Mean ± SD, Median (range)
Age of first use	20.3 ± 6.9 18.0 (11.0 – 55.0)
Duration of use (year)	4.8 ± 4.0 4.0 (0.1 – 24.3)
Days of use	
Lifetime	1010.4 ± 1707.7 680.0 (28.5 – 24358.0)
Past two years	309.1 ± 213.4 273.0 (20.0 – 728.0)
Past one year	153.9 ± 116.2 130.0 (20.0 - 910.0)
Past month	1.8 ± 5.4 0.0 (0 – 30.0)
Lifetime consumption (gram)	
Total	1728.3 ± 2369.8 873.9 (7.4 – 16957.0)
Total / body weight (kilogram)	36.9 ± 156.3 13.8 (0.1 – 2439.0)
Consumption in one day	2.0 ± 2.4 1.2 (0.1 – 21.0)
Consumption in the past two years (gram)	
Total	678.7 ± 1063.4 318.5 (1.1 – 7280.0)
Total / body weight (kilogram)	10.7 ± 16.1 4.8 (0.01 – 98.0)
Consumption in one day	1.9 ± 2.5 1.1 (0.01 – 24.0)
Consumption in the past one year (gram)	
Total	340.2 ± 651.1 147.1 (3.0 – 7280.0)
Total / body weight (kilogram)	5.3 ± 8.6 2.2 (0.05 – 66.3)
Consumption in one day	1.9 ± 2.5 1.0 (0.1 – 24.0)

Variables	Mean ± SD, Median (range)
Consumption in the previous month	
Total	2.4 ± 9.0 0.0 (0.0 – 72.0)
Total / body weight (kilogram)	0.03 ± 0.2 0.0 (0.0 – 1.1)
Consumption in one day	0.2 ± 0.9 0.0 (0.0 – 10.0)
Lifetime dependence, n (%)	251 (96.5)
Low	74 (28.5)
Medium	76 (29.2)
High	101 (38.8)
Lifetime abuse, n (%)	8 (3.1)
Current dependence, n (%)	31 (11.9)
Low	11 (4.2)
Medium	14 (5.4)
High	6 (2.3)
Current abuse, n (%)	15 (5.8)

SD: standard deviation

Table 3. Daily cocaine consumption by age and duration of use.

	All Cocaine users (N = 260)	Male (N = 176)	Female (N = 84)	p-value [a]
Consumption in one day (gram) in past one year, mean ± SD, median (range)	1.8 ± 2.1 1.0 (0.1-13.0)	1.8 ± 2.1 1.1 (0.2-13.0)	1.8 ± 2.0 0.9 (0.1-10.2)	0.434
90th percentile	4.0	40	4.6	
95th percentile	6.0	5.7	6.0	
99th percentile	11.5	12.3	-	
		Duration of use < 5 years) N = 148	Duration >/= 5 years N = 112	
Consumption in one day (gram) in past one year. mean ± SD, median (range)		2.0 ± 2.8 1.1 (0.1 – 24.0)	1.8 ± 1.1 1.1 (0.2 – 12.0)	0.497
90th percentile		4.0	4.0	
95th percentile		6.0	6.0	
99th percentile		19.3	11.8	

[a] t-test; SD: standard deviation

Patterns of other drug use

Two hundred and thirty-seven (91%) cocaine users reported poly-drug use. The three most commonly used drugs were ketamine, cannabis and methamphetamine (ICE), which were used by 71%, 68% and 52% of the poly-drug users, respectively. The age at first use of other drugs ranged from 16 (cough medicine) to 20 (ICE) years. The mean duration of regular use varied from 2 (ecstasy) to 4 (ketamine) years. The average number of days of use per month in their regular use period varied from 14 (ecstasy) to 24 (ketamine). The frequency of lifetime dependence on these drugs ranged from 69% (ketamine) to 20% (ecstasy). Current dependence on these drugs was uncommon (0%–6%) (Table 4).

Table 4. Descriptive statistics of other drug use patterns of the entire sample.

	Ketamine n = 184	Cannabis n = 177	ICE n = 136	Ecstasy n = 125	Hypnotics n = 112	Cough medicine n = 26
Age of first use	16.4 ± 4.4[b]	17.5 ± 5.3[b]	19.7 ± 6.6	17.3 ± 5.1[b]	18.6 ± 6.0[b]	16.1 ± 2.4
Duration (years)	4.2 ± 4.7[b]	2.4 ± 3.4[b]	2.4 ± 3.6 [b]	2.0 ± 2.5[b]	2.2 ± 2.6[b]	2.4 ± 3.6[b]
Days of use per month[a]	24.0 ± 10.3[b]	15.7 ± 11.7[b]	21.2 ± 10.1 [b]	14.2 ± 18.1 [b]	18.6 ± 31.1[b]	20.0 ± 12.0 [b]
Consumption in one day[a]	3.1 ± 3.4¶[b]	2.6 ± 4.1‡[b]	1.2 ± 1.1¶ [b]	1.5 ±1.1†[b]	3.9 ± 6.8‡	1.4 ± 0.9†
Current dependence, n (%)	6 (3.3)	4 (2.3)	6 (4.4)	1 (0.8)	0 (0.0)	0 (0.0)
Low	3 (1.6)	3 (1.7)	1 (0.7)	1 (0.8)	0 (0.0)	0 (0.0)
Medium	1 (0.5)	1 (0.6)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
High	2 (1.1)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Lifetime dependence, n (%)	128 (69.6)	52 (29.4)	73 (53.7)	25 (20.0)	24 (21.4)	9 (34.6)
Low	35 (19.0)	30 (16.9)	17 (12.5)	14 (11.2)	11 (9.8)	2 (7.7)
Medium	41 (22.3)	13 (7.3)	26 (19.1)	8 (6.4)	5 (4.5)	1 (3.8)
High	52 (28.3)	9 (5.1)	44 (32.4)	3 (2.4)	8 (7.1)	6 (23.1)

Unit: tab†; piece‡; bottle§; gram¶

[a] During period of regular use

[b] Missing data

ICE: methamphetamine

Psychotic symptoms

Eighty-six percent (n = 223) and 18% (n = 48) of the cocaine users had lifetime and current psychotic symptoms, respectively. Regarding the pattern of psychotic symptoms, 57% (n =149) had TPS; 15% (n = 38) had PPS, and for these subjects, the mean time elapsed between their last use of cocaine and the day of assessment was 122 (range, 30–304) days; 11% (n = 28) had psychotic symptoms and were not yet in the detoxification stage; and one subject had flashbacks or psychotic symptoms only during the months of cocaine abstinence. In terms of subtypes of psychotic symptoms, more than two thirds of the subjects reported lifetime delusions (79%) and hallucinations (71%). Delusion of reference (74%) was the most common delusion, followed by persecutory delusion (39%). Auditory hallucination was the most common type of hallucination (60%), followed by visual (39%) and tactile (19%) hallucinations. Twelve percent of the sample reported thought broadcasting. Negative symptoms were rare (Table 5).

Table 5. Frequency of lifetime psychotic symptoms (n = 260).

Variables	Lifetime	Current	Past
Psychotic symptoms, n (%)	223 (85.8)	48 (18.5)	211 (81.2)
Delusion (any type), n (%)	205 (78.8)	43 (16.5)	178 (68.5)
Delusion of reference, n (%)	192 (73.8)	37 (14.2)	156 (60.0)
Persecutory delusion, n (%)	102 (39.2)	24 (9.2)	79 (30.4)
Somatic delusion, n (%), n (%)	25 (9.6)	4 (1.5)	21 (8.1)
Grandiose delusion, n (%)	23 (8.8)	5 (1.9)	18 (6.9)
Delusion of being controlled, n (%)	18 (6.9)	3 (1.2)	15 (5.8)
Other delusion, n (%)	3 (1.2)	2 (0.8)	1 (0.4)
Religious delusion, n (%)	1 (0.4)	2 (0.8)	0 (0.0)
Delusion of guilt, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Jealous delusion, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Erotomanic delusion, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Hallucination (any type), n (%)	185 (71.2)	24 (9.2)	173 (66.5)
Auditory hallucination, n (%)	157 (60.4)	20 (7.7)	137 (52.7)
Visual hallucination, n (%)	101 (38.8)	8 (3.1)	92 (35.4)
Tactile hallucination, n (%)	49 (18.8)	8 (3.1)	41 (15.8)
Olfactory hallucination, n (%)	20 (7.7)	1 (0.4)	19 (7.3)
Gustatory hallucination, n (%)	12 (4.6)	0 (0.0)	12 (4.6)
Thought broadcasting, n (%)	30 (11.5)	2 (0.8)	29 (11.2)
Thought insertion, n (%)	3 (1.2)	2 (0.8)	1 (0.4)
Thought withdrawal, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Catatonic behaviour, n (%)	1 (0.4)	1 (0.4)	0 (0.0)
Disorganized speech, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Crossly disorganized behaviour, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Grossly inappropriate affect, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Avolition, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Alogia, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Affective flattening, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Duration of psychotic symptoms after last use of cocaine (days); Mean ± SD; median (range)	27.3 ± 71.4 1.0 (0.0 – 730.0)	89.5 ± 68.5 61.0 (0.0 – 212.0)	26.4 ± 71.4 1.0 (0.0 – 730.0)
Duration of psychotic symptoms lasted for more than 30 days after last use of cocaine n (%)	42 (18.8)	29 (60.4)	37 (17.5)

Correlates of the presence of psychotic symptoms

Compared with subjects without lifetime psychotic symptoms, those with lifetime psychotic symptoms were more likely to be a current smoker (46% vs 60%, p = 0.049) (Table 6). In terms of cocaine use patterns, they had an earlier onset of cocaine use in term of age (23 vs 20 years, p = 0.032); had a longer duration of cocaine use (4 vs 5 years, p = 0.021); had a higher total lifetime consumption of cocaine (1,116 vs 1,830 grams, p = 0.013), even taking into account body weight (kg) (18 vs 40 grams, p = 0.013); and were more likely to be cocaine-dependent (89% vs 98%, p = 0.039) (Table 7). In terms of other substance use, they were more likely to have lifetime use of ICE (35% vs 55%, p = 0.032) and cannabis (51% vs 71%, p = 0.023) (Table 8). In the logistic regression model, lifetime cocaine dependence (odds ratio [OR] = 1.5, 95% confidence interval [CI] = 1.1–2.0, p = 0.008), lifetime ICE use (OR = 2.9, 95% CI = 1.3–6.6, p = 0.009) and smoking history (OR = 2.1, 95% CI = 1.0–4.1, p = 0.042) were found to be independent predictors of psychotic symptoms (Table 9).

