Research report on

Cocaine Induced Psychosis: a Literature Review

Submitted to

Beat Drug Fund Association

Submitted by

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Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder

BDNF: brain-derived neurotrophic factor

CEQ: cocaine experience questionnaire

CIP: cocaine-induced psychosis

CSP: cortical silent period

DβH : Dopamine β-hydroxylase

DSMIV: Diagnostic and Statistical Manual of Mental Disorders,4th edition

ERPs: event-related potentials

CIDI-SAM: Composite International Diagnostic Interview – Substance Abuse Module

CIP: Cocaine induced psychosis

MIP: methamphetamine-induced psychosis

NSF: N-ethylmaleimide sensitive factor

PPD: primary psychotic disorders

PRISM: Psychiatric Research Interview for Substance and Mental Disorders

SAPS-CIP: Scale for Assessment of Positive Symptoms for Cocaine-Induced Psychosis

SCID: Structured Clinical Interview for DSM-IV

SSADDA: Semi-Structured Assessment for Drug Dependence and Alcoholism

SNP: single neucleotide polymorphism

Background

As one of the most potent naturally occurring central nervous system stimulants, cocaine has a long history of use and abuse (Ellenhorn et al., 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, which 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 headaches (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 about 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., 2008). Cocaine consumption can induce transient psychotic symptoms or complete psychosis (Roncero et al., 2014(a)). Studies conducted in psychiatric settings have reported prevalences of cocaine-induced psychosis (CIP) ranging between 29% (Roncero et al., 2012) and 86.5% (Vorspan et al., 2012). Common psychotic symptoms

of cocaine use include paranoid delusions and hallucinations. Other clinical features are 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 most frequently report the delusion that they are surrounded by agents of the law or by 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 the skin (Roncero et al., 2012).

CIP refers to 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% (Herrero et al., 2008) in young cocaine users not seeking treatment to 40.6% (Roncero et al., 2014(b)) in outpatient clinics (Roncero et al., 2014(a)). According to our own database, of 71 current cocaine users attending a local substance abuse clinic, 49% had psychosis, 23% had a mood disorder and 3% had an anxiety disorder (Tang, unpublished).

Risk factors for CIP include higher consumption of cocaine (Floyd et al., 2006), early age of onset of use (Floyd et al., 2006), longer 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 may be related to CIP (Cubells et al., 2000; Gelernter et al., 1994). Other possible biomarkers of CIP are deficits in evoked potentials (Boutros et al., 2006) and brain-derived neurotrophic factor (Corominas-Roso et al., 2013(a)). The pathogenesis of CIP may include a blockage of dopamine reuptake, increased levels of norepinephrine and serotonin and a sensitising response (Tang et al., 2014).

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

A systematic review of data on the prevalence, clinical features and risk factors for CIP is lacking. We therefore conducted a comprehensive literature review on the risk factors, frequency, symptoms, pathomechanism and treatment of CIP. The findings of this study will be beneficial for policymaking in the areas of education, prevention campaigns and service provision for local cocaine users.

Objectives

To identify the risk factors, frequency, symptoms, pathomechanism and treatment of CIP through a comprehensive literature review.

Methods

Data sources

The principal investigator (WK Tang) conducted a PubMed search using the keywords 'cocaine' and 'psychosis' to identify relevant articles (limits: English language, published between 1966 and 2018, human studies, abstracts available) in April 2018. In total, 415 abstracts were screened by hand to exclude preclinical studies, review articles that had been superseded by more recent reviews and other papers judged to be of lesser relevance to the study objectives. Reference lists were used to identify further relevant articles.

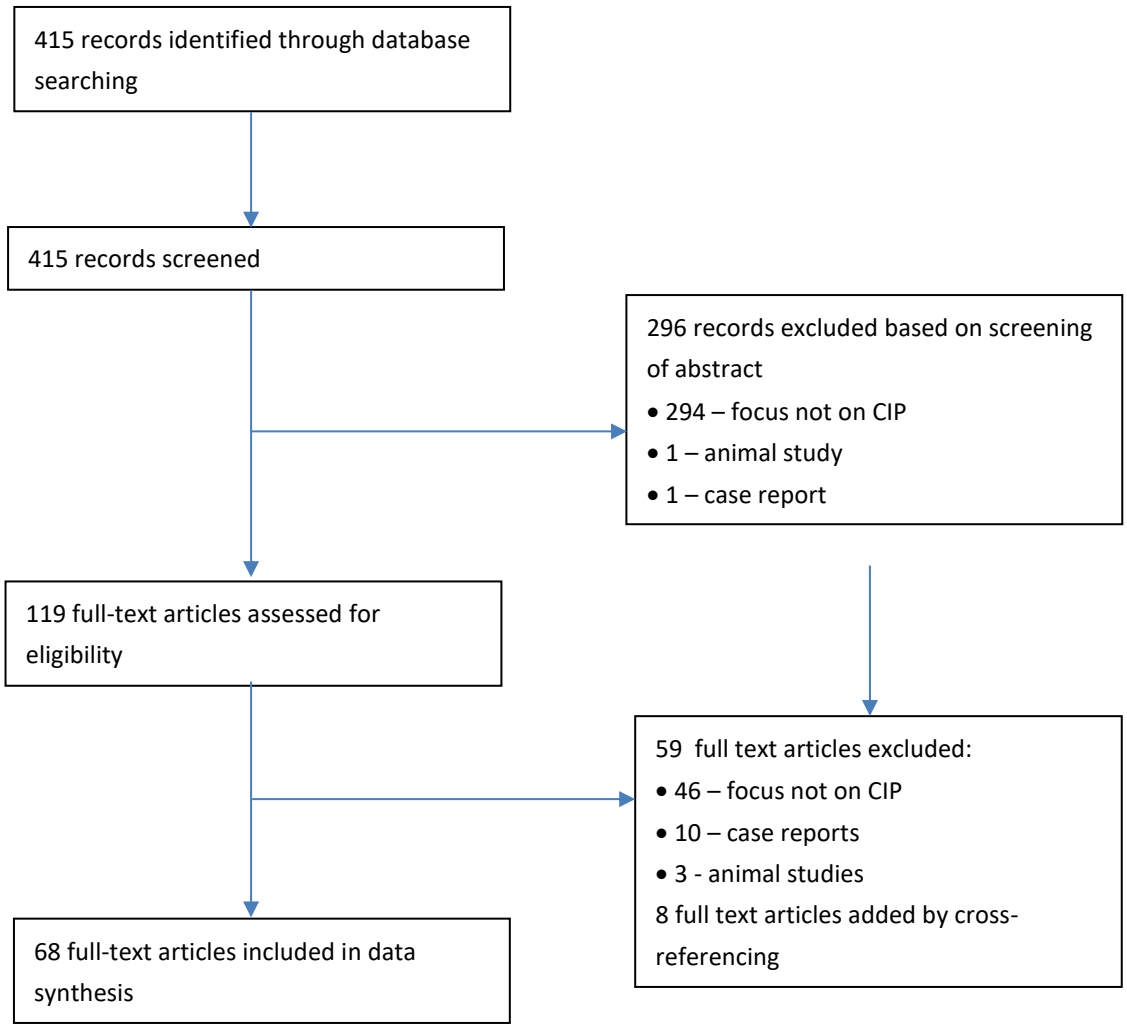
Data extraction

The principal investigator screened the titles and abstracts of all 415 records, 296 of which did not meet the eligibility criteria. Full-text versions of the remaining 119 articles were then screened by the principal investigator. This screening excluded a further 59 papers. Finally, eight articles were added by cross-referencing (Figure 1).

Data synthesis

A standardised form was created to record data extracted from each eligible record. Information regarding the design, size, scope, sample, methods, results and limitations of each study was then entered by a research assistant and checked independently for accuracy and completeness by the principal investigator (Marshall & Werb, 2010).

Figure 1. Systematic search of English-language articles



Results

Prevalence of CIP

Studies examining the prevalence of CIP are listed in Table 1. These studies differed in their methodologies. For instance, subjects were variously recruited from psychiatric hospitals (Manschreck et al., 1988), drug treatment or rehabilitation centres (Vergara-Moragues et al., 2012(a)), the community (Herrero et al., 2007) and unspecified sites (Gelernter et al., 1994). The extent of cocaine use amongst the subjects included regular use (Herrero et al., 2007), pathological use (Araos et al., 2015) and dependence (Vergara-Moragues et al., 2012(a)). Common exclusion criteria were a history of primary psychotic disorder (PPD) (Roncero et al., 2017) and other drug dependence (Brady et al., 1991).

Assessments of psychosis were commonly carried out using standardised instruments, such as the Structured Clinical Interview for DSM-IV (SCID, Roncero et al., 2017), Psychiatric Research Interview for Substance and Mental Disorders (PRISM; Herrero et al., 2007), Cocaine Experience Questionnaire (CEQ, Gelernter et al., 1994) and Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA, Zayats et al., 2013). A few studies relied on clinical interviews (Roncero et al., 2014(c)), self-reports (Herback et al., 2006) or reviews of medical records (Manschreck et al., 1988).

In five studies, the diagnosis of CIP was made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria (Herrero et al., 2007) (Table 2). Other definitions of CIP included ‘cocaine-induced paranoia’

(Gelernter et al., 1994), ‘psychotic symptoms caused by use’ (Roncero et al., 2014 (c)) and unspecified criteria (Manschreck et al., 1988).

The limitations of these studies include retrospective design (Manschreck et al., 1988), self-report of psychotic symptoms (Herback et al., 2006), a selective sampling frame such as psychiatric hospital (Manschreck et al., 1988), small sample size (Trape et al., 2014) and concurrent use of other substances (Vergara-Moragues et al., 2012(a)).

The prevalence of CIP ranged from 5% amongst 139 subjects recruited outside health-care services (Herrero et al., 2007) to 75% amongst 243 subjects recruited through clinical referral (Tang et al., 2007). The median prevalence of CIP was 53%. In a review paper, the prevalence of CIP ranged from 7% to 41% (Roncero et al., 2014 (b)). In two studies, only the prevalence of psychosis in general was reported, and it ranged from 11% to 29% (Manschreck et al., 1998; Herback et al., 2006).

Table 1. Studies examining the prevalence of CIP.

