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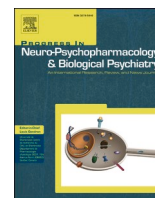
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## A systematic review and meta-analysis of the prevalence of cocaine-induced psychosis in cocaine users

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### 1. Introduction

Cocaine is by far the most commonly used illicit psychostimulant in the Americas and in Europe (UNODC, 2019). In 2017, there were 18 million global cocaine users according to the United Nations World Drug Report, and its production remains at record levels (UNODC, 2019).

Cocaine is an unspecific monoamine reuptake inhibitor that increases extracellular concentrations of dopamine, noradrenaline and serotonin (Fitzgerald, 2013; Howell and Negus, 2014). It directly affects mesolimbic dopamine neurotransmission in the reward pathway by increasing extracellular dopamine concentrations through the inhibition of dopamine reuptake in the ventral tegmental area (Porrino et al., 2007; Smith and Laiks, 2018). On a phenomenological level, cocaine can increase energy, positive emotions and confidence. However, this psychostimulant is highly addictive, and its use can have severe medical, psychosocial and psychiatric consequences (Davis, 1996; Karila et al., 2012; Vonmoos et al., 2014). Among its psychiatric consequences, several studies strongly suggest a relationship between cocaine use and the development of acute psychosis, commonly known as ‘cocaine-induced psychosis’ (CIP). It has long been known that during cocaine use, delusions and paranoid reactions occur (Brady et al., 1991; Satel et al., 1991). These symptoms can mimic the positive symptoms of schizophrenia (Ujike, 2002). Some psychotic symptoms seem to be more prevalent in patients with CIP than in those with schizophrenia. This concerns visual hallucinations and in particular tactile hallucinations that are associated with delusions of parasitosis (Brewer et al., 2008; Mitchell and Vierkant, 1991).

The diagnostic criteria for CIP have evolved over the last decades, with an emphasis on the distinction between transient and persistent symptoms (Roncero et al., 2014b). Indeed, in most cases, cocaine-induced psychotic symptoms (CIPS) are transient and usually disappear with abstinence (Vorspan et al., 2012). However, these symptoms can become more severe with continued cocaine use and can last for many weeks after the last use of the substance. Therefore, chronic

cocaine users can develop a ‘substance-induced psychotic disorder’ (SIPD) secondary to cocaine, described as a ‘cocaine-induced psychotic disorder’ (CIPD) in the DSM (APA, 2013; Roncero et al., 2014a). Some authors suggest that CIPS and CIPD should be considered two distinct psychiatric entities (10). Nevertheless, only a subset of cocaine users affected by CIPS will develop a CIPD, and this distinction is rarely evoked in studies on the subject (Roncero et al., 2014a). In this context, it is important to keep in mind that SIPD can transition to schizophrenia which represents an unfavorable outcome (Murrie et al., 2020). Murrie and colleagues did not identify any study reporting transition rates for CIPD, but the mean transition rate for patients with amphetamine-induced psychotic disorder was 22%.

Due to the heterogeneity in definitions of CIP, different classifications are used to assess psychotic symptoms following cocaine use. A categorical approach is employed in the DSM, which specifies narrow criteria that lead to a diagnosis of CIPD (SIPD). Various measurement tools have initially been developed to detect CIPS, such as the Cocaine Experience Questionnaire (CEQ) (Satel et al., 1991). This scale focuses on clinical aspects considered to be typical in individuals with CIP and mainly measures ‘cocaine-induced paranoia’ and other features, such as hallucinations. More recently, the Scale for Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP) was developed (Cubells et al., 2005). The SAPS-CIP is a semi-structured clinical interview used to evaluate the presence of CIP at any moment of a person’s lifetime. This scale was adapted from the scale for the assessment of positive symptoms that is commonly used for patients with primary psychotic disorders (Andreasen, 1984). Compared to the CEQ, this scale presents similar sensitivity, but it also enables the quantification of the severity of the CIP. Despite these advances in scale development, the distinction between CIP and schizophrenia remains challenging (Vergara-Moragues et al., 2016).

Some studies report that the prevalence of CIP among current cocaine users is moderate and ranges from 40 to 66% (Elangovan et al., 1993; Mooney et al., 2006). In addition, several authors have studied the

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lifetime prevalence of CIP and found a much wider range from 9.6 to 91% (Gonzalez-Saiz et al., 2014; Reid et al., 2004). Notably, most studies include specific populations and vary considerably with respect to the inclusion criteria, the diagnostic criteria for CIP and the presence of other comorbid substance use disorders.

To the best of our knowledge, there is no available meta-analysis on the prevalence of CIP in cocaine users despite its commonly acknowledged clinical relevance. Therefore, we conducted a meta-analysis of the prevalence of CIP in current cocaine users and the lifetime prevalence of CIP related to lifetime cocaine use. Furthermore, since various criteria for CIP have been used, we aimed to conduct a subgroup analysis to determine the impact of defining CIP as CIPS or CIPD/SIPD on its prevalence.

## 2. Methods

### 2.1. Registration

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher et al., 2009) and the Meta-analysis for Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). On 14 July 2020, the PRISMA protocol was published in the International Prospective Register of Systematic Reviews (registration number CRD42020179683).