Table 6. Demographic characteristics of subjects with and without lifetime psychotic symptoms.

	With psychotic symptoms n = 223	Without psychotic symptoms n = 37	p-value
Age, mean ± SD	27.3 ± 7.0	28.4 ± 10.5	0.721[a]
Gender (male), n (%)	153 (68.6)	23 (62.2)	0.275[b]
Education (year), mean ± SD	9.6 ± 2.0	9.4 ± 1.7	0.622[a]
Marital status, n (%)			
Single	178 (79.8)	29 (78.4)	0.568[c]
Married	40 (17.9)	6 (16.2)	
Separated	4 (1.8)	2 (5.4)	
Widowed	1 (0.4)	-	
Occupation, n (%)			
Employed	32 (14.3)	6 (16.2)	0.464[b]
Unemployed	191 (85.7)	31 (83.8)	
Source of referral, n (%)			
Non-residential	49 (22.0)	10 (27.0)	0.312[b]
Residential	174 (78.0)	27 (73.0)	
Family psychiatric history, n (%)	30 (13.5)	4 (10.8)	0.448[b]
Has a religious belief, n (%)[*]	106 (47.5)	17 (45.9)	0.752[c]
Accommodation, n (%)			
Public housing	122 (54.7)	22 (59.5)	0.741[c]
Private housing	80 (35.9)	11 (29.7)	
Home Owner Scheme housing	18 (8.1)	4 (10.8)	
Other	3 (1.3)	0 (0.0)	
Smoking history, n (%)			
Current	134 (60.1)	17 (45.9)	0.049[c]
Previous	87 (39.0)	18 (48.6)	
Non-smoker	2 (0.9)	2 (5.4)	
Onset age, mean ± SD	13.6 ± 2.2	13.4 ± 3.7	0.484 [a]

[a]Mann-Whitney test; [b]Fisher Exact test; [c]Chi-square test.; SD: standard deviation

Table 7. Cocaine use patterns in subjects with and without lifetime psychotic symptoms.

Variables	With psychotic symptoms n = 223 Mean ± SD, Median (range)	Without psychotic symptoms n = 37 Mean ± SD, Median (range)	p-value [a]
Age of first use	19.8 ± 6.2 18.0 (12.0 – 53.0)	23.1 ± 9.8 20.0 (11.0 – 55.0)	0.032
Duration of use (year)	4.9 ± 3.8 4.1 (0.1 – 22.0)	3.9 ± 4.7 2.0 (0.3 – 24.3)	0.021
Days of use			
Lifetime	1068.0 ± 1817.9 732.0 (28.5 – 24358.0)	663.1 ± 676.2 398.7 (48.0 – 2821.0)	0.022
Past two years	313.1 ± 217.5 273.0 (20.0 – 728.0)	284.7 ± 187.2 248.1 (20.0 – 697.7)	0.591
Past one year	157.0 ± 119.4 130.0 (20.0 – 910.0)	134.1 ± 93.3 113.8 (20.0 – 333.7)	0.401
Past month	1.8 ± 5.5 0.0 (0.0 – 30.0)	1.7 ± 4.9 0.0 (0.0 – 20.0)	0.883
Lifetime Consumption(gram)			
Total	1830.3 ± 2423.0 940.6 (7.4 – 16957.0)	1116.1 ± 1939.4 453.7 (19.2 – 10712.0)	0.013
Total / body weight (kilogram)	40.0 ±168.0 14.2 (0.1 – 2439.0)	18.2 ± 36.3 8.1 (0.3 – 214.2)	0.013
Consumption in one day	2.1 ± 2 1.3 (0.1 – 21.0)	1.5 ± 1.3 1.1 (0.2 – 6.3)	0.269
Ice consumption in past two years (gram)			
Total	709.1 ± 1115.8 336.7 (1.1 – 7280.0)	496.0 ± 646.7 208.3 (3.7 – 2790.7)	0.311
Total / body weight (kilogram)	11.1 ± 16.8 5.3 (0.01 – 98.0)	7.9 ± 11.0 3.5 (0.1 – 55.8)	0.341
Consumption in one day	2.0 ± 2.7 1.1 (0.01 – 24.0)	1.4 ± 1.3 1.0 (0.2 – 5.0)	0.270
Consumption in the past one year (gram)			
Total	354.4 ± 685.7 163.8 (3.0 – 7280.0)	253.5 ± 369.1 83.4 (3.7 – 1334.7)	0.147
Total / body weight (kilogram)	5.5 ± 8.9	4.0 ± 6.2	0.130

Variables	With psychotic symptoms n = 223 Mean ± SD, Median (range)	Without psychotic symptoms n = 37 Mean ± SD, Median (range)	p-value [a]
	2.5 (0.05 – 66.3)	1.1 (0.1 – 26.7)	
Consumption in one day	2.0 ± 2.6 1.1 (0.1 – 24.0)	1.4 ± 1.3 0.9 (0.2 – 5.0)	0.103
Consumption in the previous month (gram)			
Total	2.5 ± 9.2 0.0 (0.0 – 72.0)	2.1 ± 8.0 0.0 (0.0 – 40.0)	0.936
Total / body weight (kilogram)	0.04 ± 0.2 0.0 (0.0 – 1.1)	0.04 ± 0.1 0.0 (0.0 – 0.7)	0.928
Consumption in one day	0.2 ± 0.9 0.0 (0.0 – 10.0)	0.1 ± 0.4 0.0 (0.0 – 2.0)	0.970
Current dependence, n (%)	28 (12.6)	3 (8.1)	0.559[b]
Low	10 (4.5)	1 (2.7)	
Medium	13 (5.8)	1 (2.7)	
High	5 (2.2)	1 (2.7)	
Current abuse, n (%)	11 (4.9)	4 (10.8)	0.242[b]
Lifetime dependence, n (%)	218 (97.8)	37 (100.0)	0.039[b]
Low	62 (27.8)	12 (32.4)	
Medium	62 (27.8)	14 (37.8)	
High	94 (42.2)	7 (18.9)	
Lifetime abuse, n (%)	5 (2.2)	4 (10.8)	0.090[b]

[a] Mann-Whitney; [b] Fisher's exact test; SD: standard deviation

Table 8. Other drug use in subjects with and without lifetime psychotic symptoms.

Lifetime use	With psychotic symptoms n=223	Without psychotic symptoms n=37	p-value[a]
ICE	123 (55.2)	13 (35.1)	0.032
Cannabis	158 (70.9)	19 (51.4)	0.023
Cough medicine	25 (11.2)	1 (2.7)	0.143
Ketamine	161 (72.2)	23 (62.2)	0.243
Ecstasy	107 (48.0)	18 (48.6)	0.726
Hypnotics	95 (42.6)	17 (45.9)	0.723

[a] Fisher's exact test
ICE: methamphetamine

Table 9. Logistic regression of predictors of psychotic symptoms.

		95% Cl for OR		
Variables	OR	Lower	Upper	p-value
Smoking history	2.1	1.0	4.1	0.042
Age of Cocaine onset	1.0	0.9	1.0	0.077
Duration of Cocaine use (years)	-	-	-	-
Days of Cocaine use (Lifetime)	-	-	-	-
Lifetime total Cocaine consumptions (gram)	-	-	-	-
Lifetime total cocaine consumption / body weight	-	-	-	-
Lifetime Cocaine dependence	1.5	1.1	2.0	0.008
Lifetime ICE use	2.9	1.3	6.6	0.009
Lifetime Cannabis use	-	-	-	-

ICE: methamphetamine

Correlates of PPS

The average duration of psychotic symptoms after last cocaine use was 129 days in the PPS group and 3 days in the TPS group. Compared with subjects with TPS, those with PPS had a lower education level ($p = 0.010$) and a family history of psychiatric illness ($p = 0.019$) (Table 10). Subjects with PPS and TPS did not differ in terms of cocaine use patterns (Table 11). However, the PPS group was more likely than the TPS group to report lifetime use of ICE (87% vs 50%, $p < 0.001$) and cough medicine (21% vs 9%, $p = 0.043$) (Table 12). In the logistic regression model, education level (OR = 0.8, 95% CI = 0.6–1.0, $p = 0.039$), family history of psychiatric illness (OR = 3.0, 95% CI = 1.0–8.1, $p = 0.028$) and lifetime ICE use (OR = 6.9, 95% CI = 2.5–19.2, $p < 0.001$) were found to be predictors of PPS (Table 13).

Table 10. Demographic characteristics of subjects with TPS and PPS.

	PPS n=38	TPS n=149	TPS vs PPS (p-value)
Age, mean ± SD	27.0 ± 8.6	27.3 ± 6.9	0.366[a]
Gender (male), n (%)	24 (63.2)	102 (68.0)	0.564[b]
Education (year), mean ± SD	8.9 ± 1.9	9.7±2.0	0.010[a]
Marital status, n (%)			
Single	28 (73.7)	123 (82.6)	0.561[c]
Married	9 (23.7)	22 (14.8)	
Separated	1 (2.6)	3 (2.0)	
Widowed	0 (0.0)	1 (0.7)	
Occupation, n (%)			
Employed,	6 (15.8)	12 (8.1)	0.213[b]
Unemployed	32 (84.2)	137 (91.9)	
Source of referral, n (%)			
Non-residential	9 (23.7)	18 (12.1)	0.064[b]
Residential	29 (76.3)	131 (87.9)	
Family psychiatric history, n (%)	10 (26.3)	17 (11.3)	0.019[b]
Has a religious belief, n (%)	19 (50.0)	65 (43.3)	0.276[c]
Accommodation, n (%)			
Public housing	23 (60.5)	82 (55.0)	0.140[c]
Private housing	15 (39.5)	48 (32.2)	
Home Owner Scheme housing	0 (0.0)	16 (10.7)	
Others	0 (0.0)	3 (2.0)	
Smoking history, n (%)			
Current	27 (71.1)	78 (52.3)	0.104[c]
Previous	11 (28.9)	69 (46.3)	
Non-smoker	0 (0.0)	2 (1.3)	
Onset age, mean ± SD	13.4 ± 2.4	13.6 ± 2.0	0.311[a]
Duration of psychosis after last use of cocaine (days)	129.4 ± 117.0 90.5 (30.0 – 730.0)	2.8 ± 5.3 1.0 (1.0 – 28.0)	<0.001[a]
75th percentile	180.5	1.0	
90th percentile	212.0	7.0	

[a] Mann-Whitney; [b] Fisher's Exact Test; [c] Chi-square test.

TPS: Transient psychotic symptoms; PPS: Persistent psychotic symptoms; SD: standard deviation.