Study citation/country	Study sample	Assessment and criteria of CIP	Findings
Roncero et al., 2014(b)	Literature review	-	7% to 41% had CIP
Herrero et al., 2007 Spain	N = 139, 63% male, mean age = 24 Subjects with regular cocaine use Recruited outside health-care services by targeted sampling and chain referral methods	PRISM DSM-IV criteria	5% had substance induced psychosis
Vergara-Moragues et al., 2012(a) Spain	N = 227, 91% male, mean age = 35 Patients with cocaine dependence Recruited from a substance abuse clinic	PRISM DSM-IV criteria	11.5% / 9.3% had lifetime / current CIP
Roncero et al., 2017 Spain	N = 767, 80% male, mean age = 37 Patients with cocaine dependence Recruited from an addiction and dual diagnosis unit	SCID DSM-IV criteria	13% had CIP
Araos et al., 2015 Spain	N = 82, 82% male, mean age = 37 Patients with pathological use of cocaine. Recruited from outpatient treatment program for cocaine addiction	PRISM DSM-IV criteria	13% had CIP

Roncero et al., 2014(c) Spain	N = 143, 82% male, mean age = 34 Patients with cocaine dependence Recruited from outpatient and inpatient drug unit	PRISM Had psychotic symptoms and were not aware that these symptoms were caused by cocaine.	41% had CIP
Brady et al., 1991 USA	N = 55, sex distribution unknown, mean age = 30 Patients with cocaine dependence Recruited from inpatient unit for the treatment of cocaine dependence	Semi-structured interview	53% had CIP
Roncero et al., 2013(c) Spain	N = 173, 80% male, mean age = 34 Patients with cocaine dependence Recruited from a substance use disorders unit	Structured interview Had psychotic symptoms.	54% had CIP
Gelernter et al., 1994 USA	N = 104, 96% male, mean age = 34 Subjects with cocaine dependence Recruitment site and method unknown	CEQ Cocaine induced paranoia	54% had CIP
Kalayasiri et al., 2010; Kalayasiri et al., 2006 USA	N = 1140, 50% male, mean age = 39 Subjects with cocaine dependence Recruited by advertisement or referral	SSADDA Cocaine induced paranoia	65% had CIP
Trape et al., 2014 France	N = 53, 85% male, mean age = 40 Patients with cocaine dependence Recruited from six therapeutic communities	CEQ Cocaine induced paranoia	66% had CIP
Zayats et al., 2013 USA	N = 2192, Subjects with cocaine dependence Recruited sites unknown	SSADDA DSM-IV criteria	68% had CIP

Tang et al., 2007 **USA**	N = 243, 59% male, mean age = 40 Subjects with cocaine dependence Recruited through clinical referral, advertising, and word of mouth	CEQ Cocaine induced paranoia	75% had CIP
Cubells et al., 2005 **USA**	N = 241, 59% male, mean age = 40 Subjects with cocaine dependence Recruited through clinical referral, advertising, and word of mouth	CEQ Cocaine induced paranoia	75% had CIP
Morton et al., 1999	Literature review	-	29% to 53% had psychosis
Herback et al., 2006 **USA**	N = 266, 100% male, mean age = 49 Patients with cocaine dependence and without psychosis at baseline Recruited from an inpatient substance use disorders unit	Self-report Psychotic disorders for which they received treatment	11% had psychosis
Manschreck et al., 1988 **USA**	N = 106, 81% male, mean age = 27 Patients with cocaine disorders Recruited from a psychiatric hospital	Review of medical record	29% had psychosis

CEQ=Cocaine Experience Questionnaire; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, PRISM=Psychiatric Research Interview for Substance and Mental Disorders, SCID=Structured Clinical Interview for DSM-IV (SCID), Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA).

Table 2. DSM-IV diagnostic criteria for substance (Amphetamines)-induced psychotic disorder.

A. Prominent hallucinations or delusions.
B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):
(1) **the symptoms in criteria A developed during, or within a month of, Substance Intoxication or Withdrawal;**
(2) **substance use is etiologically related to the disturbance.**
C. The disturbance is not better accounted for by a psychotic disorder that is not substance induced such as:
(1) **the symptoms precede the onset of the substance use;**
(2) **the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of what would be expected given the type or amount of substance used or the duration of use;**
(3) **there is other evidence that suggests the existence of an independent non-substance-induced Psychotic Disorder (e.g., a history of recurrent non-substance-related episodes).**
D. The disturbance does not occur exclusively during the course of a delirium.

Pattern of psychotic symptoms in CIP

Studies examining the pattern of psychotic symptoms in CIP are listed in Table 3. These studies differed in their methodologies. Subjects were recruited from drug treatment or rehabilitation centres (Vergara-Moragues et al., 2016) or psychiatric hospital (Manschreck et al., 1988). Common exclusion criterion was a history of PPD (Brady et al., 1991; Roncero et al., 2014(c)). Assessments of psychotic symptoms were carried out using standardised instruments, such as the PRISM (Roncero et al., 2014(c)) and Scale for Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP, Trape et al., 2014), other structured interviews (Roncero et al., 2013(c)) or by reviewing medical records (Manschreck et al., 1988). The limitations of these studies include retrospective design (Manschreck et al., 1988), selective sampling frame such as a hospital (Manschreck et al., 1988), small sample size (Brady et al., 1991), concurrent use of other substances (Vergara-Moragues et al., 2016) and lack of systematic assessment of psychotic symptoms (Manschreck et al., 1988).

Delusions are common in CIP. One study reported that 93% of subjects with CIP experienced delusion (Manschreck et al., 1988). The frequency of persecutory delusion ranged from 44% to 90%, with a median of 71%. Other types of delusion included reference (43% to 69%), jealousy (19% to 26%), sin or guilt (10% to 39%), grandiosity (5% to 19%) and somatic (3% to 28%). Hallucinations are also common in CIP. One study reported that 96% of subjects with CIP experienced hallucinations (Brady et al., 1991). The frequency of auditory hallucination ranged from 31% to 87%. The frequency of visual hallucinations ranged from 26% to 71%. Other types of

hallucinations were tactile (21% to 48%), somatic (3% to 28%) and olfactory (12% to 29%). Other reported psychotic symptoms include disorganised behaviour or speech and catatonic behaviours Other clinical features of CIP include negative symptoms (Manschreck et al., 1988), confusion (Manschreck et al., 1988) and stereotypies (Brady et al., 1991).

Table 3. Studies examining the prevalence of psychotic symptoms amongst patients with CIP.

Study citation / country	Study sample	Assessment of psychotic symptoms	Findings
Vergara-Moragues et al., 2016 Spain	N = 87, 78% male, mean age = 36 Patients with CIP Recruited from centres for the treatment of substance abuse	PRISM	(1) Delusions: persecution (71%), reference (69%), jealous (23%), bizarre (21%), somatic (13%), grandiosity (10%), depressant (10%). (2) Hallucinations: auditory (52%), visual (36%), tactile (21%), olfactory/gustatory (6%). (3) Others: disorganized speech (6%), disorganized or catatonic behaviour (13%), negative symptoms (9%).
Roncero et al., 2014(c) Spain	N = 58, 86% male, mean age = 33 Patients with CIP Recruited from outpatient and inpatient drug unit	PRISM	(1) Delusions: persecution (86%), reference (43%), jealous (19%), grandiosity (5%), somatic (3%), bizarre (2%). (2) Hallucinations: auditory (57%); visual (55%), tactile (48%), olfactory (12%).
Trape et al., 2014 France	N = 53, 85% male, mean age = 40 Patients with cocaine-induced paranoia Recruited from a substance abuse clinic	SAPS-CIP	(1) Delusions: persecution (66%), reference (43%), sin or guilt (39%), thought (35%), somatic (28%), jealous (26%), grandiosity (19%), religious (14%), control (14%). (2) Hallucinations: auditory (87%); visual (71%), somatic/tactile (52%), olfactory (29%).
Roncero et al., 2013(c) Spain	N = 173, 80% male, mean age = 34 Patients with cocaine dependence	Structured interview	(1) Paranoid beliefs and suspiciousness (44%). (2) Hallucinations: auditory (31%), visual (26%), somatic (10%).

Study citation / country	Study sample	Assessment of psychotic symptoms	Findings
	Recruited from a substance use disorders unit		
Manschreck et al., 1988 USA	N = 106, 81% male, mean age = 27 Patients with cocaine disorders Recruited from a psychiatric hospital	Review of medical record	(1) Delusions (93%). (2) Hallucinations (83%). (3) Thought disorder (48%), confusion (42%), unusual behaviour (42%).
Brady et al., 1991 USA	N = 55, sex distribution unknown, mean age = 30 Patients with cocaine dependence Recruited from inpatient unit for the treatment of cocaine dependence	Semi-structured interview	(1) Paranoid delusions (90%). (2) Hallucinations (96%): auditory (83%), visual (38%), tactile (21%). (3) behavioural stereotypies (27%).

PRISM=Psychiatric Research Interview for Substance and Mental Disorders, SAPS-CIP=Scale for Assessment of Positive Symptoms-Cocaine Induced Psychosis.

Pattern of psychotic symptoms in cocaine users

Studies examining the pattern of psychotic symptoms of cocaine users are listed in Table 4. These studies differed in their methodologies. For instance, subjects were recruited from psychiatric hospitals (Roncero et al., 2017), drug abuse clinics (Roncero et al., 2014(a)), the emergency department of general hospitals (Pavarin et al., 2011), the community (Smith et al., 2009), or a combination of different settings (Jeri et al., 1978). Assessments of psychotic symptoms were made using standardised instruments, such as the Composite International Diagnostic Interview – Substance Abuse Module (CIDI-SAM; Smith et al., 2009), SAPS-CIP (Vergara-Moragues et al., 2014) and PRISM (Vorspan et al., 2012), or via clinical interview (Jeri et al., 1978), questionnaire (Roncero et al., 2013 (b)) or review of medical records (Lowenstein et al., 1987). The limitations of these studies include retrospective design (Pavarin et al., 2011), self-report of psychotic symptoms (Roncero et al., 2013 (a)), small sample size (Roncero et al., 2013 (b)), and a lack of systematic assessment of psychotic symptoms (Kaye & Darke, 2004).

Psychotic symptoms are common amongst cocaine users. In three review papers, the frequency of any psychotic symptom ranged from 12% to 100%. In individual studies, the prevalence of psychotic symptoms ranged from 2% in a retrospective review of medical records of a general hospital (Lowenstein et al., 1987) to 87% in a study of 105 subjects recruited from a drug abuse clinic and a harm reduction clinic, with a median of 63%.

Delusions are prevalent amongst cocaine users. Roncero et al. (2013 (b)) reported that 48% of 21 patients with cocaine dependence had delusions. The frequency of persecutory delusion ranged from 27% to 55%, with a median of 42%. Other delusion types were reference (14% to 39%), jealousy (8% to 20%), sin/guilt (15% to 20%), grandiosity (2% to 30%), religious (3% to 6%), somatic (1% to 22%), being controlled (2% to 13%) and thought (3% to 25%). Hallucinations are also common in cocaine users, with 3% to 38% (median = 28%) of users reporting hallucinations. The reported modalities of hallucinations included auditory (24% to 38%), visual (13% to 42%), somatic/tactile (8% to 31%) and olfactory (7% to 10%). Other symptoms reported include paranoia (2% to 35%) (aggressive/agitated behaviour (25% to 41%), stereotyped behaviour (46% to 68%) and unusual social/sexual behaviour (41% to 65%).

