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Review Article

Relationships between the use of amphetamines and psychotic symptoms: a systematic review

Relações entre o uso de anfetaminas e sintomas psicóticos: uma revisão sistemática

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ABSTRACT: Amphetamines are substances that act in the central and peripheral nervous system and can cause intense damage and trigger psychotic symptoms (delusions, hallucinations). This review aimed to identify studies with essential information to understand the relationships between the use of these substances and the development of psychotic conditions, whether transient (happening only during use), persistent (during use and after abstinence), or when evolving to primary disorders, like schizophrenia. A search in two databases allowed the selection of references to meet the study objectives. Different studies sought to explain the action mechanisms of these drugs, and the neurological, biochemical, physiological, and molecular factors involved in psychotic disorders, looking for evidence of connections between the three situations described previously. Significant similarities between the conditions were identified through neuroimaging exams, analysis of clinical presentations, statistical evidence, among other. However, future studies are necessary to clarify some aspects of this topic and improve the etiological, clinical, and diagnostic classification and the treatment of these patients.

Keywords: Methamphetamine; Psychotic disorders; Psychiatry.

RESUMO: Anfetaminas são substâncias com ações no sistema nervoso central e periférico com potencial de causar dano intenso e de desencadear sintomas psicóticos (delírios, alucinações). Esta revisão procurou identificar trabalhos com informações essenciais para a compreensão das relações entre o uso dessas substâncias por indivíduos e o desenvolvimento de quadros psicóticos, tanto transitórios, ocorridos apenas durante o uso, quanto persistentes durante e após o período de abstinência, ou evoluindo para transtornos primários, como a esquizofrenia. Através de busca em dois bancos de dados foi possível selecionar as referências que supriram os objetivos. Diversas pesquisas buscaram desvendar os mecanismos de ação dessas drogas, e as bases neurológicas, bioquímicas, fisiológicas e moleculares dos transtornos psicóticos, procurando evidências das ligações entre as três situações citadas anteriormente, e similaridades significativas entre os quadros foram identificadas, incluindo em exames de neuroimagem e análises de quadros clínicos, além de comprovações estatísticas. Contudo, futuros estudos são necessários para esclarecer alguns aspectos desse tema e melhorar classificação etiológica, clínica e diagnóstica, além do manejo desses pacientes.

Palavras-chave: Metanfetamina; Transtornos psicóticos; Psiquiatria.

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INTRODUCTION

Amphetamines are stimulant drugs and a class of synthetic sympathomimetic amines that act on the central nervous system[1]. These drugs act by inhibiting the reuptake of dopamine, noradrenaline/adrenaline and serotonin, the so-called monoamines, leading to increased concentration of these neurotransmitters[2]. Medications belonging to this group of substances are used for the treatment of narcolepsy, obesity, and attention deficit hyperactivity disorder (ADHD), and cause several physical and/or behavioral reactions, including tachycardia, tachypnea, increased blood pressure, sleep disturbances, euphoria, appetite suppression, among others[3,4]. The routes of administration of amphetamines, including its most common illicit analogue, methamphetamine, may be inhalation, intravenous and oral[2,5].

According to the United Nations World Drug Report 2019[6], in 2017, 29 million people aged 15–64 all over the world had used amphetamines or other related stimulants and 21.3 million of them of them used methylenedioxymethamphetamine (MDMA), a drug popularly known as "ecstasy". The use of methamphetamine is of great concern to global public health specialists. This is explained by the increasing popularity of the drug, mainly in parts of Asia and America[6], and because, in addition to the risk of dependence, it is possible that the use of this substance can cause intense psychotic episodes[7,8,9].

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition[10], substance/medication-induced psychotic disorder is defined as the presence of delusions and/or hallucinations, with evidence of the development of symptoms during or after substance use or during withdrawal. In addition, (1) there must be evidence that the substance used is capable of producing the specific condition; (2) symptoms cannot occur exclusively during the course of a *delirium* and (3) evidence of an independent psychotic disorder must be investigated[10]. Methamphetamine-induced psychotic disorder is so statistically significant that it is called "methamphetamine-associated psychosis". It is studied not only to correlate the action of the substance and the symptoms, but also with the objective of understanding its implications and its association with the disorders within the schizophrenia spectrum, considered primary psychotic disorders[11,12,13].

There are still many gaps in the knowledge of the scientific community regarding these disorders, especially in the identification of causality and etiology and in the definition of clinical classifications. The relevance of the topic is evident if we consider all the impacts that arise when amphetamines are used (with possible dependence) at the same time as a psychotic episode. There are impairments in the cognitive function of users, and immeasurable physical and psychological suffering, including self-injury due to, for instance, hallucinations[2]. Furthermore, health care systems and care centers are also damaged by the high rates of trips to emergency departments among this population, with an additional stress load for professionals responsible for welcoming and caring for these patients, who can present with aggression, agitation and non-cooperation[14].

Therefore, using the articles identified as the best sources in the current literature, this review aims to identify essential information and main problems still to be solved in relation to epidemiology, pathophysiological characteristics, clinical conditions, diagnosis, and management of individuals with history of use of amphetamines or related drugs and psychotic symptoms.

METHOD

This is a retrospective study developed through a systematic literature review. Articles extracted from the *PubMed* and *Medline* databases and six additional studies from other sources were used to construct this article.

The research descriptors were chosen based on the Health Sciences Descriptors, a well-known trilingual vocabulary for indexing articles in scientific journals. The following keywords were used in both databases: "Amphetamines" + "Psychotic Disorders". No unfavorable results were found.

Studies published between January 1, 2010 and December 31, 2019 were analyzed, establishing a time frame of 10 years. The second filter applied was "*full text*", aiming to guarantee that only articles available in full would be selected and excluding citations or patents. The last filter used was related to the languages of the articles: only studies written in English or Portuguese were selected. The results were counted and recorded.