### 2.2. Outcomes

The primary outcome was the prevalence of CIP among current or lifetime cocaine users who have no pre-existing primary psychotic or mood disorder with psychotic features. In current users, we aimed to detect current CIP, and in lifetime users, we focused on lifetime CIP. While we were initially focusing on CIPD (SIPD), our systematic review revealed that in most articles, specific instruments targeting CIPS were used. Therefore, we decided to combine CIPS and CIPD (SIPD) under the term CIP. Importantly, we targeted the prevalence of current CIP in current users and lifetime CIP in lifetime users.

### 2.3. Search strategy

The PubMed, MEDLINE, Embase, PsycINFO and PsycARTICLE databases were searched up to 31st August 2020 using a combination of MeSH terms and specific search terms (keywords): (schizo\* or psychotic or psychosis) and ('cocaine' or 'crack' or 'coke' or 'coca leaves' or 'speedball' or 'psychoactive substance').

The following search limits were applied: English language, human studies and adult population. The titles, abstracts, and/or methods of all papers that were identified in the literature search were inspected independently by two authors (MS and NZ). The full texts of articles and reviews were obtained, and snowball searches of reference lists were conducted by cross-referencing key papers and other relevant articles identified by the electronic searches.

### 2.4. Eligibility criteria

We included studies that (a) had a cross-sectional, case-control or cohort design that included participants with current or past cocaine use (use, abuse, dependence); (b) reported the prevalence of cocaine use; (c) either excluded patients with primary psychotic (schizophrenia, schizoaffective disorder) and mood disorders with psychotic features (bipolar disorder or major depression with psychotic features) or had clearly distinguished these populations from the CIP population.

Studies were excluded for the following reasons: (a) the diagnosis of CIPS, CIPD or SIPD was based exclusively on retrospective chart review; (b) the included population was limited to patients with CIPS, CIPD or SIPD, as such studies would inflate prevalence rates; (c) the included population did not use cocaine as the main drug of choice; (d) there was

no report of the prevalence of CIPS, CIPD or SIPD (lifetime or current CIPS). Case reports and qualitative studies were also excluded.

### 2.5. Data extraction

Two authors (MS and NZ) extracted data from the retrieved articles using a predefined data extraction form. The following data were extracted: year that the study was conducted, geographical area, setting, population, type of study, assessment tools used to diagnose CIP, mean age, percentage of men, proportion of abuse and dependence on cocaine, age at onset of cocaine use and duration of use, comorbid substances, and route of administration of the drug. Any disagreements were resolved by consensus or by the decision of a third reviewer (SK).

### 2.6. Risk of bias

Two authors (MS and NZ) independently evaluated the risk of bias using a specific tool built for the assessment of prevalence studies developed by Hoy and colleagues (Hoy et al., 2012). This tool consists of 10 items addressing external validity (case selection, nonresponse bias) and internal validity (measurement bias, bias related to the analysis) in addition to a summary item to assess the overall risk of bias. Response options for individual items were either low or high risk of bias. If there was insufficient information in the article, the item was deemed to be at high risk of bias. As described by Hoy and colleagues, the summary for the overall risk was based on a judgment of the overall risk of study bias based on the 10 individual items. Two authors (MS and NZ) independently performed assessments.

CIPS cases were defined in some studies by the presence of only one psychotic symptom. Since this threshold is much lower than that used for the majority of studies assessing CIPS and because such specific criteria could inflate the prevalence estimates, these studies were considered to have a high risk of bias for the case definition item (item 6).

### 2.7. Statistical analysis

The prevalence of CIP and its variance in each study was computed. A random effects meta-analysis model was chosen to take into account the anticipated heterogeneity among the included studies (DerSimonian and Kacker, 2007). The variance within and between studies was used to calculate the variance of the pooled prevalence. Between-study heterogeneity was assessed using the  $I^2$  statistic and the  $Q$  test, which describes the percentage of variability due to heterogeneity between studies rather than the sampling error (Higgins et al., 2003). An  $I^2$  value below 25% indicates low heterogeneity, an  $I^2$  value between 25 and 50% indicates moderate heterogeneity, an  $I^2$  value between 50 and 75% indicates substantial heterogeneity, and an  $I^2$  value more than 75% indicates considerable heterogeneity. For binomial data, prevalences were used as effect sizes. Publication bias was not investigated, as the chance of the publication of a study reporting a prevalence for our main outcome generally does not vary with the reported prevalence. All meta-analyses were carried out using R software version 3.1.1. using the metafor package (Viechtbauer, 2010).

Since two previous meta-analysis found a wide range of prevalences when studying methamphetamine, we anticipated finding similarly broad ranges (Lecomte et al., 2018; Murrie et al., 2020). Therefore, the logits of proportions method was employed for the statistical analysis (Berkson, 1944). We decided to perform separate analyses based on potential influences on prevalence estimates: the current and lifetime prevalence of CIP.

Additionally, residual heterogeneity and inconsistency were explored with sensitivity analyses. Subgroup analyses were conducted based on different variables that were a priori considered as potential sources of variance in the estimates of prevalence: (a) CIP definition (CIPS vs CIPD/SIPD); (b) risk of bias (low versus high); (c) instrument

used to assess CIP diagnosis; (d) geographical area; (e) the total number of inclusions; and (f) percentage of individuals with a cocaine use disorder in the studies. Furthermore, meta-regressions for potential moderators were planned (e.g., year of publication of the study).