Table 4. Studies examining the prevalence of psychotic symptoms amongst cocaine users.

Study citation / country	Study sample	Assessment of psychotic symptoms	Findings
Tang et al., 2014	Literature review	-	50% to 75% had psychotic symptoms.
Roncero et al., 2014(b)	Literature review	-	29% to 87% had psychotic symptoms.
Roncero et al., 2012	Literature review	-	12% to 100% had psychotic symptoms.
Morton et al., 1999	Literature review	-	Paranoia (68-84%).
Roncero et al., 2017 Spain	N = 767, 80% male, mean age = 37 Patients with cocaine dependence Recruited from a psychiatric hospital	Clinical interview	Any psychotic symptoms (55%), tactile/somatic hallucinations (7%).
Roncero et al., 2014(a) Spain	N = 231, 78% male, mean age = 36 Patients with cocaine dependence Recruited from a drug abuse clinic	Structured interview	Any psychotic symptoms (66%).
Vergara-Moragues et al., 2014 Spain	N = 114, 87% male, mean age = 36 Patients with problematic cocaine use Recruited from outpatient drug dependence treatment centres	SAPS-CIP	(1) Any psychotic symptoms (84%). (2) Delusions: persecution (43%), jealousy (20%), sin/guilt (20%), grandiosity (10%), religious (3%), somatic (12%), reference (25%), being controlled. (2%), and delusions of mind reading, broadcasting, insertion, withdrawal (3%).

Study citation / country	Study sample	Assessment of psychotic symptoms	Findings
			(3) Hallucinations: auditory (36%), visual (38%), somatic/tactile (29%) and olfactory (10%). (4) Others: aggressive/agitated behaviour (25%), stereotyped behaviour (46%), unusual social/sexual behaviour (41%).
Roncero et al., 2014(c) Spain	N = 143, 82% male, mean age = 34 Patients with cocaine dependence Recruited from outpatient and inpatient drug unit	PRISM	(1) Any psychotic symptoms (68%). (2) Delusions: persecution (35%), reference (14%), jealous (8%), grandiosity (2%), somatic (1%), bizarre (1%). (3) Hallucinations: auditory (38%), visual (42%), tactile (31%), olfactory (7%).
Vorspan et al., 2012 France	N = 105, 78% male, mean age = 38 Patients with cocaine dependence or abuse Recruited from drug abuse clinic and harm reduction clinic.	PRISM	(1) Any psychotic symptoms (87%). (2) Delusions: persecution (55%), grandiosity (30%), reference (28%), thought broadcasting, insertion or withdrawal (25%), somatic (22%), sin (15%), jealous (13%), influence (13%), religion (6%). (3) Hallucinations: any (28%), auditory (24%), visual (13%), tactile (8%). (4) Others: aggressive/agitated behaviour (41%), stereotyped behaviour (58%), unusual social/sexual behaviour (65%).
Smith et al., 2009 USA	N = 475, 80% male, mean age = 34 Crack cocaine users, intravenous drug users, and heroin snorters Recruited from community via street outreach	CIDI-SAM	Psychotic symptoms (77%).

Study citation / country	Study sample	Assessment of psychotic symptoms	Findings
Kaye & Darke 2004 Australia	N = 212, 68% male, mean age = 29 Patients with cocaine use Recruited via advertisement and word of mouth	Structural Interview	(1) Paranoia (33%). (2) Hallucinations (9%).
Jeri et al., 1978 Peru	N = 188, 96% male, mean age unknown Patients with cocaine use Recruited from mental hospital, general hospital and private psychiatric hospitals	Clinical interview	(1) Paranoia (35%). (2) Hallucinations (35%).
Roncero et al., 2013(a) Spain	N = 287, 81% male, mean age = 36 Patients with cocaine dependence Recruited from a drug abuse clinic	Questionnaire	(1) Any psychotic symptoms (60%). (2) Delusions: reference (39%), persecution (27%). (3) Hallucinations: any (28%), auditory (24%), visual (13%), tactile (8%).
Roncero et al., 2013(b) Spain	N = 21, 81% male, mean age = 36 Patients with intravenous cocaine use Recruited from a drug abuse clinic	Questionnaire	(1) Delusions: 48%. (2) Hallucinations: 38%. (3) Stereotyped movements: 68%.
Brower et al., 1988 USA	N = 100, sex and age distribution unknown Cocaine users	Unknown	Psychotic symptoms (66%).

Study citation / country	Study sample	Assessment of psychotic symptoms	Findings
	Recruited from a psychiatric emergency room		
Lowenstein et al., 1987 **USA**	N = 1275, sex and age distribution unknown Patients with cocaine abuse Recruited from emergency room and wards of a general hospital	Review of medical records	Psychosis, paranoia and/or hallucination (2%).
Brody et al., 1990 **USA**	N = 216, 76% male, mean age = 30 Cocaine using patients Emergency department	Review of medical records	(1) Psychotic symptoms (9%). (2) Hallucination (3%). (3) Paranoia (2%).
Pavarin et al., 2011 **Italy**	N = 674, 84% male, mean age = 33 Patients with cocaine use Retrieved from databases of emergency departments	Review of medical records	(1) Paranoia (17%). (2) Psychotic symptoms (12%). (3) Hallucination (4%).

CIDI-SAM=Composite International Diagnostic Interview – Substance Abuse Module, PRISM=Psychiatric Research Interview for Substance and Mental Disorders, SAPS-CIP=Scale for Assessment of Positive Symptoms-Cocaine Induced Psychosis.

Risk factors for CIP/psychotic symptoms in cocaine users

Studies examining the prevalence of CIP or psychotic symptoms are shown in Table 5. These studies differed in their methodologies. For instance, subjects were recruited from hostels (Alexander et al., 2017), outpatient and inpatient drug units (Roncero et al., 2014(c)), psychiatric hospitals (Manschreck et al., 1988), general hospitals (Pavarin et al., 2011), and the community (Smith et al., 2009). The extent of cocaine use amongst the subjects included non-dependent use (Pavarin et al., 2011), regular use (Kaye & Darke 2004), problematic use (Vergara-Moragues et al., 2014), and dependence (Alexander et al., 2017). A history of PPD was a common exclusion criterion in these studies (Roncero et al., 2014(c)). The limitations of these studies include retrospective design (Pavarin et al., 2011), a selective sampling frame such as a psychiatric hospital (Manschreck et al., 1988), small sample size (Mahoney et al., 2010), and a lack of systematic assessment of psychotic symptoms (Pavarin et al., 2011).

Risk factors for CIP/psychotic symptoms can be broadly classified into four groups based on demographics, characteristics of cocaine use, personal history of psychological or psychiatric problems, and other risk factors (Tang et al., 2014). Reported demographic risk factors include male gender (Roncero et al., 2012) and both younger (Tang et al., 2014) and older age (Kalayasiri et al., 2010). The following risk factors for CIP/psychotic symptoms associated with the use of cocaine have been reported: younger age of first use (Roncero et al., 2012), longer duration of use (Flord et al., 2006), current use (Herback et al., 2006), more frequent use (Vergara-Moragues et al., 2014), heavy use (Roncero et al., 2012), dependence (Kalayasiri et al., 2010),

injection, (Roncero et al., 2012), nasal use (Kalayasiri et al., 2010), inhalation by smoking (Trape et al., 2014), and use of crack cocaine (Morton et al., 1999). Use or dependence on cannabis (Roncero et al., 2012), methamphetamine (Alexander et al., 2017), tobacco (Roncero et al., 2013(c)) and sedatives and alcohol (Kalayasiri et al., 2010) also increase the risk of CIP/psychotic symptoms.

Psychological or psychiatric problems associated with CIP/psychotic symptoms include attention deficit hyperactivity disorder, antisocial personality disorder (Tang et al., 2007), borderline personality disorder (Roncero et al., 2013 (c)), major mental disorder (Manschreck et al., 1988), psychosis (Roncero et al., 2012), psychosis proneness (Satel & Edell, 1991), neuroticism personality trait (Roncero et al., 2014 (a)), and trait anxiety (Rosse et al., 1995). Other risk factors for CIP/psychotic symptoms are low body mass index (Rosse et al., 1995), neurobiological vulnerability (Roncero et al., 2012), genetic factors, and concurrent treatment with drugs with dopaminergic system activity (Roncero et al., 2014 (b)).

Table 5. Studies examining the risk factors of CIP/psychotic symptoms in cocaine users.

Study citation / country	Study sample	Dependent variable	Findings
Tang et al., 2014	Literature review	CIP	(1) Demographics: male, younger age. (2) Drug use: early onset, longer duration, higher number of episodes of lifetime use, inhalation or intravenous use, other substance use, e.g. cannabis. (3) Comorbid ADHD and antisocial personality disorder. (4) Others: genetic factors.
Roncero et al., 2014(b)	Literature review	CIP	(1) Drug use: early onset and higher quantity of cocaine use; intravenous use; other substance use, e.g. cannabis. (2) Comorbid ADHD, psychosis, antisocial personality disorder and borderline personality disorder. (3) Others: low body mass index, genetic factors, concurrent treatment with drugs with dopaminergic system activity.
Egan et al., 1979	Literature review	CIP	Drug use: dose and chronicity of use.
Morton et al., 1999	Literature review	Psychosis	Drug use: use of crack cocaine.
Roncero et al., 2012	Literature review	Psychotic symptoms	(1) Demographics: male, older age.

Study citation / country	Study sample	Dependent variable	Findings
			(2) Drug use: early onset and higher quantity of cocaine use, injecting, cannabis use. (3) Comorbid ADHD, psychosis and antisocial personality disorder. (4) Others: low body mass index, genetic factors and neurobiological vulnerability.
Alexander et al., 2017 Canada	N = 103 (29 with CIP, 74 without CIP), 75% male, median age = 46 Patients with cocaine dependence Recruited from hostels	CIP	Drug use: current Ice and cannabis dependence.
Roncero et al., 2014(c) Spain	N = 143, 82% male, mean age = 34 Patients with cocaine dependence Recruited from outpatient and inpatient drug unit	CIP	Drug use: younger age of onset of cocaine addiction, cannabis abuse or dependence.
Trape et al., 2014 France	N = 53, 85% male, mean age = 40 Patients with cocaine dependence Recruited from a substance abuse clinic	CIP	Drug use: amount spent for cocaine, age of first cannabis use, smoking habits.
Roncero et al., 2013(c) Spain	N = 173, 80% male, mean age = 34 Patients with cocaine dependence Recruited from a substance use disorders unit	CIP	(1) Demographics: male. (2) Drug use: higher weekly consumption of cocaine, cannabis and tobacco dependence. (3) Comorbid antisocial personality disorder and borderline personality disorder.