After the quantitative analysis explained above and, considering the significant number of pre-selected articles, it was necessary to conduct a qualitative analysis, carried out by reading the titles and abstracts of all publications. The remaining studies after this process were read, interpreted, and analyzed. Finally, those that would serve as reference within the guidelines of this review were selected. Later, we verified if the objectives were achieved through this methodology.

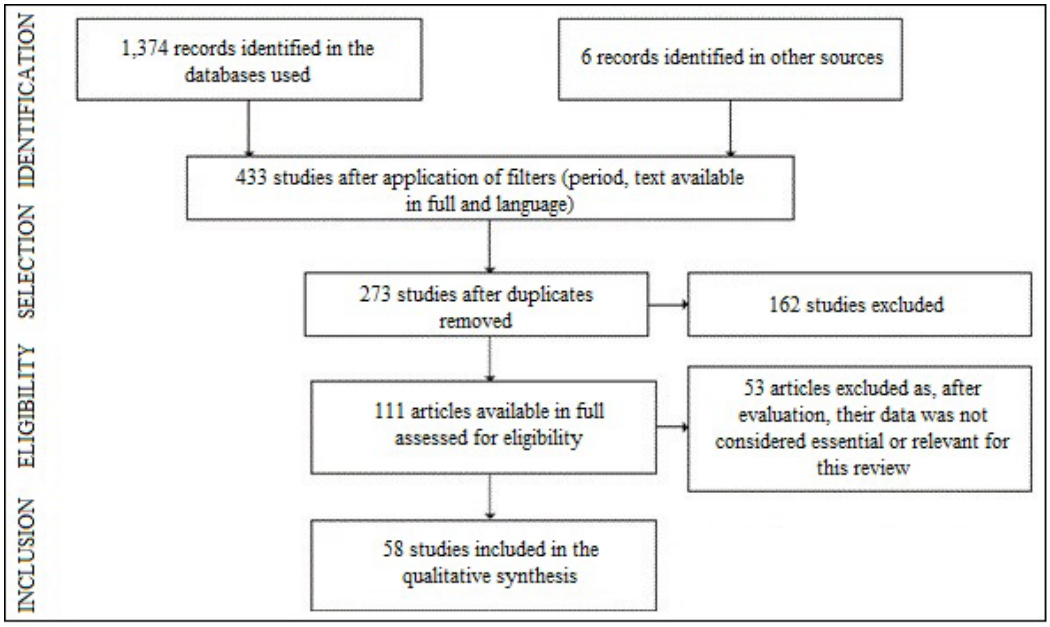

Figure 1. Flowchart of the construction of the systematic review in its different phases

As shown in the flowchart in Figure 1, elaborated according to the PRISMA model (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), the search initially identified 1,374 reports. After the application of the filters described above, the number of articles decreased to 433.

After the exclusion of duplicates, the first qualitative analysis was conducted by reading and interpreting the titles and abstracts of the studies found, which allowed the pre-selection of 111 full-text articles that were later read, analyzed, and interpreted. The criteria used for the exclusion of articles were the selection and exclusion of studies that were not correlated with the guidelines proposed for the present study. Finally, 58 studies were selected and used in this review and are cited in the bibliographic references at the end of this article.

RESULTS

All substances in the amphetamine class can trigger psychiatric symptoms at some level, due to their general mechanisms of action. Among these symptoms, psychotic conditions are the most reported, and occur not only acutely, during use, but also chronically[15,16]. The Euro-DEN (The European Drug Emergencies Network) database – a system that gathers information about patients using emergency services due to conditions caused by the recreational use of psychoactive substances in ten countries – registers that psychotic conditions caused by the use of a single drug are more frequently associated with amphetamines, which represented about 32.4% of cases[9].

Some articles address specific derivatives/analogues and their relationship to psychosis. The substances used as appetite suppressants for the treatment of obesity and those used in the treatment of ADHD are the most cited among those that are legal, and, in this review, they represented 5.76% of the studies found. A case report on the irregular use of phentermine, derived from amphetamine, described the occurrence of recurrent psychosis after the administration of the drug in a 25-year-old female patient, who had concerns about her body image and was seeking weight loss[17]. A cohort study carried out in the United States between 2004 and 2015[18], including 221,846 young people diagnosed with ADHD aged between 13 and 25 years, found that one in approximately six hundred and sixty patients who were using amphetamine or methylphenidate (a derivative) for treatment had a record of psychotic symptoms. Also, regarding the use of this type of drug for therapeutic purposes, there are records of psychotic conditions associated with overuse of lisdexamfetamine and dextroamphetamine[4].

However, about 65.38% of the studies address this relationship with the analogue methamphetamine – consequently, most of the information cited here will be related to this substance. It is known that the use of this illicit drug leads to significantly high levels of psychological damage, stress, depressive and psychotic symptoms, which make life difficult for users, even during periods of withdrawal[19]. Therefore, it is of extreme epidemiological and clinical importance to understand the interactions of all factors involved in a psychotic condition triggered by a substance capable of promoting so much damage.

DISCUSSION

The psychotic disorders described in the chapter of the latest edition of the Diagnostic and Statistical Manual of Mental Disorders – DSM-V can be divided into 3 main

groups: 1) schizophrenia spectrum, composed of: delusional disorder, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, and schizophrenia; 2) substance/medication-induced psychotic disorders; and 3) psychotic disorders due to other medical conditions[10]. Historically, substance-induced psychotic disorders were identified and described as disorders secondary to specific and known causes, without further characterization at first, while schizophrenia was considered a disease with a likely genetic cause, with no apparent reason to investigate the association between the two groups[20].

