Highlights

- The prevalence of substance-induced psychotic disorder is 36.5% in methamphetamine misusers
- This prevalence is higher when the time period of assessment is lifetime
- It is also higher in studies including only persons with methamphetamine use disorder
SHORT COMMUNICATION

THE PREVALENCE OF SUBSTANCE-INDUCED PSYCHOTIC DISORDER IN METHAMPHETAMINE MISUSERS: A META-ANALYSIS

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Abstract

There is little consensus regarding the prevalence of methamphetamine-induced psychotic disorder (MIPD). A search of the literature was performed, effect size estimates were calculated with event rates and were aggregated with a random-effects model. Seventeen studies were included in the meta-analysis, resulting in a composite event rate of 36.5%. The event rate of MIPD was significantly higher when the period of assessment was lifetime (42.7%) and when only individuals with methamphetamine use disorders (MUD) (43.3%) were included. The prevalence of MIPD in the reviewed studies is elevated. These results highlight the need for detection and prevention strategies, and population studies.

Key words

Methamphetamine – psychosis – meta-analysis
1. Introduction

According to the Global burden of disease study (Degenhardt et al., 2010), 17.2 million people around the globe reported using methamphetamines in the past year. Methamphetamine abuse, a chronic or intensive (large quantities) administration of the drug, is linked to multiple social, and health problems, including mental health disorders (Barr et al., 2006). Methamphetamine-induced psychotic disorder (MIPD) is one of the most studied methamphetamine-linked mental health problem, yet research yields inconsistent results. For instance, studies assessing prevalence rates of methamphetamine-induced psychotic disorders suggest rates as high as 76% (Salo et al., 2013) of MIPD whereas others suggest rates of 40% (Chen et al., 2003) or even as low as 7% (McKetin et al., 2006). These differences can be explained by difficulties establishing diagnoses of MIPD or substance-induced psychotic disorders (SIPD) in methamphetamine users that clearly distinguish individuals with primary psychotic disorders who abuse methamphetamines from methamphetamine users who develop transient or more persistent meth-induced psychotic disorders. Many studies also focused on psychotic symptoms, which are quite common in methamphetamine users, rather than psychotic disorders meeting specific ICD or DSM criteria. Of importance, methamphetamine abusers are often poly-substance abusers who also present with a variety of psychiatric conditions above and beyond psychotic disorders (Lecomte et al., 2010), which can complicate the diagnostic process. Furthermore, most data have been collected in clinical or forensic settings, likely inflating prevalence rates in some studies. Likewise, the assessment of lifetime versus current substance-induced psychotic disorders may also influence prevalence estimates. Finally, results may have been influence by the fact that most studies included populations of users all meeting diagnostic criteria of methamphetamine use disorder (MUD; abuse or dependence), whereas other studies did not. For studies including MUD individuals exclusively, estimates of current MIPD/SIPD ranged from 4% (Akindipe et
al., 2014) to 70.9% (Farnia et al., 2016) while estimates of lifetime MIPD/SIPD ranged from 23.8% (Salo et al., 2011) to 76.3% (Salo et al., 2013). For studies including mixed populations of MUD individuals and methamphetamine users, estimates of current MIPD/SIPD ranged from 7% (McKetin et al., 2006) to 34.1% (Matsumoto et al., 2014), while estimates of lifetime MIPD/SIPD ranged from 31.1% (Kalayasiri et al., 2014) to 37.5% (Wallace et al., 2009). A better estimate of the prevalence rate is needed to guide clinicians offering addictions treatment and who might need to work more closely with psychiatric teams. Furthermore, prevalence rates can help guide prevention strategies and health policies. The objective of this study was to gain a clearer picture of reported prevalence rates by conducting a meta-analysis on the prevalence of MIPD or SIPD in methamphetamine users and by targeting only studies using stringent diagnostic criteria.

2. Methods

2.1. Selection procedures

2.1.1. Search strategies

A systematic search was performed in the electronic databases PubMed, EMBASE and Google Scholar using the key words “methamphetamine” and “psychosis” or “psychotic”. This search identified studies before January 1st, 2017. Studies were also searched by cross-referencing. Abstracts were screened by JD and SP, and full articles by JD, SP and TL.

2.1.2. Selection criteria

Studies were included if they met the following criteria: 1) had involved subjects with methamphetamine use or MUD; 2) had employed validated criteria to evaluate SIPD or MIPD; and 3) had excluded primary psychotic disorders or distinguished MIPD/SIPD from primary psychotic disorders. For each paper included in the meta-analysis, we relied on the
authors’ choice of MIPD vs SIPD to designate the population of interest. Some authors have opted for SIPD instead of MIPD, given that methamphetamine is sometimes used along with other psychotogenic substances, such as cannabis and cocaine. Finally, when multiple articles dealt with the same population, we selected the article with the largest sample. Studies were excluded if: 1) the assessment of MIPD/SIPD was based on retrospective chart review; 2) the sample only consisted of people with MIPD/SIPD; 3) the psychiatric variable of interest was the prevalence or severity of psychotic symptoms (not MIPD/SIPD); and 4) the primary objective was to perform a case-control comparison of methamphetamine users with and without SIPD/MIPD using cognitive, biological or neuroimaging measures. Noteworthy, several overlapping studies from the Japanese Genetics Initiative on Drug Abuse were all excluded as they enrolled 100% of MIPD individuals. Disagreement on the inclusion of studies was resolved by consensus.