Study citation / country	Study sample	Dependent variable	Findings
Kalayasiri et al., 2010; Kalayasiri et al., 2006 USA	N = 1140, 50% male, mean age = 39 Subjects with cocaine dependence Recruited by advertisement or referral	CIP	(1) Demographics: older age. (2) Drug use: early age of onset and higher quantity of cocaine use, severity of dependence, cocaine smoking, nasal use or injection; alcohol, cannabis or sedative dependence.
Tang et al., 2007 USA	N = 243, 59% male, mean age = 40 Subjects with cocaine dependence Recruited through clinical referral, advertising, and word of mouth	CIP	(1) Drug use: cannabis dependence. (2) Comorbid ADHD and antisocial personality disorder.
Flord et al., 2006 USA	N = 51, 59% male, mean age = 36 Subjects with cocaine dependence Recruited from inpatient detoxification centres and local newspaper	CIP	Drug use: duration of use.
Roose et al., 2005 USA	N = 69, 87% male, mean age = 32 Patients with cocaine dependence Recruited from an inpatient substance abuse unit	CIP	Lower body mass index.
Rosse et al., 1995 USA	44 subjects with cocaine dependence, 75% male, mean age = 32 Recruited from an inpatient substance abuse research unit	CIP	Trait anxiety.
Satel & Edell 1991	N=20, 100% male, mean age unknown	CIP	Psychosis proneness.

Study citation / country	Study sample	Dependent variable	Findings
USA	Recruited from inpatient and outpatient substance abuse program		
Brady et al., 1991 USA	N = 55, sex distribution unknown, mean age = 30 Patients with cocaine dependence Recruited from inpatient unit for the treatment of cocaine dependence	CIP	(1) Demographics: male. (2) Drug use: higher quantity and longer duration of cocaine; intravenous use.
Herback et al., 2006 USA	N = 266, 100% male, mean age = 49 Patients with cocaine dependence and without psychosis at baseline Recruited from an inpatient substance abuse disorders unit	Psychosis	Drug use: non-abstinent cocaine use.
Manschreck et al., 1988 USA	N = 106, 81% male, mean age = 27 Patients with cocaine disorders Recruited from a psychiatric hospital	Psychosis	(1) Drug use: higher lifetime consumption. (2) Prior major mental disorder.
Roncero et al., 2017 Spain	N = 767, 80% male, mean age = 37 Patients with cocaine dependence Recruited from a psychiatric hospital	Psychotic symptoms	(1) Drug use: younger age of first use of cocaine. (2) Comorbid adult ADHD.
Roncero et al., 2014(a) Spain	N = 231, 78% male, mean age = 36 Patients with cocaine dependence Recruited from a drug abuse clinic	Psychotic symptoms	Comorbid neuroticism personality trait.

Study citation / country	Study sample	Dependent variable	Findings
Vergara-Moragues et al., 2014 Spain	N = 114, 87% male, mean age = 36 Patients with problematic cocaine use Recruited from outpatient drug dependence treatment centres	Psychotic symptoms	Drug use: more frequent use, fewer abstinence periods, higher severity of dependence.
Vorspan et al., 2012 France	N = 105, 78% male, mean age = 38 Patients with cocaine dependence or abuse Recruited from drug abuse clinic and harm reduction clinic	Psychotic symptoms	Drug use: cocaine dependence, weekly use, intravenous use.
Pavarin et al., 2011 Italy	N = 674, 84% male, mean age = 33 Patients with cocaine use Retrieved from databases of emergency departments	Psychotic symptoms	Drug use: non acute (after 12 hours) use of cocaine, non-dependent use of cocaine.
Mahoney et al., 2010 USA	N = 42, 64% male, mean age = 40 Subjects with cocaine dependence Non treatment seeking users from community	Psychotic symptoms	Demographics: women / men were more likely to report auditory and tactile hallucinations / delusion of grandeur during periods of no drug use, respectively. Women were more likely to report olfactory and tactile hallucinations and delusion of grandeur during drug use.
Smith et al., 2009 USA	N = 475, 80% male, mean age = 34 Crack cocaine users, intravenous drug users, and heroin snorters Recruited from community via street outreach	Psychotic symptoms	Drug use: abuse or dependence.
Mooney et al., 2006	N = 44, 52% male, mean age = 34 Subjects with cocaine dependence	Paranoia / Suspiciousness	Demographics: older and male.

Study citation / country	Study sample	Dependent variable	Findings
USA	Recruited from community through word of mouth, fliers, and newspaper advertisement	during cocaine use in laboratory setting	
Kaye & Darke 2004 Australia	N = 212, 68% male, mean age = 29 Patients with regular cocaine use Recruited via advertisement and word of mouth	Psychotic symptoms	Drug use: injection.
Brower et al., 1988 USA	N = 100, sex and age distribution unknown Cocaine users Recruited from a psychiatric emergency room	Psychotic symptoms	Drug use: higher number of days and amount of cocaine use in past one month.
Reid et al., 2004 USA	N =23, 100% male, mean age = 45 Subjects with cocaine dependence Recruited from outpatient substance abuse treatment programs and by word of mouth	Sensitization to CIP	Sensitization to CIP was negatively correlated with drug dependence severity and cocaine craving.
Barlett et al., 1997 USA	N = 18, sex and age distribution unknown Recruited from inpatient treatment unit for cocaine dependence	Sensitization to CIP	Subjects with sensitization had longer duration of regular cocaine use and lower dose escalation of over time.

ADHD = Attention Deficit Hyperactivity Disorder, CIP= Cocaine Induced Psychosis.

Clinical course of CIP

Studies examining the clinical course of CIP or psychotic symptoms are listed in Table 6. Data on the clinical course of CIP are very limited. Based on clinical experience, Satel et al. (1991) suggested that psychotic symptoms following cocaine use almost always disappear within eight to 36 hours of taking the drug. Mendoza and Miller (1992) also commented that based on clinical experience, psychotic symptoms in occasional users may abate in a matter of hours or days. In chronic users, psychotic symptoms may persist for days to a few weeks. In a study of 55 patients with cocaine dependence admitted into an inpatient unit, psychotic symptoms lasted for less than 24 hours after the last cocaine use (Brady et al., 1991). In an intervention study of 16 patients with cocaine dependence, the reduction of cocaine after three weeks of treatment was associated with a reduction in psychotic symptoms (Vorspan et al., 2011). In summary, the duration of CIP is usually brief, lasting hours to several days.

Table 6. Studies examining the clinical course of CIP/psychotic symptoms.

Study citation / country	**Study sample**	**Duration of follow up**	**Findings**
Vorspan et al., 2011 France	N = 16, 53% male, mean age = 41 Patients with cocaine dependence	3 weeks	Psychotic symptoms reduced after three weeks of treatment. There was a significant correlation between psychotic symptoms and dose reduction.

Study citation / country	Study sample	Duration of follow up	Findings
	Recruited from an outpatient program for drug dependence		
Brady et al., 1991 USA	N = 55, sex distribution unknown, mean age = 30 Patients with cocaine dependence Recruited from inpatient unit for the treatment of cocaine dependence	-	Psychotic symptoms lasted less than 24 hours.
Mendoza & Miller 1992; Mendoza et al., 1992 USA	Clinical experience	-	In occasional users, psychotic symptoms may abate in a matter of hours or days. In chronic users, psychotic symptoms may persist for days to a few weeks.
Satel et al., 1991	Clinical experience	-	Psychotic symptoms almost always disappear by eight to 36 hours post binge.

Treatment of CIP

Data on the treatment of CIP are very limited. There has been no published clinical trial on the treatment of CIP. A review paper (Tang et al., 2014) suggested that treatment of CIP included supportive measures, initial medical workup and psychopharmacology. Supportive measures include the following: 1) establish a therapeutic relationship; 2) provide reassurance that the patient is safe and symptoms are self-limiting; 3) correct dehydration by oral administration of fluid; 4) provide a calm and non-stimulating environment; and 5) use physical restraint only as a last resort. The initial medical workup requires close behavioural observation, frequent vital sign monitoring and basic investigations (including a urine drug screen, blood alcohol level, complete metabolic panel and electrocardiogram). In terms of psychopharmacology, benzodiazepines +/- antipsychotic are useful for agitation in CIP. Possible choices of antipsychotics are olanzapine, risperidone and quetiapine. Chlorpromazine or clozapine should be avoided, as they lower the seizure threshold. Antipsychotic medication should be continued until the sedative effect is evident and the patient is either asleep or calm. CIP usually requires short-term treatment only and continuation of antipsychotics beyond 72 hours is usually unnecessary.

Neuroimaging of CIP

Only one neuroimaging study of CIP has been published. This study involved 103 subjects (29 with CIP and 74 without CIP) (Willi et al., 2016). There was no cocaine-naive control group, 75% of the subjects were male and the median age of the sample was 46. All of the subjects had current cocaine dependence, and the sample was recruited from hostels. Individuals with PPD and gross brain abnormalities such as chronic head trauma were excluded. Each subject received a structural magnetic resonance imaging examination. Subjects with CIP had smaller thalamus and left hippocampus volumes than those without CIP. These grey matter volume reductions could have represented neurodevelopmental substrates for psychosis that existed prior to drug use, akin to the neurodevelopmental hypothesis of schizophrenia (Weinberger et al., 1986). Alternatively, volumetric reductions could have reflected a heightened susceptibility to the neurotoxic effects of chronic psychostimulant exposure, in line with the neurotoxicity model (Hsieh et al., 2014).

Genetics of CIP

Genetic studies of CIP and psychotic symptoms are listed in Table 7. The list includes three review papers and four original studies. The findings of the reviews suggest that CIP is associated with dopamine and monoamine pathway gene variants (dopamine β-hydroxylase (DβH) gene, dopamine transporter gene, dopamine receptor gene and cathecol-O-methyl transferase gene). Three of the original studies examined dopamine pathway genes. Cubells et al. (2000) studied four DβH gene variants in forty-five subjects with cocaine dependence. DβH converts dopamine to norepinephrine in the brain and is related to vulnerability to psychosis. CIP was assessed using the CEQ and defined as the presence of cocaine-induced paranoia. The Del-a haplotype was found to be less frequent in subjects without CIP. The limitations of this study included its small sample size and retrospective assessment of CIP. Kalayasiri et al. (2007) performed a self-administration of cocaine experiment in 31 non-treatment-seeking subjects with cocaine dependence. Paranoia was assessed using a visual analogue scale. The DβH (-1021C → T) gene variant was analysed. TT homozygotes exhibited greater paranoia over time than either CT or CC individuals during the experiment. Gelernter et al. (1994) examined the dopamine receptor gene variable number of tandem repeats in 104 subjects with cocaine dependence. Cocaine-induced paranoia was assessed using the CEQ. In a subgroup of white subjects (n = 58), cocaine-induced paranoia was associated with allele 9. All three studies suggested that dopamine pathway genes could be related to the risk of CIP.