However, as reported by Castle and Buckley[21], neurobiological and anatomical studies carried out later found out that schizophrenia was a multifactorial syndrome, and researchers, using drugs that induce psychotic symptoms and neuroimaging techniques capable of capturing brain alterations, developed several theories to explain the etiology and pathology of psychotic disorders – one of them is the "dopaminergic hypothesis". Developed based on observations of conditions triggered by amphetamines, it is based on the concept that positive symptoms (e.g., delusions, hallucinations, aggression) are the result of increased dopamine function in the mesolimbic pathway, while negative symptoms (affective blunting, social isolation, anhedonia, apathy) are associated with the reduced dopamine stimulation in the mesocortical pathway[22]. An indication that these associations are real is the effective use of typical antipsychotics in the treatment of psychotic disorders, which, when blocking D2 receptors indiscriminately, can lead to a secondary decrease in the concentration of mesocortical dopamine, causing or worsening negative symptoms[23].

According to Peleg-Raibstein et al. (2009), cited by Murray et al.[20] (p.663), another part of the neurochemical explanation of schizophrenia, based on the dopaminergic hypothesis, is called the "sensitization hypothesis", which postulates that a sensitized dopamine system is responsible for the genesis of psychotic symptom. This was confirmed by studies demonstrating that each dose of amphetamine administered to a subject caused greater dopamine release in their striatum. These features seem to be common in the pathology of schizophrenia and amphetamine-induced psychosis (methamphetamine in particular), making the latter an excellent model for a deeper study of disorders in the schizophrenia spectrum[24]. In addition, another variable already elucidated is the mechanisms through which amphetamines trigger the increase in extracellular dopamine concentration: amphetamine is a competitive substrate for dopamine transporters; it blocks the reuptake of the neurotransmitter, entering neurons and moving the dopamine present in the vesicles, causing its release and efflux in the neuron cytosol, which, in turn, increases the stimulation of receptors and the activity for dopamine locomotion[25].

There are several studies that can be cited when analyzing the relationship between the development of schizophrenia and an individual's history of drug use. Finnish researchers, for example, analyzed the hospital history of 18,478 Finnish individuals between 1987 and 2003, since their first hospitalization for substance-induced psychosis and until the first hospitalization with a diagnosis of schizophrenia spectrum disorder, death or the end of 2003, and found that, over an 8-year period, those admitted for amphetamine-induced psychosis had a 30% risk of receiving a schizophrenia spectrum diagnosis[26]. Another interesting study, carried out in the same year in Norway, showed that the use of amphetamines is a significant risk factor for readmission of schizophrenic patients who had a history of drug use. In addition, it found that individuals with a history of schizophrenia have a known tendency of using drugs, which exacerbates their condition and causes readmission in 78.7% of cases[27].

As for methamphetamine, a cohort study conducted in California, U.S., accessed the hospital discharge records from 1990 to 2000 of patients who were initially free from persistent psychosis symptoms. Among them, 42,412 patients with methamphetamine-related disorders were selected, along with a control group of patients hospitalized for appendicitis in the same period. The analysis of which group had the highest rate of evolutions to schizophrenia showed that the risk is 9.37 times higher for drug users when compared to non-users[28].

Researchers who identified significant relationships between amphetamine use and later development of schizophrenia spectrum disorders reported that their study made them realize that if health professionals understood the characteristics of individuals with this clinical condition and prognosis, they could tailor the way these patients are treated and identify those who could receive a different early intervention to improve their quality of life[15,29]. A meta-analysis of 17 studies from 3 continents, with a total of 4,095 individuals analyzed, found that the prevalence of substance-induced psychotic disorder is 36.5% among methamphetamine users. This led the authors to conclude that, considering the exorbitant rate of psychosis induced by methamphetamine, its use should be considered a risk factor for schizophrenia, as is already the case with the use of cannabis[8].

An important addition is that the combined use of other drugs and amphetamines/methamphetamine is more common than its isolated use[29]. A study conducted by Voce et al.[23], with 154 methamphetamine users who had psychotic symptoms found high rates of use of other drugs, as also found in a study by McKetin et al.[30] with 278 participants of a cohort study who had a diagnosis of methamphetamine-induced psychotic disorder, and in a study by Bousman et al.[31], which analyzed 40 methamphetamine users with substance-induced psychotic disorder. Figure 2 shows which drugs were associated with amphetamine use and their percentages in relation to the number of users in each study cited above.

ASSOCIATED DRUGS AND PERCENTAGES
Tobacco(98%); Cannabis (79%); Alcohol (65%); Benzodiazepine (51%) and Heroin (48%)[23]
Tobacco (89%); Alcohol (62%) and Cannabis (57%)[30]
Alcohol (68%); Cannabis (47%); Nicotine (33%); Cocain (25%); Hallucinogens (17%); Inhalants (11%) and Opioids (8%)[31]

Figure 2. Record of amphetamine use combined with other substances

Knowing that the interaction with other substances is so common, and that it can change the classic clinical presentations, mask problems, and get in the way of an accurate diagnosis (between schizophrenia and psychosis disorder induced by persistent methamphetamine use, for example), the professionals should evaluate these patients carefully, focusing on each individual and their personal history and analyzing drug and medication use, as central nervous system depressant substances such as benzodiazepines are legal, and concomitant use with a stimulant can make it difficult to treat this patient if the professional is not aware of the combination[23].

Isolated methamphetamine use is associated with extensive neurodegeneration, cognitive impairment, and psychosis – and several studies try to find links between these consequences[32]. Evidence suggests that glutamatergic alterations, neuronal inflammation, neurotoxicity-induced apoptosis, involvement of protein kinases as mediators, among other mechanisms, are related to the development of these conditions and that the increased dopamine function and dopamine sensitization seen in the pathology of schizophrenia also occurs in psychotic conditions triggered by drugs[33].