### 3. Results

#### 3.1. Search results

From the 1688 references retrieved in the literature search, the full texts of 226 articles were analyzed, and 20 studies were finally included for qualitative and quantitative analyses (Fig. 1). A detailed description of each included study is available in the supplementary materials (see Supplementary Table S1). All studies were cross-sectional with the exception of three challenge studies (Kalayasiri et al., 2006b; Mooney et al., 2006; Reid et al., 2004).

#### 3.2. Studies and patient characteristics

A total of 5388 patients were included. The mean sample size was 269.2 (23 to 2192 inclusions). Nearly all studies examined predominantly males, with a mean proportion of 68% (49 to 100%). Two studies included only men (Reid et al., 2004; Satel et al., 1991). The mean age across all studies was 37.0 years (23 to 45 years). The mean age of first cocaine use was reported by 11 studies ( $n = 1888$ ) and was 22.2 (19.2 to 34 years). The mean number of years of cocaine consumption was reported by 7 studies ( $n = 916$ ) and was 22.4 (20.8 to 30 years). Most studies were conducted in the United States of America ( $n = 13$ ), followed by Spain ( $n = 4$ ), the French Caribbean ( $n = 1$ ), Canada ( $n = 1$ ) and Brazil ( $n = 1$ ).

Only few studies reported concomitant use of other substances. For

those examining current cocaine use, the mean prevalence of current use of other substances was 39.5% ( $n = 2$ ) for alcohol, 50.1% ( $n = 2$ ) for opioids, 39.7% ( $n = 3$ ) for cannabis and 30.8% ( $n = 1$ ) for using other stimulants. For the studies reporting lifetime cocaine use, the lifetime prevalence for a comorbid dependence to other substances was reported as follows: 56.5% ( $n = 3$ ) for alcohol, 30% ( $n = 2$ ) for opioids and 32% ( $n = 2$ ) for cannabis.

Three studies examined current cocaine use, and 17 studies examined the lifetime use of cocaine. Based on our inclusion criteria, three studies that reported CIP were excluded. Two studies (Araos et al., 2015; Pavon et al., 2013) had overlapping samples; only the Araos study was retained because it directly provided CIP prevalence data. One study did not report in detail the population that was used to assess the prevalence of CIP (Herbeck et al., 2006). One study assessed the presence of pre-existing psychotic disorders in only some of the included patients (Vorspan et al., 2012).

All included studies used either the DSM-III or the DSM-IV to assess cocaine dependence and to exclude or diagnose individuals affected with a primary psychiatric disorder. However, different assessment instruments were used for CIP diagnosis.

It is important to note that the identified articles described the prevalence of CIP in a population of individuals who were either seeking or already in treatment, suggesting that their cocaine consumption was problematic to some extent. Indeed, most of the studies examining the lifetime use of cocaine recruited participants via outpatient treatment centers for addiction, except for one study that recruited cocaine users via an inpatient facility for the treatment of cocaine dependence (Brady et al., 1991).

For the studies reporting current use of cocaine, only outpatients were included. One study focused on consecutive referrals at a psychiatric emergency unit (Elangovan et al., 1993). In addition, two studies