Finally, Fernandez-Castillo et al. (2013) studied N-ethylmaleimide sensitive factor (NSF) gene variants in 149 subjects with psychotic symptoms, 124 subjects without psychotic symptoms and 360 healthy controls. NSF modulated neurotransmitter release. The NSF (rs183211–rs1769817) variants in both the CIP and non-CIP groups were different from those of the healthy controls.

Table 7. Studies on genetics of CIP.

Study citation / country	Study sample	Gene variant / function	Findings
Tang et al., 2014	Literature review	Dopamine pathway genes	CIP was associated with Dopamine β-hydroxylase gene, dopamine transporter gene and dopamine receptor gene.
Roncero et al., 2014; Roncero et al 2012	Literature review	Dopamine and monoamine pathway genes	CIP was associated with Dopamine β-hydroxylase gene, dopamine transporter gene and cathecol-O-methyl transferase gene.
Brouse et al., 2010	Literature review	Dopamine pathway genes	CIP was associated with Dopamine β-hydroxylase gene and dopamine transporter gene.
Cubells et al., 2000 USA	45 subjects with Cocaine dependence 145 healthy controls Mean age and sex distribution and site of recruitment unknown	DβH Del-a haplotype Dopamine β-hydroxylase Converts dopamine to norepinephrine	The Del-a haplotype was less frequent in subjects without CIP
Kalayasiri et al., 2007 USA	N = 31, 68% male, mean age = 38 Subjects with cocaine dependence Not treatment seeking volunteers	DβH (-1021C -> T) Dopamine β-hydroxylase	TT homozygotes endorsing greater paranoia over time than either CT or CC individuals

		Converts dopamine to norepinephrine	during a self-administration of cocaine experiment.
Gelernter et al., 1994 **USA**	N = 104, 96% male, mean age = 34 Subjects with cocaine dependence Recruitment site and method unknown	Dopamine receptor gene variable number of tandem repeats Psychosis may be related excessive synaptic dopamine activity	In a subgroup of white subjects (n = 58), CIP was associated with allele 9.
Fernandez-Castillo et al., 2013 **Spain**	149 subjects with psychotic symptoms 124 subjects without psychotic symptoms 360 healthy controls Mean age and sex distribution and site of recruitment unknown	NSF (rs183211–rs1769817) N-ethylmaleimide sensitive factor modulates neurotransmitters release	Both psychotic and non psychotic groups has more G-T carriers than healthy controls.

DβH=Dopamine β-hydroxylase ; NSF=N-ethylmaleimide sensitive factor

Other biomarkers of CIP

Studies of biomarkers of CIP are listed in Table 8. These studies explored event-related potentials (ERPs), cortical excitability, autonomic activity and plasma level of brain-derived neurotrophic factor (BDNF) in CIP. Difficulty inhibiting incoming irrelevant sensory stimuli (sensory gating) is a neurobiological mechanism that may contribute to the development of psychotic disorders. ERPs are physiological indices that reflect sensory gating and attentional functioning. The P50 and P200 components of ERPs are associated with early and later stages of information processing. In two separate studies, Boutros et al. (2002, 2006) examined ERPs in cocaine users with and without cocaine-induced paranoia. The first study revealed that P200 latency was prolonged in subjects with cocaine-induced paranoia, compared with those without. The second study found that mean P50 ratios were higher in subjects with more psychotic symptoms. These results raise the possibility that sensory gating and attention deficits are correlates of increased proneness to experiencing paranoia during cocaine intoxication.

The cortical silent period (CSP), a measure of cortical inhibitory processes, is affected by a number of neurotransmitter systems including γ aminobutyric acid and dopamine. In a study of cocaine users (six with cocaine-induced paranoia and thirteen without), CSP in the right hemisphere was found to be longer in the group with paranoia, suggesting that the development of psychotic symptoms may be dependent on neurotransmitter changes (Boutros et al., 2005).

Rosse et al. (1995) examined autonomic reactivity in 41 cocaine users (28 with cocaine-induced paranoia and 16 without). Subjects with cocaine-induced paranoia had greater pupillary dilation in response to a visual image of crack cocaine. This finding suggests that users with a higher level of reactivity are more prone to cocaine-induced paranoia.

Corominas-Roso et al. (2013(b)) studied plasma levels of BDNF in 40 cocaine users (22 with CIP and 18 without) and found that after 12 days of withdrawal from cocaine, BDNF levels were higher in the non-CIP group. In addition, patients with no history of psychotic symptoms experienced a significant increase in serum BDNF levels, whereas those patients with a history of psychotic symptoms experienced a decrease, although not statistically significant, in BDNF levels. This finding suggests that patients with psychotic symptoms associated with cocaine consumption share some of the BDNF deficiencies that characterize schizophrenia and psychosis.

Table 8. Studies on other biomarkers of CIP.

Study citation / country	Study sample	Type of study	Findings
Corominas-Roso et al., 2013(b) Spain	22 CIP, 68% male, mean age = 37 18 non CIP 46 healthy controls Recruited from an inpatient detoxification centre	Plasma BDNF	(1) Lowered BDNF levels in both CIP and non CIP groups, compared to healthy controls. (2) No difference between CIP and non CIP groups in baseline BDNF levels. (3) During withdrawal, BDNF level increased in the non CIP group.
Boutros et al., 2006 USA	34 subjects with cocaine dependence, 41% male, mean age = 36 Site of recruitment unknown	Event-related potentials	The P200 latency was prolonged in subjects with cocaine induced paranoia, compared with those without.
Boutros et al., 2002 USA	30 subjects with cocaine dependence, 67% male, mean age = 39 Site of recruitment unknown	Event-related potentials	The P50 ratios were higher in subjects with higher severity of cocaine induced paranoid symptoms.
Boutros et al., 2005 USA	19 subjects with cocaine dependence, 58% male, mean age = 33 Site of recruitment unknown	Cortical excitability	Cortical silent periods were longer in subjects with CIP.
Rosse et al., 1995 USA	44 subjects with cocaine dependence 75% male, mean age = 32	Autonomic reactivity	Subjects with CIP had greater pupillary dilation in response to visual image of crack cocaine.

	Recruited from an inpatient substance abuse research unit

BDNF = brain derived neurotrophic factor

Discussion

Prevalence of CIP and psychotic symptoms in cocaine users

While psychosis that occurs during a binge episode or withdrawal is usually transient, susceptibility to psychotic disorders increases with chronic cocaine use. CIP is diagnosed when the observed psychotic symptoms exceed the known and expected effects of intoxication or withdrawal from cocaine. Clinically, the most straightforward means of distinguishing CIP from another (i.e., substance-independent) psychotic disorder is through careful assessment of the temporal relationship between cocaine use and the onset of psychosis (Glasner-Edwards & Mooney, 2014). Studies examining the frequency of CIP have used varying definitions of the disorder. Additionally, not all studies have used standardised instruments to measure psychotic symptoms and or recorded the period (e.g., lifetime, current) within which psychosis is examined (Vergara-Moragues et al., 2012(a)). The prevalence of CIP ranges from 5% to 75%, with a median of 53%. A recent review reported that up to 86.5% of patients who use cocaine develop CIP (Roncero et al., 2014(b)). These figures are comparable with those for methamphetamine. The prevalence of methamphetamine-induced psychosis (MIP) ranges from 24% to 76%, with a median of 42% (Tang et al., 2017).

Psychotic symptoms are common amongst cocaine users. The prevalence of psychotic symptoms ranges from 2% to 87%, with a median of 63%. Similarly, the frequency of any psychotic symptoms in methamphetamine users ranges from 16% to 81%, with a median of 78% (Tang et al., 2017). The reported prevalence of psychotic

symptoms varies widely, reflecting differences in data collection. For example, some studies have been based on patient interviews evaluating the presence of single psychotic symptoms, whereas others have only reviewed medical records. The severity of cocaine use also ranged from use to dependence (Roncero et al., 2013(a)).

Pattern of psychotic symptoms in CIP

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. The symptoms of CIP are similar to those seen in schizophrenia. However, recovery from CIP seems to be faster, and it appears to resolve more completely than schizophrenic psychosis. There are several potential discriminators in CIP: prominent visual illusions and hallucinations, symptoms related to paranoid themes, lack of formal thought disorders and grandiose delusions (Unnithan & Cutting, 1992; Rosse et al., 1994; Vergara-Moragues et al., 2016).

The symptoms profile of CIP is also similar to that of MIP. The most frequently reported symptoms of MIP are delusions of persecution and auditory hallucinations. Other negative symptoms, such as thought broadcasting, mood instability, disorientation, self-mutilation and impaired cognitive function, have also been reported (Alam-mehrjerdi et al., 2015). There are several potential discriminators between MIP and schizophrenia: speed of onset, the dream-like quality of experiences, a tendency towards visual hallucinations, brisk emotional reactions (usually in the direction of anxiety), absence of thought disorder, and frequent aggravations (Tang et al., 2017).

Risk factors for CIP/psychotic symptoms in cocaine users

Risk factors for CIP/psychotic symptoms can be broadly classified into four groups based on demographics, characteristics of cocaine and other drug use, personal history of psychological or psychiatric problems, and family history of psychiatric illness. The risk of developing CIP is dependent on cocaine dose and, inversely, on the age of onset of drug use. In addition to chronicity, pattern, severity and route of drug administration, psychological vulnerability predisposes some individuals to develop acute psychotic symptoms and syndromes in response to cocaine use. CIP has been reported to be more common in subjects with male gender, older or younger age, attention deficit hyperactivity disorder, antisocial personality disorder or poly drug use and in subjects with a family history of psychotic disorders. Preliminary evidence suggests that a higher body mass index and a higher plasma level of BDNF may be protective against CIP (Roncero et al., 2014(b)).

The risk factors for CIP are similar to those for MIP. The risk of MIP is dependent on dose and inversely related to the age of onset of methamphetamine use. It is also influenced by the chronicity, pattern, severity and route of administration of methamphetamine. MIP is more common in subjects with older age, schizotypal or schizoid traits, affective disorders, antisocial personality disorder or poly drug use and in subjects with a family history of psychotic disorders (Tang et al., 2017).

Based on data from 173 adults with cocaine dependence in Europe (mostly men, mean age 33.6 years), a model consisting of 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 regarding other factors, such as neurobiological markers, routes of cocaine use, lifetime attention deficit hyperactivity disorder and personality dimensions (Roncero et al., 2014(b)). Research should be continued with larger samples, incorporating a local population. More naturalistic and follow-up studies should be conducted that make it possible to clearly identify and specify which variables are most closely associated with the appearance of CIP and psychotic symptoms in cocaine consumers. This would make it possible to identify the at-risk population to make an early intervention (Roncero et al., 2012).