2.1.3. Recorded variables

The variables for each article included in the meta-analysis were: sample sizes, gender (proportion of males), participants’ mean or median age, the service where the study was performed, the proportion of methamphetamine users meeting diagnostic criteria for methamphetamine dependence, the prevalence of SIPD/MIPD, and the time period of assessment of SIPD/MIPD (current vs lifetime). The prevalence of comorbid substance use disorders and the route of administration of methamphetamine (e.g. percentage of intravenous administration) was also described when available. To achieve a high standard of reporting, we followed the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ (PRISMA) guidelines (Moher et al., 2009) (see Supplementary Table 1).

2.2. Statistical analysis
Data were entered into an electronic database and analyzed with a quantitative meta-analytical approach using *Comprehensive Meta-Analysis* (CMA) software, version 2 (Borenstein M. et al., 2005). CMA software employs the same computational algorithms used by the Cochrane collaborators to weigh studies by the inverse variance method (Borenstein M. et al., 2005). The primary effect size measure was the prevalence (e.g. event rate in percentage) of SIPD/MIPD in methamphetamine users. Heterogeneity among study point estimates was assessed with the Q statistics (Paulson and Bazemore, 2010) with magnitude of heterogeneity being evaluated with the $I^2$ index (Lipsey and Wilson, 2000). As the database was characterized by high heterogeneity (see below), we employed random-effects models which are more conservative than fixed-effect models, and appear to better address heterogeneity between studies and study populations (Cooper et al., 2009). The possibility of publication bias in the present meta-analysis was examined using Begg and Mazumbar’s rank correlation test (Begg and Mazumdar, 1994). To determine whether categorical factors modified the event rate estimate, subgroup analyses were performed (Paulson and Bazemore, 2010). The influence of continuous moderator variables was tested using meta-regression analyses. Outlier studies were defined as studies having an effect size of 2 standard deviations above or below the composite effect estimate.

3. Results

3.1. Database

This literature search identified 548 potential articles. After assessment, 531 articles were excluded. The final database included 17 studies for a total of 4095 subjects (Akindipe et al., 2014; Chen et al., 2003; Ding et al., 2014; Farnia et al., 2016; Grant et al., 2007; Hides et al., 2015; Kalayasiri et al., 2014; Liu et al., 2004; Matsumoto et al., 2014; McKetin et al., 2006; Medhus et al., 2013; Salo et al., 2013; Salo et al., 2011; Sim et al., 2013; Sulaiman et al.,
2014; Veerasakul et al., 2017; Wallace et al., 2009). No studies were identified by cross-referencing. The PRISMA flowchart for the inclusion of studies in the meta-analysis and the details of the retrieved studies are described in Supplementary Figure 1 and Supplementary Table 2, respectively. Noteworthy, no study looked at methamphetamine users from the general population. Individuals included in the selected studies did not necessarily all meet criteria for MUD; however, they were all recruited from psychiatric, addiction or forensic facilities, meaning that their consumptions was problematic to some extent. Thereafter, the participants of any study or sub-analysis referring to mixed populations of MUD individuals and methamphetamine users are referred to as misusers.

3.2. Heterogeneity

The overall database was characterized by high level of between-studies heterogeneity ($Q=396.8; \ p=0.0001; \ I^2=96.0\%$) which justified the use of random-effect models in the analysis.

3.3. Publication bias

Begg and Mazumdar rank correlation test indicated no publication bias (Tau= -0.235; \ $p=0.187$).

3.4. The prevalence of SIPD or MIPD

The composite event rate of MIPD/SIPD in methamphetamine misusers was 36.5\% (Figure 1).

3.5. Categorical moderators
3.5.1. **Current versus lifetime**

The composite event rate of MIPD/SIPD was significantly higher when the time period of assessment was lifetime (42.7%) rather than current (22.1%) ($Q=6.5; \ p=0.01$) (Supplementary Table 3).

3.5.2. **Methamphetamine use versus methamphetamine use disorder**

The prevalence of MIPD/SIPD was significantly higher in studies including only individuals with methamphetamine use disorders (MUD) (43.3%) than in studies including mixed populations of MUD individuals and methamphetamine users (e.g., misusers) (23.2%) ($Q=7.2; \ p=0.007$) (Supplementary Table 3).