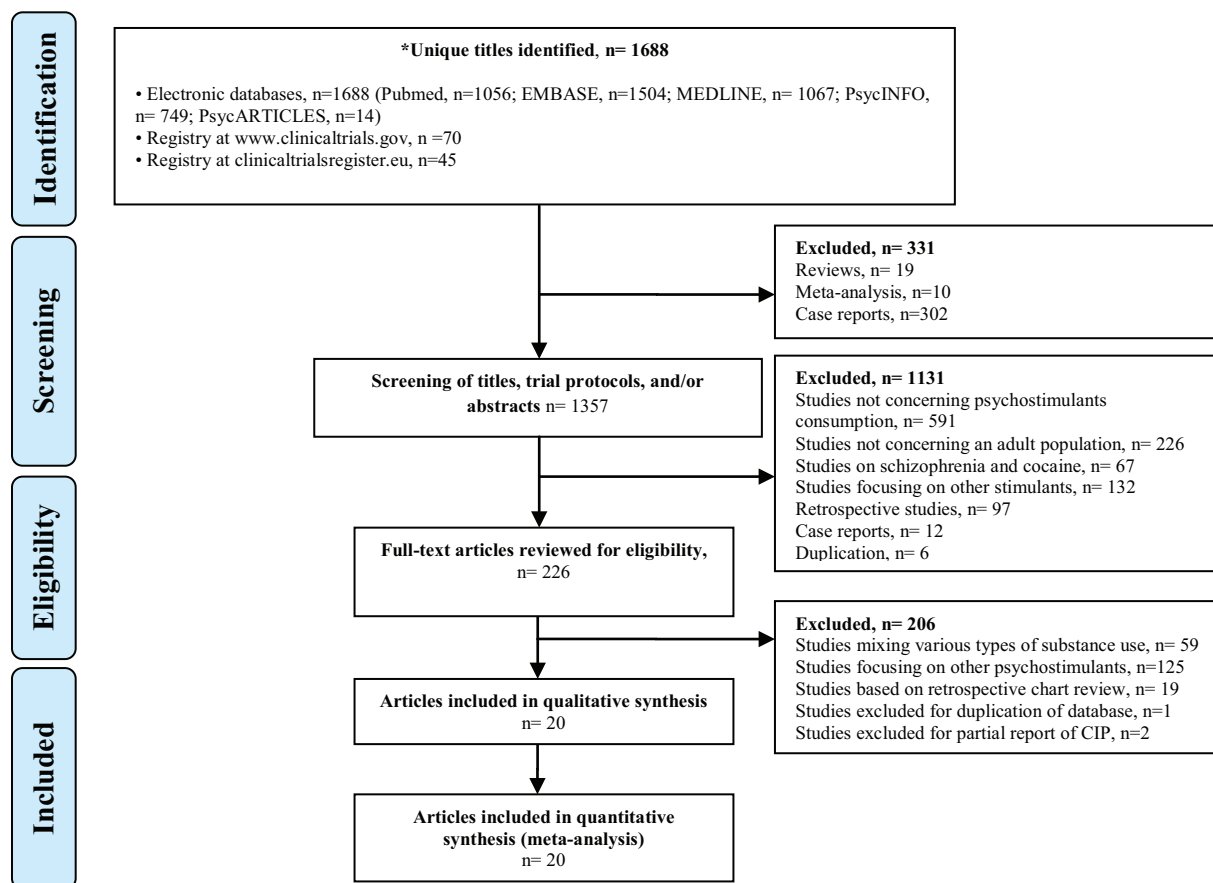


Fig. 1. Systematic review PRISMA flow-chart.

used a cocaine challenge under controlled laboratory conditions to test the induction of psychotic symptoms (Kalayasiri et al., 2006b; Mooney et al., 2006). Notably, while cocaine was the main drug of choice for participants in both current use and lifetime studies, a minority of participants fulfilled the dependence criteria for other substances.

### 3.3. Outcome measurement

Different instruments were used to establish CIP. While the focus on CIPS enables the quantification of the severity of CIP, a categorical approach was used for the diagnosis of CIPD.

In 13 studies, a detailed clinical assessment of CIPS was conducted, mostly with the Cocaine Experience Questionnaire (CEQ) (Satef et al., 1991) and the Scale for Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP) (Cubells et al., 2005). Several studies employed study-specific questions regarding CIPS (see Supplementary Table S1). Fewer criteria are required to detect CIPS than for a diagnosis of CIPD (SIPD) according to the DSM.

Five studies estimated CIPD prevalence with the use of semi-structured interviews: the Psychiatric Research Interview for Substance and Mental Diseases (PRISM) was used in four studies (Araos et al., 2015; Elangovan et al., 1993; Gonzalez-Saiz et al., 2014; Vergara-Moragues et al., 2012), and the Mini-International Neuropsychiatric Interview was used in one study to conduct a lifetime review of substance exposure (Willi et al., 2017). Importantly, the PRISM was designed specifically to differentiate among primary mental disorders and substance-induced disorders (Hasin et al., 1996). Based on these interviews, CIP was considered to be a specific categorical diagnostic (CIPD/SIPD) according to the DSM.

Most studies directly reported the prevalence of CIP. However, for 3 studies, the CIPS prevalence had to be extracted by a detailed examination of the reported results, as these studies did not exclude patients with primary psychosis from their analyses (Araos et al., 2015; Elangovan et al., 1993; Vergara-Moragues et al., 2012).

### 3.4. Risk of bias

The risk of bias tool used for the assessment of prevalence studies revealed that for the current use group, 2 studies (50%) had a low risk of bias. For the lifetime use group, 15 studies (75%) had a low risk of bias (see Supplementary Table S2). It is noteworthy that two studies diagnosed CIP as only showing at least one psychotic symptom (Miguel et al., 2018; Vergara-Moragues et al., 2014).

### 3.5. CIP in current cocaine users

In the current use group (3 studies,  $n = 102$ ), the pooled prevalence of CIP was 50.2% (95% CI: 32.0–68.4), and there was substantial heterogeneity among these studies ( $I^2 = 66%$ ) (Fig. 2). A leave-one-out analysis suggested that the study by Mooney and colleagues could be an outlier. Excluding this study led to a slightly lower prevalence of CIP, i.e., 41.4% (95% CI: 29.5–54.4), and there was no heterogeneity ( $I^2 = 0%$ ). This result has to be interpreted with caution, because the Mooney study has the largest sample size of only three studies and has a low risk of bias.

Since these studies used different definitions of CIP, we conducted a subgroup analysis by separating the studies that examined CIPD (SIPD) and those that reported CIPS (Fig. 2). The prevalence among the CIPD subgroup (40.0%, 95% CI: 14.9–71.7) was slightly lower than that for the CIPS subgroup (55.2%, 95% CI: 32.8–75.7), and there was substantial heterogeneity among these studies ( $I^2 = 72%$ ). The CIPS versus CIPD moderators did not explain the heterogeneity, as the residual heterogeneity was still high ( $I^2 = 72%$ ). Furthermore, the two CIPS studies were the two studies with a low risk of bias according to our risk of bias tool in this subgroup (see Supplementary Fig. S1).