According to Baig[34], the increase in the dopaminergic concentration in the striatum of the mesolimbic pathway leads to an increase in the release of glutamate and, consequently, in its concentration in the cortex. These actions and reactions involving dopaminergic, glutamatergic and, in sequence, GABAergic neurons prove that these systems are associated between themselves and with complex neural circuits involved in several pathological explanations of mental disorders[35]. Subsequently, excess cortical glutamate causes damage to the interneurons of the gamma-aminobutyric acid system, known as the GABA neurotransmitter[24]. The loss of cortical GABAergic functionality causes dysregulation in thalamocortical signaling, which may result in the onset of psychotic symptoms. It is not clear if this damage to the GABAergic system has a direct role in psychosis or only in changes in associated cognitive functions.[35].

Shin et al.[32] suggested that genetic predispositions linked to the dopaminergic and serotonergic systems may contribute to the development of psychotic conditions after the use of methamphetamine. As for the serotonin system in particular, two studies[36,37] found brain regions of this system apparently impaired by induced neurotoxicity due to drug abuse, including limbic structures and basal ganglia, both in methamphetamine-dependent humans and in animal models of addiction. In addition, there is evidence that methamphetamine exposure can alter the expression of proteins in the striatum, which are key to neural regulation (neural protection, neuroplasticity, maintenance of the cellular cytoskeleton, energy regulation, and maintenance of synaptic vesicles)[38].

The glutamatergic system has variations of GRIAs (genes encoding AMPA receptor subunits), which are associated with chemical dependence and psychosis. However, the association between these variations and specific methamphetamine dependence and methamphetamine-associated psychosis is still being investigated, with no significant results to date[39]. Another example is a study conducted with methamphetamine-dependent men with associated psychosis symptoms[40], who were genotyped for 2 single nucleotide polymorphisms of GRIN1 (responsible for encoding a subunit of the NMDA glutamatergic receptor). Variations of GRIN1 were previously identified as risk factors for schizophrenia and drug dependence, supporting the hypothesis that glutamatergic dysfunction plays a role in the emergence of psychosis. However, the results of this study were not significant, and more studies are necessary to deepen the understanding of these relationships.

The association between addictive disorders (chemical dependence), methamphetamine-induced psychosis and schizophrenia are cited several times in studies about these topics. The simplest mechanism described is that amphetamines release dopamine in the nucleus *accumbens* through the mesolimbic pathway, which leads to a feeling of euphoria and interacts with the reward system, generating feedback loop, and, consequently, addiction[2]. One study showed that the synaptic protein expression is affected by methamphetamine in the dorsal striatum, a brain region known for its relationship with addiction, and identified that these changes may persist even in abstinence[38]. A neuroimaging study by Vuletic et al.[41] investigated neural circuits associated with methamphetamine dependence and found differences in cerebral perfusion and brain glucose metabolism among

drug users.

In the molecular area, it has been reported that methamphetamine exposure causes the release of central and peripheral monoamine neurotransmitters, which may have neurotoxic effects (increased oxidative stress, ubiquitin-proteasome system dysfunction, endoplasmic reticulum stress, inflammation, among others) on dopaminergic systems and other neurotransmitters[42]. A study carried out in Cape Town, South Africa[43] obtained similar results with blood, clinical and neuroimaging analyzes in humans, and experimentally with rat brains, demonstrating that: 1) genes involved in circadian clock dysregulation may be prominent players in psychosis, and are detectable in peripheral blood and *post-mortem* brain profiles; 2) ubiquitin-proteasome system abnormalities have emerged as a common denominator in studies investigating psychosis, schizophrenia and bipolar disorder – in clinical practice there is overlap and comorbidity between affective disorders, schizophrenia and substance-induced disorders; 3) a gene involved in ubiquitin-mediated proteolysis downregulation had a significant association with methamphetamine-associated psychosis; and 4) t volume changes both in the anterior *corpus callosum* and in the *nucleus accumbens*, and lower bilateral hippocampal volumes were found in subjects with methamphetamine-associated psychosis. The findings are evidence that similar molecular and neurocognitive mechanisms may be involved in the pathophysiology of schizophrenia and psychosis, and the methamphetamine-associated psychosis paradigm should be used as an exemplar.

Neuroimaging studies, mainly using Functional Magnetic Resonance Imaging (fMRI), identified functional and morphological cortical and subcortical changes associated with cognitive dysfunction in methamphetamine users with or without psychosis. In addition, studies have provided evidence that both acute and chronic methamphetamine use are associated with neurotoxicity and cognitive impairment[44]. Researchers have highlighted important issues regarding cortical and subcortical regions possibly affected by methamphetamine use and psychosis, suggesting that patients with amphetamine dependence with or without psychosis have impaired affect regulation, with cortical differences such as lower cortical thickness and smaller hippocampal volume among individuals with both variables, which is consistent with neuroimaging findings in other psychotic disorders[45]. A study by Uhlmann et al.[46] found that, as in schizophrenia, methamphetamine-induced disorder is also associated with impaired white matter integrity, and that a frontal white matter pathology is partially responsible for the impulsive behavior associated with the use of alcohol, drugs and the consequent psychosis.

Studies report that chronic methamphetamine use and substance-induced psychosis are associated with dysfunction in several neural networks and that there is still significant evidence of these deficits in individuals with psychosis even when possible acute effects of methamphetamine are excluded[47]. After evaluation of several fMRI of brain structures and functional connectivity maps in patients with methamphetamine dependence, methamphetamine-associated psychosis and schizophrenia, a study found clear evidence that structural and functional abnormalities are associated with the development of methamphetamine-associated psychosis when this group is compared to the others[48].