Clinical course of CIP

Data on the clinical course of CIP are very limited. Most patients with CIP recover within a few days, whereas psychotic symptoms may last for a few weeks. In contrast, some patients with MIP do not remit for weeks or months, exhibiting the so-called 'prolonged type' of psychosis (Harro, 2015). Several theories may explain the finding that psychosis can become chronic and persistent amongst stimulant users. Pre-existing schizophrenia may be unmasked or triggered by stimulant use, and stimulant-induced psychosis may share a very similar clinical course to that of schizophrenia; alternatively, stimulant-induced psychosis and primary psychosis are not distinct diagnostic entities, but rather fall along a continuum of psychosis (Glasner-Edwards & Mooney, 2014).

It is uncertain whether CIP can re-emerge with repeat usage or under stressful conditions. In 25% to 38% of methamphetamine users, psychosis can re-emerge with repeat usage or in stressful situations (Grant et al., 2012). The triggers of recurrence of CIP are largely unknown. Triggers of MIP recurrence include the resumption of methamphetamine use, other substance use, sleep deprivation and psychosocial stressors (Glasner-Edwards & Mooney, 2014). CIP seems to have a favourable course. In contrast, MIP is predictive of poor outcomes; more than half of those who could be reached at follow-up about six years after the index episode had experienced a relapse of psychosis or had a current alcohol use disorder (Harro, 2015).

Bramness et al. (2012) hypothesised a vulnerability-to-stress paradigm to explain the relationship between stimulant-induced and primary psychosis. Exposure

to stimulants, including cocaine, should be viewed as a stressor in the acute phase for vulnerable individuals. For individuals with lower vulnerability, higher doses of stimulants are needed, whereas individuals with higher vulnerability require lower doses to precipitate acute psychosis. In addition, due to their sensitising effects, stimulants may play a role in the development of vulnerability. Repeated use of stimulants could increase vulnerability, thereby increasing the chances of developing psychotic symptoms even in the absence of acute exposure to stimulants.

Treatment of CIP

The remission of psychotic symptoms within a few days of abstinence from cocaine suggests that for a large majority of those who present with these symptoms, pharmacological intervention is not required. Large randomised clinical trials of treatment regimens for the treatment of acute CIP have not 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. Little is known about the safety and efficacy of antipsychotics for children and adolescents with CIP, and a sizable number of those who present 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) or sleep medications may be prescribed to target anxiety/agitation or 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 abstinence from cocaine 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).

Neuroimaging of CIP

In the only published neuroimaging study of CIP, smaller thalamus and left hippocampus volumes were found in subjects with CIP (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. In addition, the volume reduction may represent a biological vulnerability to the neurotoxic effects of cocaine.

Grey matter structural abnormalities in substance-induced psychosis have been previously investigated. Grey and white matter deficits have been found in MIP (Breen et al., 2016), including reduced amygdala and hippocampal volumes. Reduced regional activation, dopamine transporter density and changes in metabolite concentrations have also been found (Sekine et al., 2001; Howells et al., 2014; Fassbender et al., 2015). The severity of positive symptoms was found to correlate with dopamine transporter density and metabolic disturbances (Sekine et al., 2001). Together, these findings suggest that subcortical pathology following methamphetamine use may contribute to the development of MIP (Gururajan et al., 2012). These findings are in line with the hypothesis that longer exposure to methamphetamine reduces dopamine transporter level, and a reduction in dopamine receptors, both of which can contribute to the development of psychotic symptoms (Fiorentini et al., 2011). Further structural and functional neuroimaging studies are needed to provide further insight into the neurobiology of CIP.

Genetics of CIP

CIP, similar to MIP, is likely to be a complex genetic disease in which environmental factors interact with multiple polymorphic genes to influence susceptibility (Grant et al., 2012). To date, based on a small number of studies, several candidate genes have been identified that may be associated with CIP but there is a need for replication of these findings. It should be noted that the candidate genes were examined in underpowered studies, and thus the results may reflect type II errors; further replication is required prior to dismissing them as potential markers.

There is evidence that genetic variation in dopamine systems is associated with risk for CIP (Tang et al., 2014). Possible candidate genes include genes that encode dopamine receptors and transporters and enzymes and other proteins. Notably, evidence suggests 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 may contribute to the development of psychosis following cocaine use.

There is reasonably strong evidence that genetic variation in neurotransmitter systems and in neural development or growth is associated with a risk of developing stimulant-induced psychosis (Grant et al., 2012). Possible candidate genes include genes that encode BDNF, dopamine receptors and transporters and enzymes, serotonin receptors and transporters, μ-opioid receptors, glutathione S-transferases and other proteins (Tang et al., 2017). Evidence suggests there is substantive overlap between markers of genetic vulnerability to stimulant-induced psychosis and schizophrenia

(Glasner-Edwards & Mooney, 2014). Together, these findings suggest that genetic risk factors affecting different signalling systems may contribute to the development of psychosis following stimulant use (Tang et al., 2017).

Priorities for future genetic research on CIP are (a) to replicate genetic associations within and across ethnically diverse populations; (b) to increase statistical power by using larger population cohorts to minimize false-negative associations; (c) to adapt high-throughput approaches such as genome-wide association scans; and (d) to identify allele-specific in vivo activity in humans and non-human animals (Grant et al., 2012).

Other biomarkers of CIP

There is preliminary evidence to suggest that sensory gating deficit (as measured by ERPs) and plasma BDNF levels may be 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). Sensory gating 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 two 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 deficits have been reported in patients with schizophrenia and first-degree relatives of schizophrenic patients (Boutros et al., 2004). Dopamine, noradrenaline and GABA mediated mechanisms have been implicated in the function of sensory gating. Hence, it is reasonable to postulate that the decreased gating observed in CIP may reflect dysregulation of dopamine, noradrenaline and GABA 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). BDNF 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(a)). One study reported an increase in serum levels of BDNF during the first 2 weeks of cocaine withdrawal (Corominas-Roso et al., 2012). 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(a)). In contrast, in the CIP group, BDNF levels showed a decreasing trend during early abstinence. Low plasma BDNF levels have been reported in schizophrenic patients (Xiu et al., 2009) and first-episode psychosis (Rizos et al., 2008). In these patients, postnatal stress appears to mediate the BDNF decrease and its consequences for brain structure (Mondelli et al., 2011). The most frequently studied single nucleotide polymorphism (SNP) of the BDNF gene, the Val66Met SNP (Petryshen et al., 2010), is associated with changes in intracellular trafficking and secretion of the protein (Chen et al., 2004) and affects serum BDNF levels (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 characterize psychosis.

Conclusions

Cocaine abuse commonly results in the development of acute psychosis. The prevalence of CIP ranges from 5% to 75%, with a median of 53%. The prevalence of psychotic symptoms ranges from 2% to 87%, with a median of 63%. These figures are comparable with those for methamphetamine. 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. The symptoms of CIP are similar to those seen in MIP and schizophrenia.

Risk factors for CIP/psychotic symptoms can be broadly classified into four groups based on demographics, characteristics of cocaine and other drug use, personal history of psychological or psychiatric problems, and family history of psychiatric illness. The risk of developing CIP is dependent on the onset, chronicity, dose, pattern and severity of cocaine use and route of cocaine administration. Psychological vulnerability, such as male gender, comorbid attention deficit hyperactivity disorder, antisocial personality disorder or poly drug use also increase the chance of psychosis. The variation in findings between studies is likely to be due to many factors, not limited to methodological differences in study design or cultural and demographic factors. Long-term studies that track cocaine users are necessary to collect sufficient evidence to understand the relationship between cocaine use and the development of CIP.

A number of putative neuroimaging, genetic and plasma biomarkers of CIP has been identified. Smaller thalamus and left hippocampus volumes may be related to CIP. Possible candidate genes for CIP include genes that encode dopamine receptors and transporters and enzymes and other proteins whereas a higher plasma level of BDNF may be protective against CIP.

In the majority of patients, CIP is transient and pharmacological intervention is normally not necessary.

Most patients with CIP recover within a few days, whereas psychotic symptoms may last for a few weeks. Neuroleptics, such as olanzapine, risperidone and quetiapine, can be used for the short-term management of persistent psychotic symptoms in CIP. Short-term anxiolytics (e.g., benzodiazepines) or sleep medications may be prescribed to target anxiety/agitation or insomnia, respectively. Psychiatric medications may be prescribed to manage comorbid conditions such as major depression or anxiety disorders. Long-term treatment of CIP should focus on abstinence from cocaine 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.

References

Alam-mehrjerdi Z, Mokri A, Dolan K. Methamphetamine use and treatment in Iran: a systematic review from the most populated Persian Gulf country. Asian Journal of Psychiatry. 2015;1617-25.

Alexander PD, Gicas KM, Willi TS, Kim CN, Boyeva V, Procyshyn RM, Smith GN, Thornton AE, Panenka WJ, Jones AA, Vila-Rodriguez F, Lang DJ, William MacEwan G, Honer WG, Barr AM. A comparison of psychotic symptoms in subjects with methamphetamine versus cocaine dependence. Psychopharmacology (Berl). 2017;234:1535-47..

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing. 2013.

Araos P, Pedraz M, Serrano A, Lucena M, Barrios V, GarcÃa-Marchena N, Campos-Cloute R, Ruiz JJ, Romero P, SuÃ¡rez J, Baixeras E, de la Torre R, Montesinos J, Guerri C, RodrÃguez-Arias M, MiÃ±arro J, MartÃnez-Riera R, Torrens M, Chowen JA, Argente J, Mason BJ, PavÃ³n FJ, et al. Plasma profile of pro-inflammatory cytokines and chemokines in cocaine users under outpatient treatment: influence of cocaine symptom severity and psychiatric co-morbidity. Addiction Biology. 2015;20:756-72.

Barceloux DG. Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants. John Wiley & Sons Inc Publication. 2012.

Bartlett E, Hallin A, Chapman B, Angrist B. Selective sensitization to the psychosis-inducing effects of cocaine: a possible marker for addiction relapse vulnerability? Neuropsychopharmacology. 1997;16:77-82.

Boutros NN, Zouridakis G, Overall J (1991): Replication and extension of P50 findings in schizophrenia. Clinical EEG. 1991;22:40–45.

Boutros NN, Campbell D, Petrakis I, Krystal J, Caporale M, Kosten T. Cocaine use and the mid-latency auditory evoked responses. Psychiatry Research. 2000;96: 117–126.

Boutros NN, Gelernter J, Gooding CD, Cubells J, Young A, Krystal JH, Kosten T. Sensory gating and psychosis vulnerability in cocaine-dependent individuals: preliminary data. Biological Psychiatry. 2002;51:683–6.