### 3.6. CIP in lifetime cocaine users

In lifetime cocaine users (17 studies,  $n = 5286$ ), the pooled prevalence of CIP was 55.6% (95% CI: 50.2–61.0), and there was a considerable level of heterogeneity between studies ( $I^2 = 97%$ ) (Fig. 3). A leave-one-out analysis did not reveal any outliers among the included studies.

For the current use group, we conducted a subgroup analysis by separating studies that defined CIP as CIPS and those that defined CIP as CIPD (SIPD) (Fig. 3). The studies assessing CIPS reported a high prevalence of 68.4% (95% CI: 62.8–73.5). In contrast, studies requiring a CIPD diagnosis had a prevalence of 16% (95% CI: 10.6–23.2). In both subgroups, considerable heterogeneity remained ( $I^2 = 89%$  and 89%, respectively). These subgroups could only slightly reduce the observed heterogeneity, with a residual heterogeneity of 89%.

This subgroup analysis was repeated among only studies with a low risk of bias. Fourteen studies were retained (see Supplementary Fig. S2). The resulting CIP prevalence remained similar at 55.6% (95% CI: 50.5–60.6), and there was considerable heterogeneity among these studies ( $I^2 = 97%$ ). A small reduction of the residual heterogeneity was observed ( $I^2 = 86%$ ). For the CIPS subgroup, the CIP prevalence was 68.3% (95% CI: 63.2–73.1), and there was considerable heterogeneity

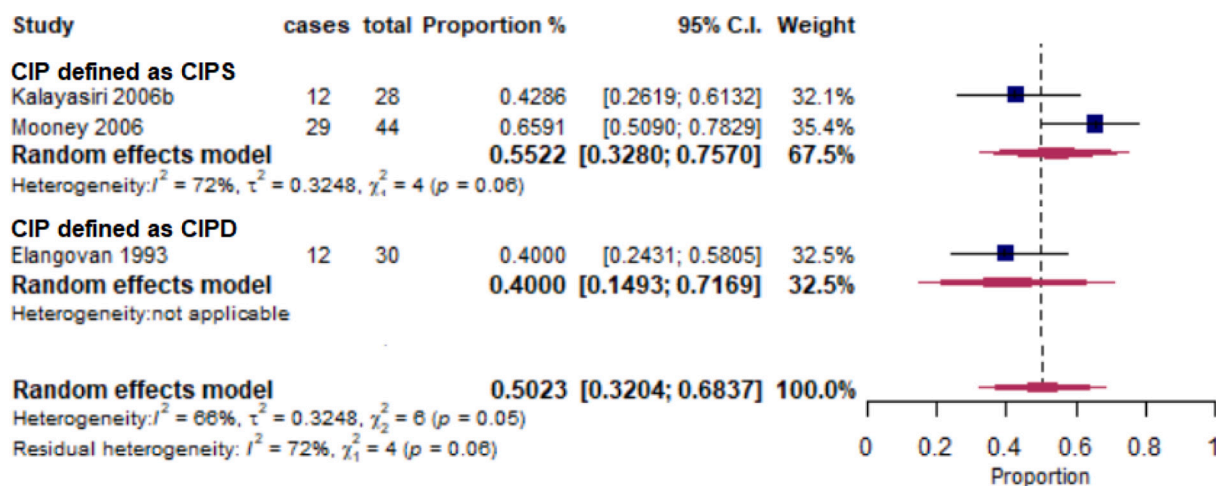


Fig. 2. Prevalence of CIP among current cocaine users regarding the CIP definition as CIPS or CIPD (SIPD). Forest plots are used to visualize the prevalence in each study and the combined estimated prevalence with their 95% confidence intervals (95% CI). The composite event rate of cocaine-induced psychotic symptoms - or substance-induced psychotic disorder - was 50.2% in current users of cocaine.