Table 11 Descriptive statistics of cocaine use patterns.

Variables	PPS n=38 Mean ± SD, Median (range)	TPS n=149 Mean ± SD, Median (range)	TPS vs PPS p-value [a]
Age of first use	20.7 ± 7.9 18.0 (13.0 – 48.0)	19.7 ± 5.9 18.0 (12.0 – 53.0)	0.883
Duration of use (year)	4.1 ± 3.5 3.2 (0.1 – 14.0)	5.0 ± 3.9 4.4 (0.2 – 22.0)	0.167
Days of use			
Lifetime	944.6 ± 1108.4 560.5 (30.3 – 5096.0)	1149.0 ± 2133.8 780.0 (28.5 – 24358.0)	0.271
Past two year	305.9 ± 222.3 257.8 (20.0 – 728.0)	323.3 ± 220.5 299.0 (20.0 – 728.0)	0.685
Past one year	126.1 ± 87.2 97.5 (20.0 – 364.0)	155.3 ± 107.8 143.0 (20.0 – 364.0)	0.274
Lifetime consumption (gram)			
Total	1499.9 ± 1613.4 1204.4 (24.3 – 6546.7)	2041.9 ± 2689.4 1025.2 (7.4 – 16957.0)	0.416
Total / body weight (kilogram)	24.9 ± 29.8 15.8 (0.4 – 141.5)	31.7 ± 41.7 15.9 (0.1 – 186.3)	0.488
Consumption in one day	2.2 ± 2.4 1.2 (0.2 – 11.4)	2.2 ± 2.7 1.5 (0.1 – 21.0)	0.829
Consumption in the past two years (gram)			
Total	629.4 ± 856.2 273.0 (9.3 – 3086.4)	784.5 ± 1254.2 374.4 (1.1 – 7280.0)	0.528
Total / body weight (kilogram)	10.3 ± 14.4 3.9 (0.1 – 56.1)	12.1 ± 18.4 5.8 (0.01 – 98.0)	0.565
Consumption in one day	1.9 ± 2.2 1.0 (0.05 – 11.4)	2.1 ± 2.9 1.2 (0.1 – 24.0)	0.710
Consumption in the past one year (gram)			
Total	250.2 ± 326.5 135. (6.9 – 1402.9)	380.9 ± 789.9 173.3 (3.0 – 7280.0)	0.370

Variables	PPS n=38 Mean ± SD, Median (range)	TPS n=149 Mean ± SD, Median (range)	TPS vs PPS p-value [a]
Total / body weight (kilogram)	4.0 ± 5.2 1.8 (0.1 – 21.6)	5.7 ± 9.7 2.7 (0.05 – 66.3)	0.414
Consumption in one day	1.7 ± 1.7 1.0 (0.1 – 6.5)	2.1 ± 2.9 1.3 (0.1 – 24.0)	0.595
Lifetime dependence, n (%)	37 (97.4)	147 (98.7)	1.000[b]
Low	17 (44.7)	36 (24.2)	
Medium	7 (18.4)	46 (30.9)	
High	13 (34.2)	65 (43.6)	
Lifetime abuse, n (%)	1 (2.6)	2 (1.3)	0.496[b]

[a] Mann-Whitney; [b] Fisher's Exact test.

TPS: Transient psychotic symptoms; PPS: Persistent psychotic symptoms; SD: standard deviation.

Table 12. Other drug use in the TPS and PPS groups.

Lifetime use	PPS n=38	TPS n=149	p-value[a]
ICE	33 (86.8)	74 (49.7)	<0.001
Cannabis	31 (81.6)	98 (65.8)	0.077
Cough medicine	8 (21.1)	13 (8.7)	0.043
Ecstasy	16 (42.1)	74 (49.7)	0.469
Hypnotics	20 (52.6)	64 (43.0)	0.361
Ketamine	28 (73.7)	109 (73.2)	1.000

[a] Fisher's Exact test;
ICE: methamphetamine

Table 13. Logistic regression of predictors of PPS.

		95% Cl for OR		
Variable	OR	Lower	Upper	p-value
Education	0.8	0.6	1.0	0.039
Family psychiatric history	3.0	1.0	8.1	0.028
Lifetime ICE use	6.9	2.5	19.2	<0.001
Lifetime Cough medicine use	-	-	-	-

ICE: methamphetamine

Psychiatric diagnoses

The patterns of psychiatric disorders are shown in Table 14. More than two thirds (71%) of the subjects had lifetime CIP, with the average duration of CIP being 5 days. A small proportion of the subjects had other psychoses, namely, schizophrenia or delusional disorder. Lifetime substance-induced mood disorder was also common, being found in 69% of the subjects. The predominant presentation was depressive episodes. The prevalence of lifetime diagnosis of major depressive disorder and bipolar disorder was 17% and 8%, respectively. Lifetime substance-induced anxiety disorder was found in 32% of the subjects. Obsessive–compulsive features (27%) were the most common presentation, followed by phobic symptoms (10%). Non-substance-related anxiety disorders were uncommon.

Table 14. Patterns of psychiatric diagnoses in the total sample.

	All users n = 260		
Variables, n (%)	Lifetime	Current	Past
Any psychotic disorders	222 (85.4)	51 (19.6)	173 (66.5)
Substance-induced psychotic disorder (CIP)	185 (71.2)	20 (7.7)	167 (64.2)
Delusional disorder	18 (6.9)	16 (6.2)	2 (0.8)
Schizophrenia / schizophreniform disorder	10 (3.8)	7 (2.7)	3 (1.2)
Psychotic not otherwise specified	9 (3.5)	2 (0.8)	7 (2.7)
Any mood disorders	180 (69.2)	48 (18.5)	143 (55.0)
Substance-induced mood disorder	128 (49.2)	14 (5.4)	115 (44.2)
Depressive episodes	88 (33.8)	9 (3.5)	79 (30.4)
Mixed episodes	32 (12.3)	4 (1.5)	28 (10.8)
Manic / hypomanic episodes	12 (4.6)	0 (0.0)	12 (4.6)
Major depressive disorder	43 (16.5)	23 (8.8)	22 (8.5)
Bipolar I or II disorder	20 (7.7)	12 (4.6)	9 (3.5)
Any anxiety disorders	84 (32.3)	-	-
Substance-induced anxiety disorder (any type)	79 (30.4)	-	-
With obsessive compulsive symptoms	69 (26.5)	-	-
With phobic features	25 (9.6)	-	-
With panic attacks	11 (4.2)	-	-
With generalized anxiety symptoms	5 (1.9)	-	-
Specific phobia	11 (4.2)	-	-
Panic disorder	1 (0.4)	-	-
Generalized Anxiety Disorder	0 (0.0)	-	-
Obsessive Compulsive Disorder	4 (1.5)	-	-
Agoraphobia without history of panic disorder	0 (0.0)	-	-
Social Phobia	1 (0.4)	-	-
Duration of CIP (days);	5.3 ± 22.3	-	-
mean ± SD, median (range)	1.0 (0.0 – 212.0)		
75^{th} percentile	1.0	-	-
90^{th} percentile	7.0	-	-

Correlates of lifetime substance-induced psychotic disorder (CIP)

Of the socio-demographic characteristics, only education level was different between subjects with and without CIP ($p = 0.020$), being significantly higher in the former group (Table 15). In terms of cocaine use, CIP was significantly related to the duration of use ($p = 0.004$), lifetime total days of use (0.007), lifetime total amount of use ($p = 0.022$) and lifetime total amount of use per body weight ($p = 0.025$) (Table 16). Other drug use was not related to CIP (Table 17). In the logistic regression model, younger age at first cocaine use (OR = 0.954, 95% CI = 0.917–0.993, $p = 0.020$) and total days of cocaine use in the past year (OR = 1.003, 95% CI = 1.000–1.006, $p = 0.030$) were found to be predictors of CIP (Table 18).

Table 15. Demographic characteristics of subjects with and without lifetime substance-induced psychotic disorders.

	With substance-induced psychotic disorders n = 185	Without substance-induced psychotic disorders n = 75	p-value
Age	27.4 ± 6.6	27.7 ± 9.5	0.306[a]
Gender (female), n (%)	56 (30.3)	28 (37.3)	0.306[b]
Education (year)	9.7 ± 1.9	9.2 ± 1.8	0.020[a]
Marital status (single), n (%)			
Single	148 (80.0)	59 (78.7)	0.630[c]
Married	33 (17.8)	13 (17.3)	
Separated	3 (1.6)	3 (4.0)	
Widowed	1 (0.5)	0 (0.0)	
Occupation, n (%)			
Employed	25 (13.5)	13 (17.3)	0.422[b]
Unemployed	160 (86.5)	62 (82.7)	
Source of referral, n (%)			
Non-residential	39 (21.1)	20 (26.7)	0.332[b]
Residential	146 (78.9)	55 (73.3)	
Family psychiatric history, n (%)	20 (10.8)	14 (18.7)	0.105[b]
Has a religious belief, n (%)[*]	77 (41.6)	36 (48.0)	0.312[c]
Accommodation, *n (%)*			
Public housing	102 (55.1)	42 (56.0)	0.416[c]
Private housing	62 (33.5)	29 (38.7)	
Home Owner Scheme housing	18 (9.7)	4 (5.3)	
Others	3 (1.6)	0 (0.0)	
Smoking history, n (%)			
Current	107 (57.8)	44 (58.7)	0.620[c]
Previous	76 (41.1)	29 (38.7)	
Non-smoker	2 (1.1)	2 (2.7)	
Onset age	13.7 ± 2.2	13.0 ± 3.0	0.175[a]

[a] Mann-Whitney Test; [b] Fisher's Exact Test; [c] Pearson Chi-Square test.

Table 16. Cocaine use patterns in subjects with and without lifetime substance-induced psychotic disorders.