Boutros NN, Korzyukov O, Jansen B, Feingold A, Bell M. Sensory-gating deficits during the mid-latency phase of information processing in medicated schizophrenia patients. Psychiatry Research. 2004;126:203–15.

Boutros NN, Lisanby SH, McClain-Furmanski D, Oliwa G, Gooding D, Kosten TR. Cortical excitability in cocaine-dependent patients: a replication and extension of TMS findings. Journal of Psychiatric Research. 2005;39:295-302.

Boutros NN, Gooding D, Sundaresan K, Burroughs S, Johanson CE. Cocaine-dependence and cocaine-induced paranoia and mid-latency auditory evoked responses and sensory gating. Psychiatry Research. 2006;145:147–154.

Bramness JG, Gundersen ØH, Guterstam J, Rognli EB, Konstenius M, Løberg E-M, Medhus S, Tanum L, Franck J. Amphetamine-induced psychosis-a separate diagnostic entity or primary psychosis triggered in the vulnerable? BMC psychiatry. 2012;12:221.

Brady KT, Lydiard RB, Malcolm R, Ballenger JC. Cocaine-induced psychosis. Journal of Clinical Psychiatry. 1991;52:509-12.

Breen M, Uhlmann A, Nday C, Glatt S, Mitt M, Metsalpu A, Stein D, Illing N. Candidate gene networks and blood biomarkers of methamphetamine-associated psychosis: an integrative RNA-sequencing report. Translational psychiatry. 2016;6e802.

Brody SL, Slovis CM, Wrenn KD. Cocaine-related medical problems: consecutive series of 233 patients. American Journal of Medicine. 1990;88:325-31.

Brousse G, Vorspan F, Ksouda K, Bloch V, Peoc'h K, Laplanche JL, Mouly S, Schmidt J, Llorca PM, Lepine JP. Could the inter-individual variability in cocaine-induced psychotic effects influence the development of cocaine addiction? Towards a new pharmacogenetic approach to addictions. Medical Hypotheses. 2010;75:600-4.

Brower KJ, Blow FC, Beresford TP. Forms of cocaine and psychiatric symptoms. Lancet. 1988;1:50.

Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, Lee FS. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking

and activitydependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. Journal of Neuroscience. 2004;24:4401–11.

Corominas-Roso M, Roncero C, Ribases M, Castells X, Casas M. Brain-derived neurotrophic factor and its intracellular signaling pathways in cocaine addiction. Neuropsychobiology. 2007;55:2–13.

Corominas-Roso M, Roncero C, Eiroa-Orosa FJ, et al. Serum brainderived neurotrophic factor levels and cocaine-induced transient psychotic symptoms. Neuropsychobiology. 2013(a);68:146–155.

Corominas-Roso M, Roncero C, Eiroa-Orosa FJ, Gonzalvo B, Grau-Lopez L, Ribases M, Rodriguez-Cintas L, Sánchez-Mora C, Ramos-Quiroga JA, Casas M. Brain-derived neurotrophic factor serum levels in cocaine-dependent patients during early abstinence. European Neuropsychopharmacology. 2013(b);23:1078-84.

Cubells JF, Kranzler HR, McCance-Katz E, et al. A haplotype at the DBH locus, associated with low plasma dopamine beta-hydroxylase activity, also associates with cocaine-induced paranoia. Mol Psychiatry. 2000;5:56–63.

Cubells JF, Feinn R, Pearson D, Burda J, Tang Y, Farrer LA, Gelernter J, Kranzler HR. Rating the severity and character of transient cocaine-induced delusions and hallucinations with a new instrument, the Scale for Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP). Drug and Alcohol Dependence. 2005;80:23-33.

Egan DJ, Robinson DO. Cocaine: magical drug or menace? Internationl Journal of Addiction. 1979;14:231-41.

Ellenhorn MJ , Barceloux DG . Medical Toxicology, diagnosis and treatment of human poisoning. Elsevier Science Publishers. 1988;9:267.

Fassbender C, Lesh TA, Ursu S, Salo R. Reaction time variability and related brain activity in methamphetamine psychosis. Biological psychiatry. 2015;77:465-74.

Fernàndez-Castillo N, Cormand B, Roncero C, Sànchez-Mora C, Grau-Lopez L, Gonzalvo B, Miquel L, Corominas R, Ramos-Quiroga JA, Casas M, Ribasés M. Candidate pathway association study in cocaine dependence: the control of neurotransmitter release. World Journal of Biological Psychiatry. 2012 Feb;13:126-34.

Fernàndez-Castillo N, Roncero C, Grau-Lopez L, Barral C, Prat G, Rodriguez-Cintas L, Sànchez-Mora C, Gratacòs M, Ramos-Quiroga JA, Casas M, Ribasés M, Cormand B. Association study of 37 genes related to serotonin and dopamine neurotransmission and neurotrophic factors in cocaine dependence. Genes, Brain Behavior. 2013;12:39-46.

Fiorentini A, Sara Volonteri L, Dragogna F, Rovera C, Maffini M, Carlo Mauri M, A Altamura C. Substance-induced psychoses: a critical review of the literature. Current Drug Abuse Reviews. 2011;42:28-40.

Floyd AG, Boutros NN, Struve FA, Wolf E, Oliwa GM. Risk factors for experiencing psychosis during cocaine use: a preliminary report. Journal of Psychiatric Research. 2006;40:178–182.

Freedman R, Adler LE, Waldo M, Pachtman E, Franks RD. Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug free patients. Biological Psychiatry. 1983;18:537–51.

Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al: Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2011;66:198–204.

Gelernter J, Kranzler HR, Satel SL, Rao PA. Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. Neuropsychopharmacology. 1994;11:195–200.

Gilder DA, Gizer IR, Lau P, Ehlers CL. Stimulant dependence and stimulant-associated psychosis: clinical characteristics and age of onset in a native American community sample. Journal of Addictive Medicine. 2014;8:241-248.

Glasner-Edwards S, Mooney LJ. Methamphetamine psychosis: epidemiology and management. CNS drugs. 2014;28:1115-26.

Gooding DC, Gjini K, Burroughs SA, Boutros NN. The association between psychosis proneness and sensory gating in cocaine-dependent patients and healthy controls. Psychiatry Research. 2013;210:1092-100.

Grant KM, LeVan TD, Wells SM, Li M, Stoltenberg SF, Gendelman HE, Carlo G, Bevins RA. Methamphetamine-associated psychosis. Journal of Neuroimmune Pharmacology. 2012;7:113-39.

Gururajan A, Manning EE, Klug M, van den Buuse M. Drugs of abuse and increased risk of psychosis development. Australian and New Zealand Journal of Psychiatry. 2012;46:1120-35.

Haijma SV, Van Haren N, Cahn W, Koolschijn PCM, Pol HEH, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18000 subjects. Schizophrenia Bulletin. 2013;39:1129–38.

Herbeck DM, Hser YI, Lu AT, Stark ME, Paredes A. A 12-year follow-up study of psychiatric symptomatology among cocaine-dependent men. Addictive Behavior. 2006;31:1974-87.

Honer WG, Gewirtz G, Turey M. Psychosis and violence in cocaine smokers. Lancet. 1987;2:451.

Herrero MJ, Domingo-Salvany A, Torrens M, Brugal MT, Guti_errez F. Personality profile in young current regular users of cocaine. Substance Use & Misuse. 2008;43:1378–94.

Hsieh JH, Stein DJ, Howells FM. The neurobiology of methamphetamine induced psychosis. Frontiers in Human Neuroscience. 2014;8:537.

Jeri FR, Sanchez CC, del Pozo T, Fernandez M, Carbajal C. Further experience with the syndromes produced by coca paste smoking. Bulletin on Narcotics. 1978;30:1-11.

Kalayasiri R, Kranzler HR, Weiss R, Brady K, Gueorguieva R, Panhuysen C, Yang BZ, Farrer L, Gelernter J, Malison RT. Risk factors for cocaine-induced paranoia in cocaine-dependent sibling pairs. Drug and Alcohol Dependence. 2006;84:77-84.

Kalayasiri R, Sughondhabirom A, Gueorguieva R, Coric V, Lynch WJ, Lappalainen J, Gelernter J, Cubells JF, Malison RT. Dopamine beta-hydroxylase gene (DbetaH) -1021C-->T influences self-reported paranoia during cocaine self-administration. Biological Psychiatry. 2007;61:1310-3.

Kalayasiri R, Gelernter J, Farrer L, Weiss R, Brady K, Gueorguieva R, Kranzler HR, Malison RT. Adolescent cannabis use increases risk for cocaine-induced paranoia. Drug and Alcohol Dependence. 2010;107:196-201.

Kaye S, Darke S. Injecting and non-injecting cocaine use in Sydney, Australia: physical and psychological morbidity. Drug Alcohol Review. 2004;23:391-8.

Lang UE, Hellweg R, Sander T, Gallinat J. The Met allele of the BDNF Val66Met polymorphism is associated with increased BDNF serum concentrations. Molecular Psychiatry. 2009;14:120–2.

Leikin JB, Krantz AJ, Zell-Kanter M, Barkin RL, Hryhorczuk DO. Clinical features and management of intoxication due to hallucinogenic drugs. Medical Toxicology and Adverse Drug Experience. 1989;4:324-50.

Lowenstein DH, Massa SM, Rowbotham MC, Collins SD, McKinney HE, Simon RP. Acute neurologic and psychiatric complications associated with cocaine abuse. American Journal of Medicine. 1987;83:841-6.

Mahoney JJ 3rd, Kalechstein AD, De La Garza R 2nd, Newton TF. Presence and persistence of psychotic symptoms in cocaine- versus methamphetamine-dependent participants. American Journal of Addiction. 2008;17:83-98.

Mahoney JJ 3rd, Hawkins RY, De La Garza R 2nd, Kalechstein AD, Newton TF. Relationship between gender and psychotic symptoms in cocaine-dependent and methamphetamine-dependent participants. Gender Medicine. 2010;7:414-21.

Manschreck TC, Laughery JA, Weisstein CC, Allen D, Humblestone B, Neville M, Podlewski H, Mitra N. Characteristics of freebase cocaine psychosis. Yale Journal of Biology and Medicine. 1988;61:115-22.

Marshall BD, Werb D. Health outcomes associated with cocaine use among young people: a systematic review. Addiction. 2010;105:991-1002.

Mendoza R, Miller BL. Neuropsychiatric disorders associated with cocaine use. Hospital and Community Psychiatry. 1992;43:677-8.

Mendoza R, Miller BL, Mena I. Emergency room evaluation of cocaine-associated neuropsychiatric disorders. Recent Development in Alcoholism. 1992;10:73-87.