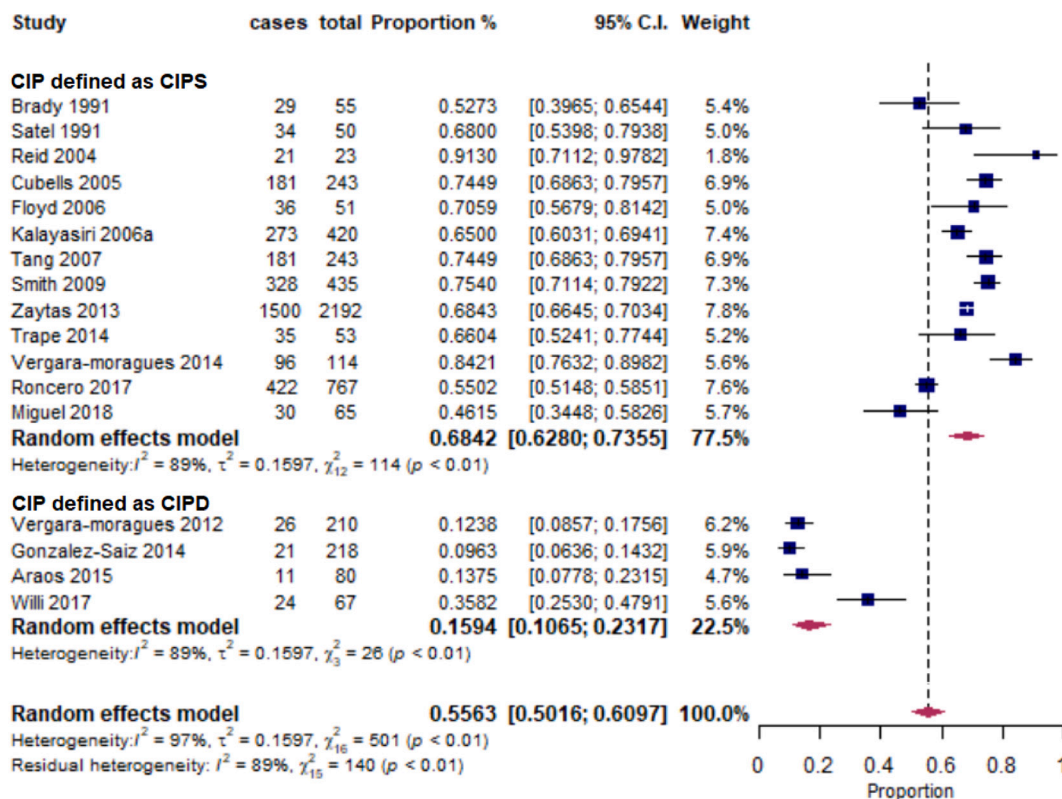


Fig. 3. Forest plot for CIP prevalence in lifetime cocaine users. A subgroup analysis is conducted according to the CIP definition as CIPS or CIPD (SIPD).

( $I^2 = 89\%$ ). For the CIPD subgroup, the CIP prevalence was 11.7% (95% CI: 7.6–17.4), and there was no heterogeneity ( $I^2 = 0\%$ ).

### 3.7. Exploring heterogeneity in the lifetime cocaine use group

Since only 3 studies were included in the current use group, we focused on the lifetime use group to explore the high level of heterogeneity observed by conducting further subgroup analyses.

### 3.8. Subgroup analyses according to the instruments used for CIP diagnosis

To further explore the impact of instruments on the CIP prevalence, additional subgroup analyses were conducted based on the different types instrument used for CIP diagnosis (Supplementary Fig. S3).

To estimate the CIPS prevalence, 6 studies used the CEQ; the prevalence rate was 70.1% (95% CI: 62.6–76.7), and there was moderate heterogeneity ( $I^2 = 50$ ). One study used the SAPS-CIP and found a CIPS prevalence rate of 84.2% (95% CI: 69.0–92.7). In addition, six studies used neither the CEQ nor the SAPS-CIP but instead used various study-specific questions to obtain the CIP prevalence. The obtained prevalence rate in these studies was 63.4% (95% CI: 55.2–70.9), and there was substantial heterogeneity ( $I^2 = 94\%$ ).

For CIPD prevalence, three studies used the PRISM and found a prevalence rate of 11.7% (95% CI: 7.4–17.9). One study used the Mini-International Neuropsychiatric Interview to conduct a lifetime review of substance exposure and found a prevalence rate of 35.8% (95% CI: 18.9–57.1).

With these subgroups, a small reduction of the residual heterogeneity was observed ( $I^2 = 87$ ).

### 3.9. Subgroup analyses for geographical area, total number of included patients and proportion of individuals with cocaine dependence

Since the subgroup analysis regarding assessment instruments only partially explained the observed heterogeneity, we conducted additional subgroup analyses.

We conducted a subgroup analysis focusing on the geographical area. A high prevalence of CIP was found in studies conducted in North America (66.5%, 95% CI: 57.6–74.3) (mainly the United States of America), while lower prevalences were found among studies conducted in South America and the Caribbean (56.1%, 95% CI: 34.2–75.5) and Europe (25.1%, 95% CI: 15.1–38.6) (Spain and France) (see Supplementary Fig. S4). Within these subgroups, considerable heterogeneity remained ( $I^2 = 91\%$ ,  $I^2 = 78\%$  and  $I^2 = 98\%$ ). This subgroup analysis did not reduce residual heterogeneity ( $I^2 = 95\%$ ).

We conducted another subgroup analysis based on the total number of included patients in each study, separating studies with fewer than 60, between 60 and 200, and more than 200 individuals (see Supplementary Fig. S5). For the first subgroup (<60 inclusions), the prevalence estimate was 69.2% (95% CI: 52.8–81.9); for the second subgroup (60 to 200 inclusions), the prevalence was 36.2% (95% CI: 22.8–52.3); and for the third subgroup (>200 inclusions), the prevalence was 59.8% (95% CI: 46.7–71.7). Despite the numerical difference in prevalence estimates, this subgroup analysis did not reduce the residual heterogeneity ( $I^2 = 96\%$ ).

Another subgroup analysis was conducted to differentiate studies where a majority of patients met the criteria for cocaine dependence ( $n = 4$ ) from those that only included patients who met the criteria for cocaine dependence ( $n = 13$ ) (see Supplementary Fig. S6). The prevalence rates were similar between groups: 53.5% (95% CI: 33.4–72.5) and 54.3% (95% CI: 44.8–67.2), respectively. There was considerable heterogeneity in both subgroups ( $I^2 = 97\%$ ), and no impact on residual heterogeneity was observed ( $I^2 = 97\%$ ).

Finally, no analysis regarding the route of cocaine administration

was conducted due to the paucity of available data.