Variables	With substance-induced psychotic disorders n = 185 Mean ± SD, Median (range)	Without substance-induced psychotic disorders n = 75 Mean ± SD, Median (range)	p-value[a]
Age of first use	19.6 ± 5.8 18.0 (12.0 – 53.0)	22.0 ± 8.9 19.0 (11.0 – 55.0)	0.079
Duration of use (year)	5.1 ± 4.0 4.7 (0.2 – 22.0)	3.9 ± 3.9 2.5 (0.1 – 24.3)	0.004
Days of use			
Lifetime	1119.7 ± 1954.6 780.0 (28.5 – 24358.0)	740.6 ± 777.0 455.0 (30.3 – 3904.0)	0.007
Past two year	320.3 ± 218.2 294.7 (20.0 – 728.0)	280.8 ± 199.5 225.3 (20.0 – 702.0)	0.202
Past one year	160.0 ± 111.8 143.0 (20.0 – 364.0)	126.9 ± 86.6 97.5 (20.0 – 333.7)	0.078
Previous month	2.0 ± 5.8 0.0 (0.0 – 30.0)	1.2 ± 4.5 0.4 (0.0 – 25.0)	0.183
Lifetime consumption (gram)			
Total	1921.0 ± 2562.0 969.4 (7.4 – 16957.0)	1263.6 ± 1757.0 659.1 (19.2 – 10712.0)	0.022
Total / body weight (kilogram)	23.6 ± 184.4 14.4 (0.1 – 2439.0)	20.7 ± 32.6 11.1 (0.3 – 214.2)	0.025
Consumption in one day	2.1 ± 2.6 1.3 (0.1 – 21.0)	1.8 ± 1.9 1.1 (0.2 – 11.4)	0.588
Consumption in the past two years (gram)			
Total	736.1 ± 1162.0 364.0 (1.1 – 7280.0)	537.2 ± 757.0 202.0 (3.7 – 3086.4)	0.138
Total / body weight (kilogram)	11.5 ± 17.2 5.8 (0.02 – 98.0)	8.7 ± 12.8 3.3 (0.01 – 56.1)	0.160
Consumption in one day	2.0 ± 2.8 1.1 (0.01 – 24.0)	1.6 ± 1.8 1.0 (0.02 – 11.4)	0.310
Consumption in the past one year(gram)			

Variables	With substance-induced psychotic disorders n = 185 Mean ± SD, Median (range)	Without substance-induced psychotic disorders n = 75 Mean ± SD, Median (range)	p-value[a]
Total	373.6 ± 736.5 167.9 (3.0 – 7280.0)	246.4 ± 345.0 93.3 (3.7 – 1402.9)	0.093
Total / body weight (kilogram)	5.7 ± 9.4 2.5 (0.05 – 66.3)	3.9 ± 5.7 1.3 (0.1 – 26.7)	0.098
Consumption in one day	2.0 ± 9.8 1.1 (0.1 – 24.0)	1.6 ± 1.5 0.9 (0.1 – 6.5)	0.209
Ice consumption in the previous month (gram)			
Total; Mean ± SD	2.7 ± 9.4 0.0 (0.0 – 72.0)	1.7 ± 8.0 0.0 (0.0 – 50.0)	0.169
Total / body weight (kilogram)	0.05 ± 1.2 0.0 (0.0 – 1.1)	0.04 ± 0.1 0.0 (0.0 - 0.8)	0.173
Consumption in one day	0.3 ± 1.0 0.0 (0.0 – 10.0)	0.1 ± 0.4 0.0 (0.0 – 2.0)	0.162
Current dependence, n (%)	27 (14.6)	4 (5.3)	0.506[b]
Low	9 (4.9)	2 (2.7)	
Medium	13 (7.0)	1 (1.3)	
High	5 (2.7)	1 (1.3)	
Current abuse, n (%)	10 (5.4)	5 (6.7)	0.770[b]
Lifetime dependence, n (%)	181 (97.8)	70 (93.3)	0.158[b]
Low	45 (24.3)	29 (38.7)	
Medium	56 (30.3)	20 (26.7)	
High	80 (43.2)	21 (28.0)	
Lifetime abuse, n (%)	4 (2.2)	4 (5.3)	0.233[b]

[a] Mann-Whitney Test; [b] Fisher's Exact Test

Table 17. Other drug use in subjects with and without substance-induced psychotic disorders.

Lifetime use	With substance-induced psychotic disorders n = 185	Without substance-induced psychotic disorders n = 75	p-value[a]
Ketamine	135 (73.0)	46 (61.3)	0.231
Cannabis	127 (68.6)	50 (66.7)	0.770
Ecstasy	93 (50.3)	33 (44.0)	0.412
ICE	90 (48.6)	46 (61.3)	0.075
Hypnotics	78 (42.2)	34 (45.3)	0.679
Cough medicine	17 (9.2)	9 (12.0)	0.499

[a] Fisher's exact test.

ICE: methamphetamine; SD: standard deviation

Table 18. Logistic regression of predictors of lifetime substance-induced psychotic disorders.

		95% Cl for OR		
Variable	OR	Lower	Upper	p-value
Education	-	-	-	-
Duration of cocaine use	-	-	-	-
Cocaine use onset age	0.954	0.917	0.993	0.020
Days of Cocaine use (lifetime)	-	-	-	-
Days of Cocaine use (past one year)	1.003	1.000	1.006	0.030
Lifetime total Cocaine consumption (grams)	-	-	-	-
Lifetime total Cocaine consumption / body weight (grams)	-	-	-	-
Total consumption in the past one year (grams)	-	-	-	-
Total consumption in the past one year / body weight (grams)	-	-	-	-
Lifetime use of ICE	-	-	-	-

Correlates of lifetime substance-induced mood disorders

Substance-induced mood disorders were not associated with socio-demographic variables or cocaine use patterns (Tables 19 and 20). In terms of other drug use, subjects with substance-induced mood disorders were more likely to report lifetime use of hypnotics ($p = 0.017$), ecstasy ($p = 0.018$) and ICE ($p = 0.007$) than those without such disorders (Table 21). The logistic regression model indicated that lifetime ICE use was a significant predictor of substance-induced mood disorders (OR = 2.0, 95% CI = 1.2–3.3, $p = 0.006$) (Table 22).

Table 19. Demographic characteristics of subjects with and without lifetime substance-induced mood disorders.

	With substance-induced mood disorders n = 128	Without substance-induced mood disorders n = 132	p-value
Age	27.9 ± 8.5	27.0 ± 6.5	0.922[a]
Gender (female), n (%)	43 (33.6)	41 (31.1)	0.692[b]
Education (year)	9.6 ± 2.0	9.5 ± 1.9	0.738[a]
Marital status (single), n (%)			
Single	102 (79.7)	105 (79.5)	0.262[c]
Married	21 (16.4)	25 (18.9)	
Separated	5 (3.9)	1 (0.8)	
Widowed	0 (0.0)	1 (0.8)	
Occupation, n (%)			
Employed	20 (15.6)	18 (13.6)	0.727[b]
Unemployed	108 (84.4)	114 (86.4)	
Source of referral, n (%)			
Non-residential	28 (21.9)	31 (23.5)	0.769[b]
Residential	100 (78.1)	101 (76.5)	
Family psychiatric history, n (%)	15 (11.7)	19 (14.4)	0.583[b]
Has a religious belief, n (%)[*]	54 (42.2)	59 (44.7)	0.828[c]
Accommodation, *n (%)*			
Public housing	66 (51.6)	78 (59.1)	0.404[c]
Private housing	46 (35.9)	45 (34.1)	
Home Owner Scheme housing	14 (10.9)	8 (6.1)	
Others	2 (1.6)	1 (0.8)	
Smoking history, n (%)			
Current	72 (56.3)	79 (59.8)	0.840[c]
Previous	54 (42.2)	51 (38.6)	
Non-smoker	2 (1.6)	2 (1.5)	
Onset age	13.3 ± 2.1	13.8 ± 2.7	0.499[a]

[a] Mann-Whitney Test; [b] Fisher's Exact Test; [c] Pearson Chi-Square test.

Table 20. Cocaine use patterns in subjects with and without lifetime substance-induced mood disorders.

Variables	With substance-induced mood disorders n = 128 Mean ± SD, Median (range)	Without substance-induced mood disorders n = 132 Mean ± SD, Median (range)	p-value[a]
Age of first use	20.6 ± 7.7 18.0 (11.0 – 53.0)	20.0 ± 6.0 18.0 (12.0 – 55.0)	0.867
Duration of use (year)	5.1 ± 4.1 4.3 (0.2 – 24.3)	4.5 ± 3.9 3.5 (0.1 – 22.0)	0.180
Days of use			
Lifetime	939.9 ± 874.6 751.8 (36.8 – 5308.0)	1078.7 ± 2239.3 616.3 (28.5 – 24358.0)	0.407
Past two year	306.1 ± 213.4 273.0 (20.0 – 702.0)	312.0 ± 214.3 271.5 (20.0 – 728.0)	0.785
Past one year	143.1 ± 100.9 130.0 (20.0 – 364.0)	158.0 ± 110.9 125.7 (20.0 – 364.0)	0.327
Previous month	1.9 ± 6.0 0.0 (0.0 – 30.0)	1.7 ± 4.9 0.0 (0.0 – 25.0)	0.872
Lifetime consumption			
Total (gram)	1949.5 ± 2434.9 995.7 (7.4 – 10192.0)	1510.6 ± 2292.8 725.4 (8.7 – 16957.0)	0.101
Total (gram) / body weight (kilogram)	30.7 ± 40.1 15.2 (0.1 – 179.1)	42.9 ± 216.4 12.6 (0.2 – 2439.0)	0.174
Consumption in one day (gram)	2.2 ± 2.8 1.5 (0.2 – 21.0)	1.8 ±1.9 1.1 (0.1 – 11.4)	0.153
Consumption in the past two years (gram)			
Total	751.4 ± 1224.5 347.8 (1.1 – 7280.0)	608.9 ± 880.7 312.0 (1.2 – 6006.0)	0.718
Total / body weight (kilogram)	11.4 ± 17.5 5.7 (0.01 – 98.0)	10.0 ± 14.7 4.8 (0.02 – 82.3)	0.793
Consumption in one day	2.0 ± 2.9 1.1 (0.02 – 24.0)	1.8 ± 2.1 1.0 (0.01 – 12.0)	0.662
Consumption in the past one year(gram)			

Variables	With substance-induced mood disorders n = 128 Mean ± SD, Median (range)	Without substance-induced mood disorders n = 132 Mean ± SD, Median (range)	p-value[a]
Total	359.3 ± 768.9 145.6 (3.0 – 7280.0)	315.3 ± 512.1 144.3 (3.7 – 4368.0)	0.947
Total / body weight (kilogram)	5.2 ± 8.6 2.4 (0.05 – 61.7)	5.2 ± 8.5 2.1 (0.1 – 66.3)	0.944
Consumption in one day	2.0 ± 2.9 1.1 (0.1 – 24.0)	1.7 ± 2.0 1.0 (0.1 – 12.0)	0.623
Ice consumption in the previous month (gram)			
Total; Mean ± SD	2.6 ± 9.7 0.0 (0.0 – 72.0)	2.3 ± 8.4 0.0 (0.0 – 50.0)	0.915
Total / body weight (kilogram)	0.04 ± 1.2 0.0 (0.0 – 1.1)	0.03 ± 1.1 0.0 (0.0 – 0.8)	0.914
Consumption in one day	0.2 ± 1.0 0.0 (0.0 – 10.0)	0.2 ± 0.8 0.0 (0.0 – 7.0)	0.926
Current dependence, n (%)	15 (11.7)	16 (12.1)	1.000[c]
Low	6 (4.7)	5 (3.8)	
Medium	5 (3.9)	9 (6.8)	
High	4 (3.1)	2 (1.5)	
Current abuse, n (%)	7 (5.5)	8 (6.1)	1.000[c]
Lifetime dependence, n (%)	96 (75.0)	127 (96.2)	1.000[c]
Low	39 (30.5)	35 (26.5)	
Medium	30 (23.4)	46 (34.8)	
High	55 (43.0)	46 (34.8)	
Lifetime abuse, n (%)	3 (2.3)	5 (3.8)	0.723[c]

[a] Mann-Whitney Test; [b] T-test; [c] Fisher's Exact Test.