Clinical conditions involving amphetamine/methamphetamine-induced psychosis disorder (MIPD) are often difficult to differentiate from primary psychotic disorders, especially schizophrenia[11]. The MIPD itself contains noticeable differences and similarities in its clinical courses, beginning with the differences in epidemiology and prognosis of the diagnostic categories, as individuals with transient MIPD have psychotic symptoms only when using methamphetamine for a period of one month, while individuals with persistent MIPD present psychosis during use and also in abstinence, for at least a month in each situation[49]. An example of these statistical differences is the fact that persecutory delusions have been recorded as the most common symptom of transient MIPD[20,31], while other findings suggest that transient MIPD is associated with persecutory delusions and tactile hallucinations. On the other hand, persistent MIPD is related to several other hallucinations and delusions, such as reference delusions and complex auditory, visual, olfactory, and tactile hallucinations. There were no significant differences in the clinical profiles of primary psychosis and persistent MIPD patients[49]. According to McKetin et al.[49], failure to differentiate the conditions is possibly because studies often focus on symptoms common to both disorders (e.g., persecutory delusions) or general categories (e.g., presence or severity of hallucinations or delusions), instead of specific types of delusions/hallucinations. It must be considered, however, that different psychotic experiences with different phenotypes may have different etiologies and clinical correlations[29].

Considering the division explained above, persistent MIPD has already been significantly associated with more severe dependence, a diagnosis of major depression (comorbidity) and a family history of primary psychosis. This suggests there can be a pre-existing vulnerability to psychosis in these individuals, raising the question of whether persistent MIPD may reflect the precipitation of schizophrenia, acting as a risk factor or unmasking schizophrenia (acting as a trigger) in vulnerable individuals[30].

A study carried out to verify if the concentration of methamphetamine in hair samples would be significantly associated with the intensity of the psychosis experiences found eight risk factors associated with MIPD: (1) being male; (2) diagnosis of antisocial personality disorder; (3) intravenous use in the past month; (4) methamphetamine

use for ≥ 16 days in the past month; (5) methamphetamine dependence; (6) history of hospitalization for mental illnesses; (7) history of hospitalization for substance abuse; and (8) younger age at first use[7]. After comparing 120 methamphetamine users without psychotic symptoms and 113 patients who tested positive for methamphetamine, the study found no significant relationship between methamphetamine concentration and symptom intensity. In a similar process, another study compared symptoms of a group of acutely admitted patients who tested positive for methamphetamine and were diagnosed with MIPD and a group of acutely admitted patients who tested negative for methamphetamine and were diagnosed with schizophrenia. The results showed no differences in positive psychotic symptoms between the two groups, and the levels of urine and blood methamphetamine concentrations were not associated with the severity of reported symptoms[50]. A study by Ma et al.[51] assessed 528 Chinese individuals with chronic methamphetamine use and, after five interviews (four of them being follow-up visits) over two years, discovered that longer periods of methamphetamine use predicted a higher risk of experiencing psychotic symptoms, classifying long periods of chronic use as a risk factor for MIPD.

Researchers have pointed out[31,52] that other psychiatric symptoms/disorders are commonly concomitant with psychosis in methamphetamine users, and this should change the approach to patients. In a sample of 40 individuals with MIPD, the prevalences of major depressive disorder, antisocial personality disorder, ADHD and bipolar I disorder were respectively 60%, 38%, 18% and 13%[31]. A study conducted in a women's prison in Japan analyzed 80 individuals in amphetamine abstinence and found that a significant factor, that affected even the intensity of psychotic conditions, was the presence of previous psychiatric comorbidity in 24% of individuals. It was also found that 20 of them (25%) had persistent psychotic symptoms, even without using the drug for more than a month[52].

The DSM-V only considers delusions and hallucinations (positive psychotic symptoms) as criteria for the diagnosis of substance/medication-induced psychotic disorder (SIPD)[10]. The absence of negative symptoms for these disorders and their inclusion exclusively on the schizophrenia spectrum may be a good starting point for differentiating them. However, the literature has mixed results regarding the presence or absence of negative symptoms in MIPD. An analysis of 94 articles[53] with a total number of 7,387 patients found that less than 20% of the studies analyzed presented a profile of negative symptoms in MIPD, and the studies that reported such characteristics found prevalences ranging from 20% to 26% within the groups of patients. Voce et al.[23] evaluated 154 individuals to identify the presence of negative symptoms, and confirmed a negative symptom syndrome which, unlike positive or affective symptoms, was not correlated with current methamphetamine use or related to familial risk for psychosis. This suggests that negative symptoms are unlikely due to the acute effect of the drug, but can be explained by one of the following hypotheses: (1) negative symptoms are consequences of neurotoxic impairment from long-term use; (2) prolonged or heavy use prompts changes in the brain structure that can precipitate negative symptoms; 3) self-medication with sedatives to relieve symptoms generates a vicious cycle; or 4) the presence of negative symptoms are artifacts of polysubstance use – and this study found a significant association between negative symptoms and frequent use of heroin and benzodiazepine (CNS depressant) in the past month.

Wang et al.[54] found that it is possible to find differences between the clinical presentation of primary psychotic disorders (schizophrenia) and MIPD, but diagnostic classifications and taxonomy are not identical in all studies and, over time and depending on management and prognosis, psychotic symptoms, like many psychiatric symptoms, may change their intensity in specific individuals. The differences between the triggering mechanisms and clinical courses of these disorders require further evaluation, especially in the long term, so that causality can be more accurately established.

Antipsychotics have been used for years and have been proven to effectively reduce acute symptoms in the short-term[34]. Studies comparing classes and subclasses of these drugs have been carried out, analyzing, for example, haloperidol, quetiapine, aripiprazole and risperidone, and have shown that there are no significant differences in the results, except for the treatment of positive symptoms (for which risperidone is more favorable) and negative symptoms (for which aripiprazole is more favorable)[55,56]. MIPD cases usually resolve in one week of abstinence, with a difficult phase with possible additional symptoms[2]. Acute cases of amphetamine intoxication, on the other hand, can be fatal and require immediate intervention, with several drugs that should be considered to control the condition, with benzodiazepines (lorazepam and midazolam) as drugs of first choice, and, if required, antipsychotics as second option in emergency care[57]. Beta-blockers, such as metoprolol, have already been used successfully to control hyperadrenergic vital signs in some cases, and it is important to consider their use[2].