### 3.10. Meta-regression

A univariate meta-regression was conducted to explore the reasons for the high level of heterogeneity observed in the lifetime use group. Since individual-level data were not available in the retained studies, we could not explore the variables linked to individuals' characteristics, such as age or sex and variables related to cocaine use (e.g., the amount of cocaine used per week or the number of years of cocaine use). Therefore, the only independent variable explored was the year of publication, which did not explain the heterogeneity (see Supplementary Fig. S7).

## 4. Discussion

### 4.1. Summary of the main findings

Our meta-analysis revealed that the prevalence of CIP is high for both current cocaine users (50.2%) and lifetime cocaine users (55.6%). However, the sample size for the current use group was very small. In addition, most results were limited by the presence of considerable heterogeneity in both the current and lifetime groups. This considerable heterogeneity reflects the large range of prevalence rates reported among studies.

The only moderator accounting for heterogeneity was the definition of CIP as either CIPS or CIPD. These analyses revealed that the CIPS prevalence was higher than the CIPD prevalence in both current users (55.7% vs 40.0%) and lifetime users (68.4% vs 15.9%). When only considering studies with a low risk of bias, CIP prevalence estimates remained comparable to the prevalence across all studies.

### 4.2. High prevalence of CIP

A high prevalence of CIP has been suggested in previous narrative reviews of the literature (Roncero et al., 2014b, Tang et al., 2014a). The present study is the first to provide meta-analytical evidence for the high prevalence of current and lifetime CIP. Since specific instruments for the assessment of CIP were used in the original studies, it was possible to distinguish between studies focusing on CIPS and those focusing on CIPD. While this approach revealed that CIPS is more prevalent than CIPD, this approach led to a small reduction of heterogeneity only in the lifetime user group.

Overall, these findings are consistent with the notion that the likelihood of developing psychosis is higher among users of cocaine and other psychostimulants than among users of other common drugs (Roncero et al., 2017). This is consistent with the fact that these substances increase striatal dopamine release, which is considered to be a key mechanism of primary psychotic disorders and which is already observable in the at-risk mental state (Bonoldi and Howes, 2013). Nevertheless, since cocaine consumption was associated with the use of other drugs in all studies, we cannot be certain that cocaine is directly responsible for the occurrence of psychotic symptoms. Some studies found that the initiation of cannabis use during adolescence is a risk factor for the occurrence and severity of CIP in cocaine-dependent individuals (Kalayasiri et al., 2006a; Trape et al., 2014). In addition, lifetime and recent use of cannabis may also be associated with CIP (Roncero et al., 2014a). However, Tang and colleagues have observed that concomitant substance use disorder does not significantly impact the prevalence of CIP after adjusting for age and gender (Tang et al., 2007). In addition, there are phenomenological differences between cocaine- and cannabis-induced psychoses, although there is certainly some overlap (Kulhalli et al., 2007; Roncero, Roncero et al., 2014a). Overall, these studies suggest that there might be an interaction of cocaine and current or previous cannabis use, but it is very unlikely that the present findings reflect cannabis-induced psychosis.

Overall, reporting of concomitant use of other substances was incomplete. In the studies reporting concomitant use an important fraction used alcohol and/or opioids in addition to cocaine, but it was not possible to determine the contribution to the prevalence of CIP. However, it has to be noted that the propensity of alcohol and opioids to cause psychotic symptoms is considered to be lower than for cannabis and stimulants, which may limit the impact on the CIP prevalence observed in the present study (Engelhard et al., 2015; Lecomte et al., 2018, Smith et al., 2009). Overall, these findings highlight the importance of assessing the use of all drugs that might be combined with cocaine.

Compared to previous findings on the prevalence of psychosis induced by psychostimulants, such as methamphetamine, our findings are not surprising. In an important meta-analysis, Lecomte and colleagues showed that individuals affected by methamphetamine use disorders present a lifetime prevalence of substance-induced psychosis of 42.7% (Lecomte et al., 2018). While our results suggest a higher prevalence of overall lifetime CIP (54.7%), the specific prevalence of CIPD is lower (16% in lifetime users). These potential differences should be interpreted with care and can potentially be explained by methodological differences between the original studies on cocaine and methamphetamine. Importantly, the original meta-analysis by Lecomte et al. did not allow us to distinguish between methamphetamine-induced psychotic symptoms versus disorder. In our meta-analysis, since specific instruments regarding CIP were used, it was possible to distinguish between studies focusing on CIPD and CIPS. Overall, this comparison suggests that the risk of developing SIPD might be higher among methamphetamine users than among cocaine users, while a comparison of the risk for substance-induced symptoms would require a more specific instrument for assessing methamphetamine users.

Importantly, the observed prevalence estimates in both groups may be underestimated because cocaine users show impaired insight into their drug-seeking behavior, as drug consumers can present a lack of awareness of their symptoms and of the severity of their dependence on the drug (Moeller et al., 2014; Niigaki et al., 2010).

### 4.3. Limitations

The considerable heterogeneity observed in the results is closely linked to the limitations of our meta-analysis.