Table 21. Other drug use in subjects with and without lifetime substance-induced mood disorders.

Life time use	With substance-induced mood disorders n = 128	Without substance-induced mood disorders n = 132	p-value[a]
Cannabis	93 (72.7)	84 (63.6)	0.143
Ketamine	91 (71.1)	93 (70.5)	1.000
ICE	78 (60.9)	58 (43.9)	0.007
Ecstasy	72 (56.3)	54 (40.9)	0.018
Hypnotics	65 (50.8)	47 (35.6)	0.017
Cough medicine	11 (8.6)	15 (11.4)	0.537

[a] Fisher's exact test.

ICE: methamphetamine; SD: standard deviation

Table 22. Logistic regression of predictors of lifetime substance-induced mood disorders.

		95% Cl for OR		
Variable	OR	Lower	Upper	p-value
Lifetime ICE use	2.0	1.2	3.3	0.006
Lifetime Ecstasy use	-	-	-	-
Lifetime Hypnotics use	-	-	-	-

Correlates of lifetime substance-induced anxiety disorders

Female cocaine users were more likely than male users to develop anxiety disorders ($p = 0.021$) (Table 23). No significant difference was observed in cocaine use patterns (Table 24) between subjects with and subjects without substance-induced anxiety disorders. Regarding other drug use, subjects with substance-induced anxiety disorders were more likely to report lifetime ICE use than those without such disorders ($p < 0.001$) (Table 25). In the logistic regression model, lifetime ICE use (OR = 3.1, 95% CI = 1.7–5.4, $p < 0.001$) was found to be an independent predictor of substance-induced anxiety disorders (Table 26).

Table 23. Demographic characteristics of subjects with and without lifetime substance-induced anxiety disorders.

	With substance-induced anxiety disorders n = 79	Without substance-induced anxiety disorders n = 181	p-value
Age	27.0 ± 7.6	27.7 ± 7.6	0.297[a]
Gender (female), n (%)	34 (43.0)	50 (27.6)	0.021[b]
Education (year)	9.3 ± 1.8	9.7 ± 1.9	0.063[a]
Marital status, n (%)			
Single	61 (77.2)	146 (80.7)	0.810[c]
Married	16 (20.3)	30 (16.6)	
Separated	2 (2.5)	4 (2.2)	
Widowed	0 (0.0)	1 (0.6)	
Occupation, n (%)			
Unemployed	71 (89.9)	151 (83.4)	0.251[b]
Employed	8 (10.1)	30 (16.6)	
Source of referral, n (%)			
Non-residential	14 (17.7)	45 (24.9)	0.260[b]
Residential	65 (82.3)	136 (75.1)	
Family psychiatric history, n (%)	10 (12.7)	24 (13.3)	1.000[b]
Has a religious belief, n (%)	35 (44.3)	78 (43.1)	0.448[c]
Accommodation, n (%)			
Public housing	47 (59.5)	97 (53.6)	0.844[c]
Private housing	25 (31.6)	66 (36.5)	
Home Owner Scheme housing	6 (7.6)	16 (8.8)	
Others	1 (1.3)	2 (1.1)	
Smoking history, n (%)			
Current	41 (51.9)	110 (60.8)	0.125[c]
Previous	38 (48.1)	67 (37.0)	
Non-smoker	0 (0.0)	4 (2.2)	
Onset age	13.2 ± 2.0	13.7 ± 2.6	0.327[a]

[a] Mann-Whitney Test; [b] Fisher's Exact Test; [c] Pearson Chi-Square test.

Table 24. Cocaine use patterns in subjects with and without lifetime substance-induced anxiety disorders.

Variables	With substance-induced anxiety disorders n = 79 Mean ± SD, Median (range)	Without substance-induced anxiety disorders n = 181 Mean ± SD, Median (range)	p-value[a]
Age of first use	20.0 ± 6.0 18.0 (12.0 – 38.0)	20.4 ± 7.2 18.0 (11.0 – 55.0)	0.699
Duration of use (year)	4.6 ± 3.8 4.0 (0.08 – 22.0)	4.9 ± 4.1 4.0 (0.2 – 24.3)	0.792
Days of use			
Lifetime	937.8 ± 960.3 575.0 (30.3 – 5308.0)	1042.0 ± 1947.6 728.0 (28.5 – 24358.0)	0.991
Past two year	303.2 ± 206.2 273.0 (20.0 – 702.0)	311.7 ± 217.0 268.7 (20.0 – 728.0)	0.898
Past one year	140.8 ± 106.1 117.0 (20.0 – 364.0)	155.00 ± 106.2 130.0 (20.0 – 364.0)	0.294
Previous month	1.7 ± 5.4 0.0 (0.0 – 30.0)	1.8 ± 5.4 0.0 (0.0 – 30.0)	0.933
Lifetime consumption (gram)			
Total	1694.5 ± 2095.2 1016.2 (24.3 – 10192.0)	1742.4 ± 2480.6 838.4 (7.4 – 16957.0)	0.718
Total / body weight (kilogram)	28.0 ± 34.9 14.0 (0.4 – 168.0)	40.6 ± 184.5 13.6 (0.1 – 2439.0)	0.638
Consumption in one day	2.0 ± 2.1 1.4 (0.2 – 11.4)	2.0 ± 2.5 1.1 (0.1 – 21.0)	0.445
Consumption in the past two years (gram)			
Total	716.1 ± 961.3 404.0 (1.1 – 4368.0)	663.0 ± 1105.8 312.0 (2.3 – 7280.0)	0.583
Total / body weight (kilogram)	12.0 ± 17.4 5.6 (0.01 – 98.0)	10.1 ± 15.6 4.6 (0.03 – 88.7)	0.570
Consumption in one day	2.1 ± 2.5 1.3 (0.01 – 12.0)	1.8 ± 2.5 1.0 (0.04 – 24.0)	0.431
Consumption in the past one year (gram)			
Total	353.1 ± 626.6 124.4 (9.0 – 4368.0)	330.2 ± 661.6 151.7 (3.0 – 7280.0)	0.814

Variables	With substance-induced anxiety disorders n = 79 Mean ± SD, Median (range)	Without substance-induced anxiety disorders n = 181 Mean ± SD, Median (range)	p-value[a]
Total / body weight (kilogram)	5.8 ±10.1 1.6 (0.2 – 66.3)	4.9 ± 7.8 2.3 (0.05 – 61.7)	0.872
Consumption in one day (gram)	2.0 ± 2.3 1.2 (0.1 – 12.0)	1.8 ± 2.5 1.0 (0.1 – 24.0)	0.510
Ice consumption in the previous month (gram)			
Total	2.1 ± 7.3 0.0 (0.0 – 40.0)	2.6 ± 9.7 0.0 (0.0 – 72.0)	0.936
Total / body weight (kilogram)	0.04 ±0.1 0.0 (0.0 – 0.8)	0.04 ± 0.2 0.0 (0.0 – 1.1)	0.944
Consumption in one day	0.3 ± 1.2 0.0 (0.0 – 10.0)	0.2 ± 0.7 0.0 (0.0 – 7.0)	0.992
Current dependence, n (%)	8 (10.1)	23 (12.7)	0.077[b]
Low	2 (2.5)	9 (5.0)	
Medium	3 (3.8)	11 (6.1)	
High	3 (3.8)	3 (1.7)	
Current abuse, n (%)	4 (5.1)	11 (6.1)	1.000[b]
Lifetime dependence, n (%)	76 (96.2)	174 (96.1)	1.000[b]
Low	34 (43.0)	40 (22.1)	
Medium	12 (15.2)	63 (34.8)	
High	30 (38.0)	71 (39.2)	
Lifetime abuse, n (%)	2 (2.5)	6 (3.3)	1.000[b]

[a] Mann-Whitney Test; [b] Fisher's Exact Test

Table 25. Other drug use in subjects with and without lifetime substance-induced anxiety disorders.

Lifetime use	With substance-induced anxiety disorders N = 79	Without substance-induced anxiety disorders N = 181	p-value[a]
Ketamine	59 (74.7)	125 (69.1)	0.378
Cannabis	57 (72.2)	120 (66.3)	0.388
ICE	56 (70.9)	80 (44.2)	<0.001
Ecstasy	42 (53.2)	84 (46.4)	0.346
Hypnotics	38 (48.1)	74 (40.9)	0.341
Cough medicine	12 (15.2)	14 (7.7)	0.075

[a] Fisher's exact test.
ICE: methamphetamine; SD: standard deviation.

Table 26. Logistic regression of predictors of lifetime substance-induced anxiety disorders.

		95% Cl for OR		
Variable	OR	Lower	Upper	p-value
Gender	-	-	-	-
Lifetime ICE use	3.1	1.7	5.4	<0.001
Cocaine current dependence	-	-	-	-
Lifetime Cough medicine use	-	-	-	-

ICE: methamphetamine

Severity and correlates of psychiatric symptoms

The mean BDI, HADSA, SDS and BPRS scores of all subjects were 13.4 ± 10.1, 4.8 ± 4.0, 9.3 ± 3.1 and 18.5 ± 1.4, respectively, and all subjects scored below the respective cut-off points. The mean total PANSS score was 33.6 ± 2.0, while the mean PANSS scores for the positive, negative and general psychopathology items were 7.1 ± 0.5, 7.1 ± 0.7 and 16.4 ± 1.1, respectively. None of the subjects scored higher than the cut-off points (Leucht et al., 2005).