3.5.3. **Interaction between population and time of period of assessment**

For studies including only individuals with MUD, the prevalence of current MIPD/SIPD is 24.5% while the prevalence of lifetime MIPD/SIPD was 44.9%. For studies including mixed populations of MUD individuals and methamphetamine users, the prevalence of current MIPD/SIPD was 16.3%, while the prevalence of lifetime MIPD/SIPD was 33.2% (Supplementary Table 4).

3.6. **Linear moderators**

Meta-regression analyses revealed that the event rate of MIPD/SIPD in methamphetamine misusers was not influenced by the mean age of participants ($\beta=-0.009; \ CI95\%: -0.1$ to 0.083; \ $p=0.852$; 13 studies) nor by the ratio of males ($\beta=0.017; \ CI95\%: -0.008$ to 0.043; \ $p=0.176$; 16 studies). There were insufficient data to examine the influence of comorbid substance use disorders and of the route of administration of methamphetamine use on the prevalence of MIPD/SIPD.
4. Discussion

It appears that on average, in the reviewed studies, 36.5% of methamphetamine misusers have a history of MIPD or SIPD. As expected, this prevalence rate is higher when only those with a diagnosis of MUD are considered (43.3%) vs mixed populations of MUD individuals and methamphetamine users (labelled as misusers) (23.2%), and also higher when lifetime (i.e. 42.7%) vs current (22.1%) MIPD/SIPD is assessed. Additional sub-analyses revealed that the prevalence was the highest for the assessment of lifetime MIPD/SIPD in studies involving only MUD individuals (44.9%), whereas it was the lowest in the case of the assessment of current MIPD/SIPD in studies involving mixed populations of MUD individuals and methamphetamine users (16.3%). Results were not influenced by age and sex. Our results further emphasize the neurotoxicity of methamphetamines on the brain (Barr et al., 2006), given that regular use of the drug, as found in those with a MUD, are linked to a prevalence rate of a MIPD/SIPD of over 40%.

Although stringent analyses were performed, our results are limited by the high heterogeneity of the studies, reflecting the large range of prevalence rates of MIPD/SIPD found. This heterogeneity may arise from the variety of criteria used to diagnose MIPD/SIPD (see Supplementary Table 2), as well as the uncertainties regarding the distinction between methamphetamine-induced psychotic symptoms versus disorder. In addition, the small number of studies did not enable us to assess the impact of poly-substance abuse or methamphetamine administration route on the prevalence of a MIPD/SIPD. However, the meta-analysis has allowed to identify two significant sources of heterogeneity, namely the time period of assessment of SIPD/MIPD (current vs lifetime) and the proportion of methamphetamine users meeting MUD criteria. Such diagnostic precisions will enable us to better understand the extent of the methamphetamine-induced psychosis phenomena. Finally,
none of the studies included were population studies - all focused on target populations, such as individuals seeking treatment, being hospitalised in psychiatric facilities or incarcerated. This means that our results can partially be explained by Berkson's bias, which refers to the higher prevalence rates of disorders that are typically found in clinical relative to community sample (Berkson, 1946). Because of this bias, one would expect that the prevalence rates reported here to be higher than the rates that would be observed in non-clinical populations of methamphetamine users. Nonetheless, the studies included in this meta-analysis come from three different continents and can therefore be generalized to clinical and forensic settings across the world.

The high prevalence of a MIPD/SIPD in methamphetamine misusers is a public health concern. As documented by (Yui et al., 2002), a MIPD can increase one’s vulnerability to experiencing future psychotic symptoms. (McKetin et al., 2017) argued that better clinical markers are needed to distinguish those who develop transient or persistent psychotic symptoms. Some studies suggest that symptoms might be slightly different between both trajectories (McKetin et al., 2017), and that younger or more persistent methamphetamine abuse, especially during youth, predicts more severe and persisting (versus transient) psychotic symptoms (Lecomte et al., 2013; McKetin et al., 2017). Better detection and prevention strategies are needed – currently, given the MIPD/SIPD prevalence rate, methamphetamine use should be considered a risk factor for schizophrenia, like cannabis is (Arseneault et al., 2002).

Epidemiological studies are needed in order to examine whether MIPD/SIPD is also diagnosed in occasional methamphetamine users from the general population. Future studies will need to pay greater attention to the influence of route of administration and of poly-substance abuse on prevalence estimates of MIPD/SIPD, as well as the functional impacts of MIPD/SIPD and the long-term rates of transition to schizophrenia-spectrum disorders. Early
treatment programs for methamphetamine abuse and prevention strategies also need to be studied, given the potential important public health consequences of methamphetamine abuse.

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Conflicts of interest

None to declare.

References


Figure 1. Meta-analysis of the prevalence of a substance-induced psychotic disorder in methamphetamine misusers. The composite event rate of methamphetamine- or substance-induced psychotic disorder was 36.5% in methamphetamine misusers.
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