The first limitation concerns the outcome measurements with the conceptual difference between CIPS and CIPD. This difference was explored in the subgroup analyses regarding CIPS and CIPD criteria and the different instruments used in studies. The different criteria used for CIPS and CIPD directly affected the prevalence of CIP. For example, when considering the semi-structured diagnostic PRISM, which is specific to CIPD, the prevalence was 11.6%, and there was no heterogeneity. This lower prevalence estimate is explained by the restrictive criteria used for CIPD (SIPD) based on the DSM. In contrast, the CEQ and the SAPS-CIP are two instruments that were established to quantify the psychotic symptoms in cocaine users ranging from transient to persistent psychotic symptoms; a high prevalence of CIP was reported in studies using these instruments (70% and 84%, respectively). Furthermore, since almost all studies were cross-sectional in design and used retrospective assessments of cocaine use history, it is difficult to draw conclusions concerning the causal association of cocaine use with CIP.

A further limitation concerns the heterogeneous and often incomplete assessment of exposure, such as assessments of the dose of cocaine and the severity of cocaine dependence. One laboratory study reported that CIP is dose-dependent (Kalayasiri et al., 2006b). Furthermore, Smith and colleagues found that psychotic symptoms increased with the severity of cocaine dependence (Smith et al., 2009). Only two other studies reported dependence severity (Vergara-Moragues et al., 2012), with similar results to Smith and colleagues. Another important issue in this context is the potential effect of cocaine dose. Only two studies on lifetime CIP reported an estimated lifetime dose of cocaine, which was

higher in patients with CIP than those without CIP. Therefore, we did not have enough data to explore severity of dependence and dose effects, and various other variables could not be explored since individual-level data were not available.

Furthermore, due to the paucity of available data, we were unable to explore the impact of polysubstance use or examine the impact of the route of administration on CIP prevalence. These two features are important, as Roncero and colleagues reported a high rate (62%) of psychotic symptoms in association with the self-injection of cocaine (Roncero et al., 2013). Since this route of administration of cocaine indicates a serious level of addiction (Gossop et al., 1994) and is associated with cannabis use (Roncero et al., 2013), it is uncertain whether this effect is specific to self-injection. The limited data available did not allow us to address this question in our meta-analysis. It was also not possible to assess differential effects of crack vs powder cocaine.

Finally, one important limitation concerns the specific populations targeted in the included studies, which mostly consisted of treatment seekers recruited in outpatient clinics, in emergency services or in hospitals. These clinical populations limit our findings to similar care contexts, as the high prevalence found herein could be inflated by selection bias and admission rate bias (Berkson, 1946). The combination of exposure to a risk and occurrence of the disease makes it more likely that an individual will be hospitalized or seek treatment. Therefore, the prevalence of CIP could be overestimated when examining patients who are seeking or receiving treatment.

#### 4.4. Clinical relevance

Prevention and treatment strategies to address cocaine use continue to fall far short of needs in many parts of the world (Soyka and Mutschler, 2016). The high prevalence of CIPS and CIPD reported herein raises concerns regarding public health and individual treatment.

A systematic evaluation of psychotic symptoms can be beneficial for the patient and the community to prevent psychotic states, hostile behavior and their associated negative consequences (Roncero et al., 2014b). Although the transition rate from CIP to schizophrenia is not known, data from patients with amphetamine-induced psychotic disorders suggest that the risk for patients with CIP may also be increased (Murrie et al., 2020). Thus, in addition to prevention of direct negative consequences of CIP, prevention of a transition to schizophrenia may be an additional treatment goal.

A screening should include transient psychotic symptoms that can have negative consequences in themselves and can precede persistent psychotic symptoms. We propose that professionals in contact with cocaine users systematically evaluate the occurrence of such symptoms. Simple screening questions regarding paranoia and hallucinations can be adapted from the CEQ or the SAPS-CIP. In case of an affirmative response, the full CEQ or the SAPS-CIP can be administered to the patient. To better target this evaluation, prospective studies are needed to examine which aspects of cocaine use (dose, years of consumption, age at onset of cocaine use, route of administration, etc.) could increase the risk of developing transient or persistent psychotic disorder or even contribute in the onset of schizophrenia. In the future, the inclusion of biomarkers to identify cocaine use at risk for CIP would be of high interest, but despite some interesting findings on the genetic predisposition for CIP the current evidence does not yet allow a clinical application (Roncero et al., 2014b).

CIP should be considered a red-flag signaling the need for assertive treatment of cocaine abuse. This includes assertive community interventions to avoiding patient drop-out and provision of state-of-the-art psychological interventions such as contingency management (Farronato et al., 2013). Reduction of cocaine consumption may be the most central part of treatment and has been shown to reduce certain psychosis-like symptoms, in particular paranoid ideation (Kluwe-Schiavon et al., 2020). Regarding pharmacological treatment, an initial treatment with benzodiazepines has been suggested for acute episodes,

but treatment with antipsychotics may be necessary if symptoms persist or re-occur (Tang et al., 2014b). However, these recommendations are not based on clinical trials, which are urgently needed for an evidence-based treatment of CIP.

## 5. Conclusions

Our findings suggest that there is a high prevalence of CIP among cocaine users who are in contact with healthcare services, in particular for the prevalence of CIPS. Most results were limited by the presence of considerable heterogeneity in both the current and lifetime. Due to limitations in the available data we were unable to quantify the impact of the severity of cocaine use and the concurrent use of other substances. Although the substantial heterogeneity remained unexplored, these results indicate the need for systematic screening for psychotic symptoms among cocaine users.

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## Declaration of Competing Interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pnpbp.2021.110263>.

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