The correlations between psychiatric symptoms, demographic characteristics and patterns of cocaine and other drug use are shown in Tables 27–29. The subsequent linear regression models are shown in Tables 30–34. The models showed that the number of days of cocaine use in the previous month (beta = 0.4, $p < 0.001$), source of referral (beta = -3.5, $p = 0.022$) and education level (beta = -0.8, $p = 0.014$) were predictors of the BDI score (Table 30); the number of days of cocaine use in the previous month (beta = 0.2, $p < 0.001$) was a predictor of the HADSA score (Table 31); and the education level (beta = -0.1, $p = 0.016$), smoking history (beta = 0.4, $p = 0.014$) and lifetime ICE use (beta = 0.3, $p = 0.042$) were predictors of the BPRS score (Table 32).

Education level was a predictor of the PANSS total (beta = -0.2, $p = 0.015$), positive (beta = -0.3, $p = 0.027$) and general psychopathology (beta = 0.1, $p = 0.043$) scores. Smoking history was a predictor of the PANSS general psychopathology score (beta = 0.3, $p = 0.012$), whereas the source of referral was a predictor of the PANSS total (beta = 0.9, $p = 0.001$) and positive psychopathology (beta = 0.2, $p = 0.005$) scores; no predictor of the PANSS negative score was found. Regarding drug factors, lifetime ICE use was a predictor of the PANSS general psychopathology score (beta = 0.3, $p = 0.026$), and lifetime ecstasy use was a predictor of the PANSS positive psychopathology score (beta = -0.1, $p = 0.027$) (Table 33). Lastly, the number of days of cocaine use in the past 2 years (beta = 0.002, $p = 0.005$), lifetime cocaine consumption in a day (beta = 1.2, $p = 0.031$) and lifetime cocaine dependence (beta = 3.4, $p < 0.001$) were predictors of the SDS score.

Table 27. Correlations between psychiatric symptoms and demographic characteristics.

Variables [a]	BDI	HADSA	BPRS	PANSS	PANSS positive	PANSS negative	PANSS GP	SDS
Age [b]	0.026	0.036	0.035	0.009	0.074	-0.077	0.033	0.070
Gender	0.095	0.045	0.113^	0.114^	0.068	-0.052	0.107^	-0.062
Education [b]	-0.140*	-0.077	-0.172**	-0.145*	-0.129*	-0.078	-0.151*	0.032
Marital Status	-0.077	-0.023	-0.094	-0.093	-0.039	0.031	-0.080	-0.086
Occupation	0.052	0.055	0.060	0.058	0.052	0.030	0.040	-0.002
Sources of referral	0.207**	0.180**	0.122	0.117^	0.170**	0.084	0.108^	-0.130*
Smoking history	0.101	0.064	0.195**	0.195**	0.107^	0.128*	0.181**	-0.051
Family psychiatry history	0.084	0.093	0.023	0.027	0.126*	0.042	0.036	0.092
Has a Religious belief	0.007	-0.019	0.020	0.021	-0.047	0.014	0.048	-0.080
Accommodation	-0.039	-0.056	0.041	0.041	-0.019	0.036	0.037	-0.002

** $p < 0.01$
*$p < 0.05$;
^$p < 0.1$
[a] Spearman correlation; [b] Pearson correlation.

Table 28. Correlations between psychiatric symptoms and cocaine use patterns.

Variables[a]	BDI	HADSA	BPRS	PANSS	PANSS positive	PANSS negative	PANSS GP	SDS
Onset Age	-0.018	0.026	0.050	0.053	0.109^	-0.033	0.068	-0.065
Duration	0.002	-0.024	0.005	-0.050	0.006	-0.057	-0.053	0.113^
Days of cocaine use								
Lifetime	-0.037	-0.049	-0.043	-0.050	-0.030	-0.040	-0.051	0.125*
Past two years	-0.073	-0.090	-0.091	-0.087	-0.056	-0.117^	-0.055	0.223**
Past one year	0.019	-0.016	-0.061	-0.069	-0.082	-0.100^	-0.024	0.207**
Previous month	0.264**	0.220**	0.028	-0.004	-0.030	-0.039	0.030	0.002
Lifetime consumption								
Total	-0.064	-0.051	-0.025	-0.028	-0.032	-0.074	0.001	0.212**
Total / body weight	0.089	-0.008	0.028	0.016	-0.013	-0.027	0.044	0.080
Consumption in one day	-0.025	0.061	0.018	0.057	0.019	0.013	0.081	0.228**
Consumption in the past two years								
Total	-0.068	-0.040	-0.045	-0.033	-0.053	-0.052	-0.009	0.210**
Total / body weight	-0.041	-0.027	-0.016	-0.012	-0.053	-0.056	0.028	0.187**
Consumption in one day	-0.033	0.000	-0.019	0.019	-0.026	0.015	0.035	0.213**
Consumption in the past one year								
Total	-0.038	-0.032	-0.048	-0.032	-0.053	-0.037	-0.015	0.177**
Total / body weight	-0.014	-0.020	-0.024	-0.015	-0.053	-0.041	0.016	0.154*
Consumption in one day	-0.068	-0.031	-0.045	-0.023	-0.049	-0.025	-0.006	0.217**
Previous month								
Total	.155*	0.119	0.003	-0.011	-0.034	-0.038	0.019	0.029
Total / body weight	.166**	0.117^	0.012	-0.003	-0.033	-0.038	0.032	0.015
Consumption in one day	.182**	.134*	0.044	0.022	-0.015	-0.032	0.065	0.041
Current dependence [b]	.174**	.168**	0.105	0.103	-0.003	0.039	0.091	0.080
Current abuse [b]	0.098	0.078	0.099	0.095	0.053	-0.049	0.094	-0.158*
Lifetime dependence [b]	0.042	0.008	-0.184**	-0.182**	-0.060	-0.008	-0.195**	0.271**
Lifetime abuse [b]	0.017	0.026	0.074	0.066	-0.032	-0.036	0.073	-0.226**

**p < 0.01.

*p < 0.05.

[a] Pearson correlation; [b] Spearman correlation.

BDI: Beck Depression Inventory; HADSA: Hospital Anxiety Depression Scale; PBRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale; GP: General psychopathology; SDS: Severity of Dependence Scale.

Table 29. Correlations between psychiatric symptoms and other drug use patterns.

Variables [a]	BDI	HADSA	BPRS	PANSS	PANSS positive	PANSS negative	PANSS GP	SDS
Lifetime use								
Hypnotics	-0.043	-0.032	-0.064	-0.065	-0.111	-0.053	-0.045	0.086
Cannabis	-0.030	0.066	0.116^	0.116^	0.074	0.094	0.104^	0.058
ICE	-0.001	-0.035	0.164**	0.165**	0.082	0.070	0.165**	-0.006
Cough medicine	0.061	0.141*	-0.021	-0.022	-0.059	0.066	-0.017	0.077
Ecstasy	-0.009	-0.027	-0.048	-0.049	-0.129*	-0.113^	-0.024	0.074
Ketamine	-0.086	-0.106^	0.004	0.002	-0.031	0.041	0.009	0.109^

**p < 0.01.
*p < 0.05.
^p < 0.1
ICE: methamphetamine
[a] Pearson correlation; [b] Spearman correlation
BDI: Beck Depression Inventory; HADSA: Hospital Anxiety Depression Scale; PBRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale; GP: General psychopathology; SDS: Severity of Dependence Scale.

Table 30. Linear regression of the BDI scores.

Variable	Unstandardized beta	95% Cl for OR Lower	Upper	p-value
Day of Cocaine use (previous month)	0.4	0.2	0.6	<0.001
Cocaine consumption in the previous month (grams)				
Total	-	-	-	-
Total / body weight (kilograms)	-	-	-	-
Consumption in one day	-	-	-	-
Current dependence of Cocaine	-	-	-	-
Source of referral (CCPSA)	-3.5	-6.6	-0.5	0.022
Education	-0.8	-1.4	-0.2	0.014

Table 31. Linear regression of the HADSA scores.

Variable	Unstandardized beta	95% Cl for OR Lower	Upper	p-value
Days of cocaine use (previous month)	0.2	0.1	0.3	<0.001
Cocaine consumption in one day (in previous month)	-	-	-	-
Current cocaine dependence	-	-	-	-
Source of referral	-	-	-	-
Lifetime ICE use	-	-	-	-

ICE: methamphetamine

Table 32. Linear regression of the BPRS scores.

Variable	Unstandardized beta	95% Cl for Lower	Upper	p-value
Education	-0.1	-0.2	-0.02	0.016
Gender	-	-	-	-
Smoking history	0.4	0.1	0.7	0.014
Lifetime ICE use	0.3	0.01	0.7	0.042
Lifetime Cocaine dependent	-	-	-	-
Lifetime Cannabis use	-	-	-	-

ICE: methamphetamine

Table 33. Linear regression of the PANSS scores.

	PANSS Total				PANSS Positive				PANSS Negative				PANSS GP			
		95% Cl for OR				95% Cl for OR				95% Cl for OR				95% Cl for OR		
Variable	B	Lower	Upper	p-value	B	Lower	Upper	p-value	B	Lower	Upper	p-value	B	Lower	Upper	p-value
Education	-0.2	-0.3	-0.03	0.015	-0.3	-0.06	-0.04	0.027					-0.1	-0.1	-0.002	0.043
Smoking history	-	-	-	-	-	-	-	-	-	-	-	-	0.3	0.1	0.6	0.012
Gender	-	-	-	-									-	-	-	-
Source of referral	0.9	0.4	1.5	0.001	0.2	0.06	0.3	0.005								
Family psychiatric history						-	-	-								
Onset age of Cocaine use					-	-	-	-								
Total days of Cocaine use in the past two years									-	-	-	-				
Total days of Cocaine use in the past one year									-	-	-	-				
Lifetime cocaine dependence		-	-	-									-	-	-	-
		-	-	-												
Lifetime ICE use		-	-	-									0.3	0.04	0.6	0.026

Lifetime use of ecstasy					-0.1	-0.2	-0.01	0.027	-	-	-	-								
Lifetime use of Cannabis	-	-	-	-													-	-	-	-

B = Unstandardized beta
ICE: methamphetamine

Table 34. Linear regression of the SDS scores.