CONCLUSIONS

Considering the individual harm and the harm to global public health caused by the use of amphetamines, especially when involving psychiatric conditions (here we highlighted "psychosis"), the studies that seek to elucidate the neurological, biochemical, physiological, and molecular effects of these substances are extremely important and attract the attention of the scientific community. Significant discoveries have been made in the last 10 years, especially

in the areas of neuroimaging and biochemistry, which helped identifying what happens in the central nervous system of amphetamine users with or without associated psychotic symptoms. Furthermore, it is obvious that there is a relationship between amphetamine use, psychotic disorders induced by these drugs and a possible evolution to a condition within the schizophrenia spectrum, which was confirmed by all the studies used in this review with this relationship in their objective.

However, there are gaps in the knowledge of certain aspects of cause and effect, etiology and definition of specific clinical presentations and treatments. Future studies should aim to establish a more precise identification of risk factors for the persistence of psychotic disorders after abstinence, as there would be benefits in implementing more intense prevention actions earlier to those with this unfavorable prognosis. A second interesting focus of research would be improving the standardization of clinical and diagnostic classifications, with better identification of symptom patterns. In addition, greater efforts should be made to establish specific treatment choices, not only for acute amphetamine intoxication leading to psychosis, but also for a more complete management in cases in which symptoms persist for longer periods. These tools can allow a more effective reception of these individuals and provide more knowledge and instruments to improve the quality of life of these people, who are in a state of social vulnerability.

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REFERENCES

1. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet. 2012;379(9810):55-70. https://doi.org/10.1016/S0140-6736(11)61138-0.
2. Mullen JM, Richards JR, Crawford AT. Amphetamine related psychiatric disorders. StatPearls Publishing; 2020 [cited 2020 March 17]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482368/.
3. Bramness JG, Gundersen ØH, Guterstam J, Rognli EB, Konstenius M, Løberg EM, 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. https://doi.org/10.1186/1471-244X-12-221.
4. Henning A, Kurtom M, Espiridion ED. A case study of acute stimulant-induced psychosis. Cureus. 2019;11(2):e4126. https://doi.org/10.7759/cureus.4126.
5. Chiang M, Lombardi D, Du J, Makrum U, Sitthichai R, Harrington A, Shukair N, Zhao M, Fan X. Methamphetamine-associated psychosis: clinical presentation, biological basis, and treatment options. Hum Psychopharmacol. 2019;34(5):e2710. https://doi.org/10.1002/hup.2710.
6. United Nations. The United Nations Office on Drugs and Crime (UNODC). World Drug Report 2019. United Nations Publications; 2019. Available from: https://wdr.unodc.org/wdr2019/
7. Lamyai W, Pono K, Indrakamhaeng D, et al. Risks of psychosis in methamphetamine users: cross-sectional study in Thailand. BMJ Open. 2019;9(10):e032711. https://doi.org/10.1136/bmjopen-2019-032711.
8. Lecomte T, Dumais A, Dugré JR, Potvin S. The prevalence of substance-induced psychotic disorder in methamphetamine misusers: a meta-analysis. Psychiatry Res. 2018;268:189-92. https://doi.org/10.1016/j.psychres.2018.05.033.
9. Vallersnes OM, Dines AM, Wood DM, Yates C, Heyerdahl F, Hovda KE, Giraudon I; Euro-DEN Research Group, Dargan PI. Psychosis associated with acute recreational drug toxicity: a European case series. BMC Psychiatry. 2016;16:293. doi: https://doi.org/10.1186/s12888-016-1002-7. Erratum in: BMC Psychiatry. 2016;16(1):405.
10. American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders (DSM-5®). Washington, DC: American Psychiatric Pub; 2013.
11. Hajebi A, Amini H, Kashani L, Sharifi V. Twelve-month course and outcome of methamphetamine-induced psychosis compared with first episode primary psychotic disorders. Early Interv Psychiatry. 2018;12(5):928-34. https://doi.org/10.1111/eip.12404.
12. Hides L, Dawe S, McKetin R, Kavanagh DJ, Young RM, Teesson M, Saunders JB. Primary and substance-induced psychotic disorders in methamphetamine users. Psychiatry Res. 2015;226(1):91-6. https://doi.org/10.1016/j.psychres.2014.11.077.
13. McKetin R, Voce A, Burns R, Ali R, Lubman DI, Baker AL, Castle DJ. Latent psychotic symptom profiles amongst people who use methamphetamine: what do they tell us about existing diagnostic categories. Front Psychiatry. 2018;9:article578. https://doi.org/10.3389/fpsyt.2018.00578.
14. Chivaurah BM, Lienert D, Coates D. Amphetamine-type-substance-related presentations to the emergency department mental health team of a local health district in Australia. Australas Psychiatry. 2019;27(4):369-73. https://doi.org/10.1177/1039856219848836.
15. Medhus S, Rognli EB, Gossop M, Holm B, Mørland J, Bramness JG. Amphetamine-induced psychosis: transition to schizophrenia and mortality in a small prospective sample. Am J Addict. 2015;14(7):586-9. https://doi.org/10.1111/ajad.12274.
16. Rognli EB, Bramness JG, Skurtveit S, Bukten A. Substance

use and sociodemographic background as risk factors for lifetime psychotic experiences in a non-clinical sample. J Subst Abuse Treat. 2017;74:42-7. https://doi.org/10.1016/j.jsat.2016.12.007.