Milby JB, Schumacher JE, McNamara C, Wallace D, Usdan S, McGill T, Michael M. Initiating abstinence in cocaine abusing dually diagnosed homeless persons. Drug and Alcohol Dependence. 2000;60:55-67.

Miller BL, Mena I, Giombetti R, Villanueva-Meyer J, Djenderedjian AH. Neuropsychiatric effects of cocaine: SPECT measurements. Journal of Addictive Diseases. 1992;11:47-58.

Mitchell J, Vierkant AD. Delusions and hallucinations of cocaine abusers and paranoid schizophrenics: a comparative study. Journal of Psychology. 1991;125:301-10.

Mooney M, Sofuoglu M, Dudish-Poulsen S, Hatsukami DK. Preliminary observations of paranoia in a human laboratory study of cocaine. Addictive Behavior. 2006;31:1245-51.

Pavarin R, Lugoboni F, Mathewson S, Ferrari AM, Guizzardi G, Quaglio G. Cocaine-related medical and trauma problems: a consecutive series of 743 patients from a multicentre study in Italy. European Journal of Emergence Medicine. 2011;18:208-14.

Mondelli V, Cattaneo A, Belvederi Murri M, Di Forti M, Handley R, Hepgul N, Miorelli A, Navari S, Papadopoulos AS, Aitchison KJ, Morgan C, Murray RM, Dazzan P, Pariante CM. Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume. Journal of Clinical Psychiatry. 2011;72:1677–84.

Narcotics Division 2017. http://www.nd.gov.hk/statistics_list/doc/en/t3.pdf

Petryshen TL, Sabeti PC, Aldinger KA, Fry B, Fan JB, Schaffner SF, Waggoner SG, Tahl AR, Sklar P. Population genetic study of the brain-derived neurotrophic factor (BDNF) gene. Molecular Psychiatry. 2010;15:810–5.

Reid MS, Ciplet D, O'Leary S, Branchey M, Buydens-Branchey L, Angrist B. Sensitization to the psychosis-inducing effects of cocaine compared with measures of cocaine craving and cue reactivity. American Journal of Addiction. 2004;13:305-15.

Rizos EN, Rontos I, Laskos E, Arsenis G, Michalopoulou PG, Vasilopoulos D, Gournellis R, Lykouras L. Investigation of serum BDNF levels in drug-naive patients with schizophrenia. Progress in Neuropsychopharmacology and Biological Psychiatry. 2008;32:1308–11.

Roncero C, Ros-Cucurull E, Daigre C, Casas M. Prevalence and risk factors of psychotic symptoms in cocaine dependent patients. Actas Espanolas Psiquiatria. 2012;40:187–197.

Roncero C, Daigre C, Grau-López L, Rodríguez -Cintas L, Barral C, Pérez-Pazos J, Gonzalvo B, Corominas M, Casas M. Cocaine-induced psychosis and impulsivity in cocaine-dependent patients. Journal of Addictive Diseases. 2013(a);32:263-73.

Roncero C, Martinez-Luna N, Daigre C, Grau-López L, Gonzalvo B, Pérez -Pazos J, Casas M. Psychotic symptoms of cocaine self-injectors in a harm reduction program. Substance Abuse. 2013(b);34:118-21.

Roncero C, Daigre C, Gonzalvo B, et al. Risk factors for cocaine-induced psychosis in cocaine-dependent patients. European Psychiatry. 2013(c);28:141–146.

Roncero C, Daigre C, Barral C, Ros-Cucurull E, Grau-López L, Rodríguez-Cintas L, Tarifa N, Casas M, Valero S. Neuroticism associated with cocaine-induced psychosis in cocaine-dependent patients: a cross-sectional observational study. PLoS One. 2014(a);9:e106111.

Roncero C, Daigre C, Grau-López L, Barral C, Pérez-Pazos J, Martínez-Luna N, Casas M. An international perspective and review of cocaine-induced psychosis: a call to action. Substance Abuse. 2014(b);35:321-7.

Roncero C, Com_ın M, Daigre C, et al. Clinical differences between cocaine-induced psychotic disorder and psychotic symptoms in cocaine-dependent patients. Psychiatry Res. 2014(c) May 30;216:398-403.

Roncero C, Grau-López L, Palma-Álvarez RF, Rodriguez-Cintas L, Ros-Cucurull E, Esojo A, Daigre C. Higher severity of cocaine addiction is associated with tactile and somatic hallucinations. European Psychiatry. 2017;42:63-9.

Roose RB, Collins JP, Fay-McCathy M, Alim TN, Wyatt RI, Deutsch SI. Phenomenologic comparison of the idiopathic psychosis of schizophrenia and drug-induced cocaine and phencyclidine psychoses: a retrospective study. Clinical Neuropsychopharmacology, 1994;4:359-369.

Rosse RB, Alim TN, Johri SK, Hess AL, Deutsch SI. Anxiety and pupil reactivity in cocaine dependent subjects endorsing cocaine-induced paranoia: preliminary report. Addiction. 1995;90:981-4.

Rosse R, Deutsch S, Chilton M. Cocaine addicts prone to cocaine-induced psychosis have lower body mass index than cocaine addicts resistant to cocaine-induced psychosis--Implications for the cocaine model of psychosis proneness. Israel Journal of Psychiatry and Related Sciences. 2005;42:45-50.

Satel SL, Edell WS. Cocaine-induced paranoia and psychosis proneness. American Journal of Psychiatry. 1991;148:1708-11.

Satel SL, Seibyl JP, Charney DS. Prolonged cocaine psychosis implies underlying major psychopathology. Journal of Clinical Psychiatry. 1991;52:349-50.

Sekine Y, Iyo M, Ouchi Y, Matsunaga T, Tsukada H, Okada H, Yoshikawa E, Futatsubashi M, Takei N, Mori N. Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. American Journal of Psychiatry. 2001;158:1206-14.

Serper MR, Chou JC, Allen MH, Czobor P, Cancro R. Symptomatic overlap of cocaine intoxication and acute schizophrenia at emergency presentation. Schizophrenia Bulletin. 1999;25:387-94.

Shaner A, Roberts LJ, Eckman TA, Racenstein JM, Tucker DE, Tsuang JW, Mintz J. Sources of diagnostic uncertainty for chronically psychotic cocaine abusers. Psychiatric Services. 1998;49:684-90.

Sherer MA, Kumor KM, Cone EJ, Jaffe JH. Suspiciousness induced by four-hour intravenous infusions of cocaine. Preliminary findings. Archives of General Psychiatry. 1988;45:673-7.

Simons CJP, Wichers M, Derom C, Thiery E, Myin-Germeys I, Krabbendam L, van Os J. Subtle Gene-environment interactions driving paranoia in daily life. Genes, Brain and Behavior 2009;8:5–12.

Smith MJ, Thirthalli J, Abdallah AB, Murray RM, Cottler LB. Prevalence of psychotic symptoms in substance users: a comparison across substances. Comprehensive Psychiatry. 2009;50:245-50.

Tang YL, Kranzler HR, Gelernter J, Farrer LA, Cubells JF. Comorbid psychiatric diagnoses and their association with cocaine-induced psychosis in cocaine-dependent subjects. American Journal of Addiction. 2007;16:343-51.

Tang YL, Kranzler HR, Gelernter J, Farrer LA, Pearson D, Cubells JF. Transient cocaine-associated behavioral symptoms rated with a new instrument, the scale for assessment of positive symptoms for cocaine-induced psychosis (SAPS-CIP). American Journal of Addiction. 2009;18:339-45.

Tang YL, Martin NL, Cotes RO. Cocaine-induced psychotic disorders: presentation, mechanism, and management. J Dual Diagnosis. 2014;10:98-105.

Tang WK, Tang A, Chan F, Zhang CX. Research Report on Ice Induced Psychosis: a Literature Review. Beat Drug Fund Association. 2017.

Thoenen H: Neurotrophins and neuronal plasticity. Science 1995;270:593–8.

Trape S, Charles-Nicolas A, Jehel L, Lacoste J. Early cannabis use is associated with severity of Cocaine-Induced Psychosis among cocaine smokers in Martinique, French West Indies. Journal of Addiction Medicine. 2014;8:33–39.

Unnithan SB, Cutting JC. The cocaine experience: refuting the concept of a model psychosis? Psychopathology. 1992;25:71-78.

Vergara-Moragues E, González-Saiz F, Lozano OM, Betanzos Espinosa P, Fernández Calderón F, Bilbao-Acebos I, Pérez García M, Verdejo García A. Psychiatric comorbidity in cocaine users treated in therapeutic community: substance-induced versus independent disorders. Psychiatry Research. 2012;200:734-41.

Vergara-Moragues E, Araos Gómez P, González-Saiz F, Rodríguez-Fonseca F. Cocaine-induced psychotic symptoms in clinical setting. Psychiatry Research. 2014;217:115-20.

Vergara-Moragues E, Mestre-Pintó JI, Gómez PA, Rodríguez-Fonseca F, Torrens M, González-Saiz F. Can symptoms help in differential diagnosis between substance-

induced vs independent psychosis in adults with a lifetime diagnosis of cocaine use disorder? Psychiatry Research. 2016;242:94-100.

Vorspan F, Bloch V, Brousse G, Bellais L, Gascon J, Lépine JP. Prospective assessment of transient cocaine-induced psychotic symptoms in a clinical setting. American Journal of Addiction. 2011;20:535-7.

Vorspan F, Brousse G, Bloch V, et al. Cocaine-induced psychotic symptoms in French cocaine addicts. Psychiatry Research. 2012;200:1074–76.

Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. Archives of General Psychiatry. 1986;3:114–24.

Willi TS, Lang DJ, Honer WG, Smith GN, Thornton AE, Panenka WJ, Procyshyn RM, Vila-Rodriguez F, Su W, Vertinsky AT, Leonova O, Rauscher A, MacEwan GW, Barr AM. Willi TS, Lang DJ, Honer WG, Smith GN, Thornton AE, Panenka WJ, Procyshyn RM, Vila-Rodriguez F, Su W, Vertinsky AT, Leonova O, Rauscher A, MacEwan GW, Barr AM. Schizophrenia Research. 2016;176:158-63.

Xiu MH, Hui L, Dang YF, Hou T De, Zhang CX, Zheng YL, Chen DC, Kosten TR, Zhang XY. Decreased serum BDNF levels in chronic institutionalized schizophrenia on long-term treatment with typical and atypical antipsychotics. Progress in Neuropsychopharmacology and Biological Psychiatry. 2009;33:1508–12.

Zayats T, Yang BZ, Xie P, Poling J, Farrer LA, Gelernter J. A complex interplay between personality domains, marital status and a variant in CHRNA5 on the risks of cocaine, nicotine dependences and cocaine-induced paranoia. PLoS One. 2013;8:e49368.