Variable	Unstandardized beta	95% Cl for OR Lower	Upper	p-value
Source of referral	-	-	-	-
Total duration of Cocaine use	-	-	-	-
Days of cocaine use				
Lifetime	-	-	-	-
Past two years	0.002	0.001	0.004	0.007
Past one years	-	-	-	-
Lifetime cocaine use				
Total	-	-	-	-
Consumption per day	1.2	0.02	0.3	0.032
Cocaine use in the past two years				
Total	-	-	-	-
Total/body weight	-	-	-	-
Consumption per day	-	-	-	-
Cocaine use in the past one year				
Total	-	-	-	-
Total/body weight	-	-	-	-
Consumption per day	-	-	-	-
Lifetime dependence	3.4	1.5	5.4	<0.001
Lifetime Ketamine use	-	-	-	-

Discussion

Characteristics of the sample

The study sample included young and middle-aged adults. The subjects had an average of 10 years of education, and less than one sixth were employed. Most of the subjects were single, living in public housing and current smokers. These characteristics are comparable to those reported for local drug users (Narcotics Division, 2018). The subjects had begun to use cocaine in their early twenties, and the average duration of use was 5 years. More than 95% of the subjects had lifetime cocaine dependence. On average, they had used cocaine for 154 days in the past year and consumed approximately 1.8 grams of cocaine in 1 day. Hence, the sample comprised chronic regular heavy users with dependence. Approximately one tenth of the subjects were currently cocaine-dependent. Apart from cocaine, ketamine, cannabis and ICE were also commonly used. According to the latest statistics of the Hong Kong Narcotics Division, cocaine was the second most popular psychotropic drug in the first quarter of 2022, followed by cannabis, ICE and ketamine.

Substance-induced psychotic disorder (CIP)

More than two thirds of the subjects had a lifetime diagnosis of CIP. In a recent review, the lifetime CIP prevalence ranged from 5% (Herrero et al., 2008) to 75% (Tang et al., 2007), with a median of 53% (Tang et al., in press). The relatively high prevalence of CIP in the present study could be attributable to the pattern of cocaine use in the sample, i.e., all subjects being long-term, regular and heavy users. One fifth of our sample had current CIP; this prevalence is higher than that reported previously (Vergara-Moragues et al., 2012), probably due to differences in the sampling population and assessment methodology.

In the univariate analysis, the presence of CIP was related to the subjects' education level; age at initiation, duration, amount and frequency of cocaine use; and lifetime ICE use. In the subsequent multivariate analysis, the age at cocaine use initiation and total days of cocaine use in the past year remained

significant. Risk factors for CIP/psychotic symptoms can be broadly classified into four groups based on demographic features, cocaine and other drug use characteristics, personal history of psychological or psychiatric problems and family history of psychiatric illness. The risk of developing CIP is dependent on the cocaine dose and, inversely, on the age at drug use initiation. In addition to the chronicity, pattern, severity and route of drug administration, psychological vulnerability predisposes some individuals to acute psychotic symptoms and syndromes in response to cocaine use. CIP has been reported to be more common in subjects who are male; have attention-deficit/hyperactivity disorder, antisocial personality disorder or poly drug use; and have a family history of psychotic disorders. Preliminary evidence suggests that a high body mass index and a high plasma concentration of BDNF are protective against CIP (Roncero et al., 2014).

Based on data from 173 adults with cocaine dependence in Europe (mostly men, mean age 33.6 years), a model comprising the amount of cocaine consumption, diagnosis of an antisocial personality disorder and a history of cannabis dependence predicted the presence of CIP with 66.2% sensitivity and 75.8% specificity (Tang et al., 2014). Future integrative models should incorporate new knowledge of other factors, such as neurobiological markers, routes of cocaine use, lifetime attention-deficit/hyperactivity disorder and personality dimensions (Roncero et al., 2014). Research should be continued with larger samples from local populations. More naturalistic and follow-up studies should be conducted to facilitate the clear identification and delineation of variables that are most closely associated with the occurrence of CIP and psychotic symptoms in cocaine users. Such work would enable the identification of at-risk populations that would benefit from early interventions (Roncero et al., 2012).

The neurobiology of CIP is not well-defined. In the only published neuroimaging study of CIP, smaller thalamus and left hippocampus volumes were found in subjects with CIP than in healthy controls (Willi et al., 2016). The findings of reduced thalamic and hippocampal volumes are consistent with reports in the schizophrenia literature (Haijma et al., 2013). The authors suggested that volume reductions in specific subcortical nuclei may be common to multiple forms of psychosis and may represent a biological

vulnerability to the neurotoxic effects of cocaine. CIP is likely to be a complex genetic disease, susceptibility to which is influenced by the interaction of environmental factors with multiple polymorphic genes (Grant et al., 2012).

Evidence suggests that genetic variations in the dopamine system are associated with the risk of CIP (Tang et al., 2014). These genetic variations may occur in genes that encode dopamine receptors, transporters, enzymes and other proteins. Evidence also supports substantive overlap between markers of genetic vulnerability to CIP and schizophrenia (Cubells et al., 2000). Together, these findings suggest that genetic risk factors affecting dopamine signalling systems contribute to the development of psychosis following cocaine use.

There is preliminary evidence suggesting that sensory gating deficit (as measured by event-related potentials) and plasma BDNF concentrations are important in determining susceptibility to CIP. Sensory gating refers to the brain's ability to filter out irrelevant incoming sensory stimuli, thus protecting the higher cortical centres from being flooded with irrelevant input and preserving the ability to handle relevant stimuli (Freedman et al., 1983). It is a neurobiological mechanism that may contribute to the development of psychotic disorders (Boutros et al., 1991). Research has suggested that chronic cocaine use can impair sensory gating and that cocaine's effects on sensory gating persist for at least 2 weeks of abstinence (Boutros et al., 2000). In addition, an association between sensory gating deficit and the emergence of paranoid symptoms during cocaine use has been reported (Boutros et al., 2002). Sensory gating deficit has been reported in patients with schizophrenia and their first-degree relatives (Boutros et al., 2004). Dopamine-, noradrenaline- and γ-aminobutyric acid-mediated mechanisms have been implicated in the function of sensory gating. Hence, it is reasonable to postulate that the decreased gating observed in CIP reflects the dysregulation of dopamine, noradrenaline and γ-aminobutyric acid tones in these subjects (Boutros et al., 2006).

BDNF is a neurotrophin (Thoenen, 1995) widely expressed in the adult mammalian brain and is a key factor in neuronal survival and neural plasticity in response to environmental stimuli and cognitive stimulation (Fritsch et al., 2011). It also plays a role in cocaine-induced neuroplasticity in different brain regions such as the prefrontal cortex, amygdala, striatum and ventral tegmental area (Corominas-Roso et al., 2007). BDNF interacts with the dopaminergic system and with other neurotransmitters involved in schizophrenia, such as glutamate (Corominas-Roso et al., 2013). One study reported an increase in serum BDNF concentrations during the first 2 weeks of cocaine withdrawal (Corominas-Roso et al., 2013). This increase may mediate neuroplastic changes in brain regions that underlie enhanced responsiveness to cocaine-related cues and drug seeking in these patients (Corominas-Roso et al., 2013). In contrast, in the CIP group, BDNF concentrations showed a decreasing trend during early abstinence. Low plasma BDNF concentrations have been reported in patients with schizophrenia (Xiu et al., 2009) and first-episode psychosis (Rizos et al., 2008). In these patients, postnatal stress appears to mediate the decrease in BDNF concentrations and its consequences for the brain structure (Mondelli et al., 2011). The most frequently studied single nucleotide polymorphism of the *BDNF* gene – Val66Met (Petryshen et al., 2010) – is associated with changes in intracellular trafficking and secretion of the protein (Chen et al., 2004) and affects serum BDNF concentrations (Lang et al., 2009). This polymorphism has also been associated with social stress-induced paranoia (Simons et al., 2009). Together, these data suggest that patients with CIP share some of the BDNF deficiencies that characterise psychosis.

Data on the clinical course of CIP are limited. However, CIP seems to have a favourable course, with most patients recovering within a few days, although the psychotic symptoms may last for a few weeks. It is uncertain whether CIP can re-emerge with repeated use or under stressful conditions. Bramness et al. (2012) hypothesised a vulnerability-to-stress paradigm to explain the relationship between stimulant-induced and primary psychosis. For vulnerable individuals, exposure to stimulants, including cocaine, should be viewed as a stressor. Individuals with lower vulnerability require higher doses of stimulants to precipitate acute psychosis, whereas individuals with higher vulnerability, such as those with a family history of psychosis,

require lower doses. In addition, due to their sensitising effects, stimulants may play a role in the development of vulnerability to psychosis. That is, repeated use of stimulants could increase vulnerability, thereby increasing the chances of developing psychotic symptoms even in the absence of acute exposure to stimulants.

The remission of psychotic symptoms within a few days of cocaine abstinence suggests that most individuals with these symptoms do not require pharmacological intervention. Large randomised clinical trials of treatment regimens for the treatment of acute CIP have not yet been conducted. Clinical experience supports the selective use of antipsychotics, such as olanzapine, risperidone and quetiapine, for the management of acute cocaine-induced psychotic symptoms and agitation. However, little is known about the safety and efficacy of antipsychotics for children and adolescents with CIP, and a sizable number of patients with first-episode CIP fall into this age range. CIP is commonly accompanied by other psychiatric symptoms, including anxiety, agitation and insomnia. Short-term anxiolytics (e.g., benzodiazepines) and sleep medications may be prescribed to target anxiety/agitation and insomnia, respectively. The length of appropriate pharmacological intervention is largely unstudied, although it has been suggested that continuation of antipsychotics beyond 72 hours is usually unnecessary (Tang et al., 2014).

Long-term treatment of CIP should focus on cocaine abstinence to prevent future episodes of psychosis. Psychosocial treatment in the form of cognitive behavioural therapy, contingency management and attendance at 12-step meetings to reduce cocaine use may be considered (Glasner-Edwards & Mooney, 2014). Psychiatric medications may be prescribed to manage comorbid conditions such as major depression or anxiety disorders, given that negative affect states, such as depression or anxiety, may increase relapse risk and worsen treatment outcomes amongst stimulant users (Glasner-Edwards & Mooney, 2014).

Pattern of psychotic symptoms

More than 80% of our subjects had lifetime psychotic symptoms. In terms of subtypes of psychotic symptoms, approximately three quarters of the subjects reported lifetime delusions, and two thirds reported hallucinations. Delusion of reference was the most common delusion, followed by persecutory delusion. Auditory hallucination was the most frequent type of hallucination, followed by visual and tactile hallucinations. Thought broadcasting was uncommon, and negative symptoms were rare. A recent literature review suggested that the most frequently reported symptoms of CIP are delusions of persecution and auditory hallucinations. Other symptoms such as disorganised behaviour or speech, catatonic behaviours, negative symptoms, confusions and stereotypies have also been reported (Tang et al., in press). The symptoms of CIP are similar to those of schizophrenia. However, recovery from CIP seems to be faster, and it appears to resolve more completely than schizophrenic psychosis. There are several potential discriminators of CIP, namely, prominent visual illusions and hallucinations, symptoms related to paranoid themes, lack of formal thought disorders and grandiose delusions (Rosse et al., 1995; Unnithan & Cutting, 1992; Vergara-Moragues et al., 2016).