17. Jo HS, Wang SM, Kim JJ. Recurrent psychosis after phentermine administration in a young female: a case report. Clin Psychopharmacol Neurosci. 2019;17(1):130-3. https://doi.org/10.9758/cpn.2019.17.1.130.

18. Moran LV, Ongur D, Hsu J, Castro VM, Perlis RH, Schneeweiss S. Psychosis with methylphenidate or amphetamine in patients with ADHD. N Engl J Med. 2019;380(12):1128-38. https://doi.org/10.1056/NEJMoa1813751.

19. Zorick T, Nestor L, Miotto K, Sugar C, Hellemann G, Scanlon G, Rawson R, London ED. Withdrawal symptoms in abstinent methamphetamine-dependent subjects. Addiction. 2010;105(10):1809-18. https://doi.org/10.1111/j.1360-0443.2010.03066.x.

20. Murray RM, Paparelli A, Morrison PD, Marconi A, Di Forti M. What can we learn about schizophrenia from studying the human model, drug-induced psychosis? Am J Med Genet B Neuropsychiatr Genet. 2013;162(7):661-70. https://doi.org/10.1002/ajmg.b.32177.

21. Castle DJ, Buckley P. Schizophrenia. 2nd ed. Oxford: Oxford University Press; 2015.

22. Maia TV, Frank MJ. An integrative perspective on the role of dopamine in schizophrenia. Biol Psychiatry. 2017;81(1):52-66. https://doi.org/10.1016/j.biopsych.2016.05.021.

23. Voce A, Burns R, Castle D, Calabria B, McKetin R. Is there a discrete negative symptom syndrome in people who use methamphetamine? Compr Psychiatry. 2019;93:27-32. https://doi.org/10.1016/j.comppsych.2019.06.002.

24. Hsieh JH, Stein DJ, Howells FM. The neurobiology of methamphetamine induced psychosis. Front Hum Neurosci. 2014;8:537. https://doi.org/10.3389/fnhum.2014.00537.

25. Goodman LS, Brunton LL, Chabner BA, Knollmann BC. Goodman and Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill; 2011.

26. Niemi-Pynttäri JA, Sund R, Putkonen H, Vorma H, Wahlbeck K, Pirkola SP. Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. J Clin Psychiatry. 2013;74(1):e94-99. https://doi.org/10.4088/JCP.12m07822.

27. Thomsen KR, Thylstrup B, Pedersen MM, Pedersen MU, Simonsen E, Hesse M. Drug-related predictors of readmission for schizophrenia among patients admitted to treatment for drug use disorders. Schizophr Res. 2018;195:495-500. https://doi.org/10.1016/j.schres.2017.09.026.

28. Callaghan RC, Cunningham JK, Allebeck P, Arenovich T, Sajeev G, Remington G, Boileau I, Kish SJ. Methamphetamine use and schizophrenia: a population-based cohort study in California. Am J Psychiatry. 2012;169(4):389-96. https://doi.org/10.1176/appi.ajp.2011.10070937.

29. McInnis P, Lee A. Methamphetamine use in an early psychosis service: a cross-sectional retrospective cohort study. Australas Psychiatry. 2019;27(4):383-7. https://doi.org/10.1177/1039856219859811.

30. McKetin R, Gardner J, Baker AL, Dawe S, Ali R, Voce A, Leach LS, Lubman DI. Correlates of transient versus persistent psychotic symptoms among dependent methamphetamine users. Psychiatry Res. 2016;238:166-71. https://doi.org/10.1016/j.psychres.2016.02.038.

31. Bousman CA, McKetin R, Burns R, Woods SP, Morgan EE, Atkinson JH, Everall IP, Grant I; Translational Methamphetamine AIDS Research Center (TMARC) Group. Typologies of positive psychotic symptoms in methamphetamine dependence. Am J Addict. 2015;24(2):94-7. https://doi.org/10.1111/ajad.12160.

32. Shin EJ, Dang DK, Tran TV, Tran HQ, Jeong JH, Nah SY, Jang CG, Yamada K, Nabeshima T, Kim HC. Current understanding of methamphetamine-associated dopaminergic neurodegeneration and psychotoxic behaviors. Arch Pharm Res. 2017;40(4):403-28. https://doi.org/10.1007/s12272-017-0897-y.

33. Sulzer D. How addictive drugs disrupt presynaptic dopamine neurotransmission. Neuron. 2011;69(4):628-49. https://doi.org/10.1016/j.neuron.2011.02.010.

34. Baig AM. Dark side of amphetamine and analogues: pharmacology, syndromic manifestation, and management of amphetamine addiction. ACS Chem Neurosci. 2018;9(10):2299-303. https://doi.org/10.1021/acschemneuro.8b00137.

35. Jiao D, Liu Y, Li X, Liu J, Zhao M. The role of the GABA system in amphetamine-type stimulant use disorders. Front Cell Neurosci. 2015;9:162. https://doi.org/10.3389/fncel.2015.00162.

36. Gross NB, Duncker PC, Marshall JF. Striatal dopamine D1 and D2 receptors: widespread influences on methamphetamine-induced dopamine and serotonin neurotoxicity. Synapse. 2011;65(11):1144-55. https://doi.org/10.1002/syn.20952.

37. Reichel CM, Ramsey LA, Schwendt M, McGinty JF, See RE. Methamphetamine-induced changes in the object recognition memory circuit. Neuropharmacology. 2012;62(2):1119-26. https://doi.org/10.1016/j.neuropharm.2011.11.033.

38. Bosch PJ, Peng L, Kivell BM. Proteomics analysis of dorsal striatum reveals changes in synaptosomal proteins following methamphetamine self-administration in rats. PLoS One. 2015;10(10):e0139829.. https://doi.org/10.1371/journal.pone.0139829.