PPS

Approximately one sixth of our subjects had PPS. In the univariate analysis, PPS was related to the subjects' education level, family history of psychiatric diseases and lifetime use of ICE and cough medicine. In the subsequent multivariate analysis, the education level, family history of psychiatric diseases and lifetime ICE were found to be predictors of PPS.

Little is known about the prevalence and risk factors of PPS in cocaine users, whereas PPS is a well-known phenomenon in ICE users. Some patients with ICE-induced psychosis do not remit for weeks or months, exhibiting the so-called 'prolonged type' of ICE-induced psychosis (Harro, 2015). Even if symptoms abate with abstinence, in 25% to 38% of ICE users, ICE-induced psychosis can re-emerge with

repeated use or under stressful situations. If relapse to psychosis follows ICE use, it typically occurs promptly, with 60% of ICE users relapsing in less than a week and 80% relapsing within a month (Grant et al., 2012). The propensity for ICE use to trigger psychosis among individuals who have previously experienced psychotic symptoms can persist for years and has been described as 'ICE sensitisation' (Glasner-Edwards & Mooney, 2014). Several theories explain how psychosis can become chronic and persistent among ICE users: (a) pre-existing schizophrenia may be unmasked or triggered by ICE use; (b) ICE-induced psychosis may share a similar clinical course to schizophrenia; or (c) ICE-induced psychosis and primary psychosis may not be distinct diagnostic entities but rather fall along a continuum of psychosis (Glasner-Edwards & Mooney, 2014). Indeed, persistent ICE-induced psychosis may have similar vulnerability biomarkers as schizophrenia. In a study on exploratory eye movements, the response search scores (a measure of exploratory eye movements) of patients with persistent ICE-induced psychosis were lowest, being significantly lower than those of patients with transient-type psychosis and healthy controls. Furthermore, the scores did not differ from those of patients with schizophrenia (Mikami et al., 2003).

Mood disorders

In this study, half of the subjects had lifetime substance-induced mood disorder, with the predominant presentation being depressive episodes. Studies have also reported that mood disorders are common amongst cocaine users. In a sample of 115 Spanish cocaine-dependent users, 24% of the subjects had clinical depression, as indicated by their symptom scores (López et al., 2007). In a group of 25 men in recuperation from substance dependency, the prevalence of depression was 32% (Paiva et al., 2017). Further, 30% of 30 cocaine abusers attending a psychiatric clinic had bipolar disorder (Nunes et al., 1989). Finally, the lifetime prevalence of mania/hypomania was 3.7%/7.4% in a sample of 298 hospitalised help-seeking cocaine abusers (Rounsaville et al., 1991).

In this study, the subjects' education level and duration of cocaine use were significant predictors of substance-induced mood disorder. In a meta-analysis, depression was reported to be modestly but consistently associated with measures of cocaine use among cocaine users (Conner et al., 2008). Greater clergy-based support was associated with fewer reported depressive symptoms in a sample of 223 cocaine users (Montgomery et al., 2014).

The neurobiology of cocaine-induced mania is unknown. Increased dopaminergic neurotransmission has been implicated in the pathophysiology of bipolar disorder (Anand et al., 2000). Stimulants such as amphetamine that increase dopamine and norepinephrine release have behavioural effects resembling mania (Jacobson & Silverstone, 1986). In one study, amphetamine challenge led to a significantly greater behavioural response in patients with bipolar disorder than in healthy subjects. However, the amphetamine-induced increase in striatal dopamine release was not significantly different between the two groups. These data are consistent with enhanced postsynaptic dopamine responsivity in patients with bipolar disorder (Anand et al., 2000).

The mechanism underlying the association between depressive symptoms and cocaine dependence is also not clear. In an animal study, the long-term effect of sub-chronic cocaine exposure was a general reduction in locomotor activity. Cocaine exposure induced alterations in BDNF concentrations similar to those observed in several animal models of depression. Finally, cocaine exposure significantly enhanced the anhedonic effect of chronic mild stress. These results suggest that sub-chronic cocaine exposure induces depressive-like behaviour, which is accompanied by modifications in BDNF expression and increased susceptibility to depressive-like behaviour following chronic stress (Zikha et al., 2014). The neurotrophic hypothesis suggests that a reduction in neuroplasticity and BDNF expression could contribute to depression and that antidepressants mediate their therapeutic benefit, in part by increasing the concentration of this factor in the hippocampus (Russo & Nestler, 2013).

Carvalho et al. (2012) postulated that the neurotoxicity induced by stimulants was associated with mood disturbance. Research in humans has demonstrated that the dopamine and dopamine transporter concentrations in the striatum and prefrontal cortex, as well as the global serotonin transporter density, all of which are theorised to be associated with depression, were reduced in patients with stimulant dependence (Sekine et al., 2006), even after stimulant abstinence (Sekine et al., 2001). Additionally, studies in rodents have revealed that stimulants can lead to substantial decreases in the concentrations of dopamine, 5-hydroxytryptamine (serotonin) and other depression-associated markers of the monoaminergic system in various brain regions (Graham et al., 2008).

A recent review suggested that substance use has a substantial effect on the recognition and management of bipolar disorder. Integrated psychosocial interventions are helpful in decreasing substance abuse. The following medications were evaluated in a previous study: lithium carbonate, valproate, lamotrigine, topiramate, naltrexone, acamprosate, disulfiram, quetiapine and citicoline (Salloum & Brown, 2017). The results of three randomised, placebo-controlled studies of dual-diagnosis patients treated with carbamazepine, lithium and valproate support the use of these agents in such patients (Vornik & Brown 2006). Another review of psychosocial interventions found that no treatment could consistently reduce both mood symptoms and substance use (Gold et al., 2018).

In terms of depression treatment in cocaine users, a recent review of clinical trials supported the use of antidepressant medications for combined cocaine dependence and depression. Most negative studies have evaluated serotonin reuptake inhibitors, while positive studies have used agents such as desipramine or buproprion. The literature on clinical trials supports the efficacy of behavioural treatments in general populations of cocaine abusers and patients with depression, but few studies have evaluated their efficacy in patients with both cocaine use disorder and depression (Rounsaville et al., 2004). Only one study showed that a standard contingency management intervention for crack cocaine abstinence significantly reduces depressive symptoms (Miguel et al., 2017).

Anxiety disorders

In this study, lifetime substance-induced anxiety disorder was found in 30% of the subjects, with obsessive–compulsive features being the most frequent presentation, affecting one third of the subjects, followed by phobic symptoms. The prevalence of anxiety disorders in previous studies on cocaine users ranged from 10% to 43%. In a study of 50 cocaine users, 10% reported anxiety (Zubaran et al., 2013). In a study of 139 young adults who were current regular cocaine users, 13% had anxiety disorders (Herrero et al., 2008). In a sample of 298 treatment-seeking cocaine abusers, 21% had anxiety disorders (Rounsaville et al., 1991). In a cohort study of 387 cocaine users, 43% qualified for an anxiety disorder (Roy et al., 2015). In a clinical trial, 14% of the 158 subjects had social phobia (Myrick & Brady, 1997). Finally, in an epidemiological study, cocaine use increased the risk of panic attacks by up to 13 folds (Anthony et al., 1989).

In this study, lifetime cocaine consumption and ICE use were identified as predictors of substance-induced anxiety disorders. Anxiety disorders in cocaine users have been shown to be associated with injecting the drug (Roy et al., 2015). The comorbidities of social phobia and post-traumatic stress disorder with cocaine use tend to occur among individuals with severe cocaine use, a personal background or family history of psychiatric disorders (Zubaran et al., 2013) and polysubstance use (Myrick & Brady, 1997). Anxiety disorders are common in ICE users (Hartwell et al., 2016).

Only a few published studies have examined treatment of anxiety disorders in cocaine users. A 12-week contingency management for crack cocaine abstinence was shown to significantly reduce anxiety symptoms in 65 cocaine users (Miguel et al., 2017). Behavioural addiction treatment was reported to reduce the prevalence of comorbid anxiety disorder over 6 months in 95 individuals with cocaine dependence (Kertesz et al., 2006). A 12-week treatment with reboxetine, a selective noradrenaline reuptake inhibitor, was demonstrated to reduce anxiety symptoms in 26 subjects with cocaine dependence (Szerman et al., 2005). In

another study, five sessions of repetitive bilateral transcranial direct current stimulation over the dorsolateral prefrontal cortex decreased anxiety in 17 male cocaine users (Batisa et al., 2015).

Limitations

First, the route of cocaine administration was not assessed in this study. Kaye and Darke (2004) found that the prevalence and extent of psychological symptoms were greater among injecting cocaine users than among non-injecting users. However, the route of administration was not a significant independent predictor of harm when other factors, such as the frequency of use and level of dependence, were taken into account (Kaye & Darke, 2004). Second, because most of the cocaine users had also abused or were dependent on other illicit substances, these substances may have contributed to the development of psychotic symptoms. Third, this study aimed to quantify the subjects' lifetime consumption of cocaine. Reliance on the subjects' ability to recall cocaine use patterns over a longer duration may have reduced the reporting accuracy due to memory deficits or impairment among cocaine-dependent users (Chang et al., 2002). Fourth, some potential confounders were not assessed, such as childhood adversity, schizotypal personality or antisocial personality. Fifth, the subjects were all recruited from various treatment facilities; hence, the findings may not be applicable to non-treatment-seeking cocaine users. Sixth, no urine testing was performed to confirm recent use of cocaine.

Future research directions

In terms of study design, a long-term prospective study may provide further insight into the complex interplay between cocaine use and CIP. A large population-based sample and an enriched sample that includes equal proportions of men and women with minimal concurrent use of other illicit substances would increase the generalisability of the findings. Healthy controls should be recruited as well. It is recommended that recent cocaine use be confirmed using urine tests. Detailed measurements of possible confounders, such

as childhood and adolescent adversity, premorbid intelligence, learning disabilities, personality disorders or a family history of psychiatric disorders, would also strengthen any future studies.

Conclusions

This study found that CIP was common among local cocaine users and that a longer duration of cocaine use increased the risk of CIP. Psychotic symptoms, such as delusions and hallucinations, were also frequent in this population. One sixth of the users had PPS, the risk factors for which are lifetime ICE use and a family history of psychiatric diseases. Lifetime mood and anxiety disorders were also frequent in our sample, with the predominant presentations being depressive episodes and obsessive–compulsive features. Lifetime ICE use was identified as a risk factor for mood and anxiety disorders.

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