39. Iamjan S, Thanoi S, Watiktinkorn P, Reynolds GP, Nudmamud-Thanoi S. Genetic variation of GRIA3 gene is associated with vulnerability to methamphetamine dependence and its associated psychosis. J Psychopharmacol. 2018;32(3):309-15. https://doi.org/10.1177/0269881117750153.

40. Chanasong R, Thanoi S, Watiktinkorn P, Reynolds GP, Nudmamud-Thanoi S. Genetic variation of GRIN1 confers vulnerability to methamphetamine-dependent psychosis in

a Thai population. Neurosci Lett. 2013;551:58-61. https://doi.org/10.1016/j.neulet.2013.07.017.

41. Vuletic D, Dupont P, Robertson F, Warwick J, Zeevaart JR, Stein DJ. Methamphetamine dependence with and without psychotic symptoms: a multi-modal brain imaging study. Neuroimage Clin. 2018;20:1157-62. https://doi.org/10.1016/j.nicl.2018.10.023.

42. Yu S, Zhu L, Shen Q, Bai X, Di X. Recent advances in methamphetamine neurotoxicity mechanisms and its molecular pathophysiology. Behav Neurol. 2015;2015:103969. https://doi.org/10.1155/2015/103969.

43. Breen MS, Uhlmann A, Nday CM, Glatt SJ, Mitt M, Metsalpu A, Stein DJ, Illing N. Candidate gene networks and blood biomarkers of methamphetamine-associated psychosis: an integrative RNA-sequencing report. Transl Psychiatry. 2016;6(5):e802. https://doi.org/10.1038/tp.2016.67.

44. Panenka WJ, Procyshyn RM, Lecomte T, MacEwan GW, Flynn SW, Honer WG, Barr AM. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Depend. 2013;129(3):167-79, https://doi.org/10.1016/j.drugalcdep.2012.11.016.

45. Uhlmann A, Fouche JP, Koen N, Meintjes EM, Wilson D, Stein DJ. Fronto-temporal alterations and affect regulation in methamphetamine dependence with and without a history of psychosis. Psychiatry Res Neuroimaging. 2016;248:30-38. https://doi.org/10.1016/j.psychresns.2016.01.010.

46. Uhlmann A, Fouche JP, Lederer K, Meintjes EM, Wilson D, Stein DJ. White matter microstructure and impulsivity in methamphetamine dependence with and without a history of psychosis. Hum Brain Mapp. 2016;37(6):2055-67. https://doi.org/10.1002/hbm.23159.

47. Ipser JC, Uhlmann A, Taylor P, Harvey BH, Wilson D, Stein DJ. Distinct intrinsic functional brain network abnormalities in methamphetamine-dependent patients with and without a history of psychosis. Addict Biol. 2018;23(1):347-58. https://doi.org/10.1111/adb.12478.

48. Zhang S, Hu Q, Tang T, Liu C, Li C, Zang YY, Cai WX. Changes in gray matter density, regional homogeneity, and functional connectivity in methamphetamine-associated psychosis: a resting-state functional resonance imaging (fMRI) study. Med Sci Monit. 2018;24:4020-30. https://doi.org/10.12659/MSM.905354.

49. McKetin R, Baker AL, Dawe S, Voce A, Lubman DI. Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. Psychiatry Res. 2017;251:349-54. https://doi.org/10.1016/j.psychres.2017.02.028.

50. Medhus S, Mordal J, Holm B, Mørland J, Bramness JG. A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards. Psychiatry Res. 2013;206(1):17-21. https://doi.org/10.1016/j.psychres.2012.09.023.

51. Ma J, Li XD, Wang TY, Li SX, Meng SQ, Blow FC, Ilgen M, Degenhardt L, Lappin J, Wu P, Shi J, Bao YP, Lu L. Relationship between the duration of methamphetamine use and psychotic symptoms: a two-year prospective cohort study. Drug Alcohol Depend. 2018;187:363-9. https://doi.org/10.1016/j.drugalcdep.2018.03.023.

52. Akiyama K, Saito A, Shimoda K. Chronic methamphetamine psychosis after long-term abstinence in japanese incarcerated patients. Am J Addict. 2011;20(3):240-9. https://doi.org/10.1111/j.1521-0391.2011.00124.

53. Voce A, Calabria B, Burns R, Castle D, McKetin R. A systematic review of the symptom profile and course of methamphetamine-associated psychosis. Subst Use Misuse. 2019;54(4):549-59. https://doi.org/10.1080/10826084.2018.1521430.

54. Wang LJ, Lin SK, Chen YC, Huang MC, Chen TT, Ree SC, Chen CK. Differences in clinical features of methamphetamine users with persistent psychosis and patients with schizophrenia. Psychopathology. 2016;49(2):108-15. https://doi.org/10.1159/000445065.

55. Farnia V, Shakeri J, Tatari F, Juibari TA, Yazdchi K, Bajoghli H, Brand S, Abdoli N, Aghaei A. Randomized controlled trial of aripiprazole versus risperidone for the treatment of amphetamine-induced psychosis. Am J Drug Alcohol Abuse. 2014;40(1):10-15. https://doi.org/10.3109/00952990.2013.861843.

56. Verachai V, Rukngan W, Chawanakrasaesin K, Nilaban S, Suwanmajo S, Thanateerabunjong R, Kaewkungwal J, Kalayasiri R. Treatment of methamphetamine-induced psychosis: a double-blind randomized controlled trial comparing haloperidol and quetiapine. Psychopharmacology (Berl). 2014;231(16):3099-3108. https://doi.org/10.1007/s00213-014-3485-6.

57. Richards JR, Albertson TE, Derlet RW, Lange RA, Olson KR, Horowitz BZ. Treatment of toxicity from amphetamines, related derivatives and analogues: a systematic review. Drug Alcohol Depend. 2015;150:1-13. https://doi.org/10.1016/j.drugalcdep.2015.01.040.

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