



# Substances led to Psychosis: A Systematic Review

Isaac Karimi<sup>1</sup>  and Nioosha Pooyanmehr<sup>2,\*</sup> 

<sup>1</sup>Laboratory for Computational Physiology, Department of Biology, Faculty of Science, Razi University, Kermanshah 67149-67346, Iran

<sup>2</sup>Faculty of Social Sciences, Razi University, Kermanshah, Iran

## Abstract:

**Background:** Psychosis is one of the mind-related disorders that has been common in the new generation, and it has an increasing trend. Psychosis is a variable feature of mood that could be a result of substance use, which includes a few psychiatric and neurologic symptoms. Common symptoms of psychoses are delusions, hallucinations, disorganized thinking, grossly disorganized, or abnormal motor behavior. An array of illicit substances and drugs that can lead to psychosis include cannabinoids, cocaine, amphetamines, methamphetamines, alcohol, *etc.*

**Objectives:** The main aim of this review was to discover, analyze, and combine the information concerning substances that could potentially cause psychoses.

**Methods:** We conducted a literature search on the following network databases: PubMed, Scholar, Science Direct, PubChem, Scopus, and Web-Of-Science. We selected 14 studies potentially relevant articles published from 1990 to 2023 for detailed evaluation. The systematic review was done adhering to PRISMA guidelines. We gathered the important primary studies of eligible systematic reviews and collected data on the interventions employed in these studies to comprehend the strategies that were pursued.

**Results:** Our result indicated that there are a few substances, which include Cannabinoids, Alcohol, Amphetamine, Cocaine, Nicotine, Kratom, Cathinone, *etc.*, that may lead to psychoses with average to high possibility.

**Conclusion:** Evidence regarding frequently encountered substances that might contribute to psychosis presents an opportunity to develop customized interventions in the form of user-friendly menus aimed at meeting individuals' requirements and urging them to refrain from consumption.

**Keywords:** Psychosis, Illicit drugs, Youth, Antibiotics, Neurologic symptoms, Alcohol.

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\*Address correspondence to this author at the Faculty of Social Sciences, Razi University, Kermanshah, Iran; E-mail: [nishapooyan01@gmail.com](mailto:nishapooyan01@gmail.com)

Cite as: Karimi I, Pooyanmehr N. Substances led to Psychosis: A Systematic Review. Open Psychol J, 2024; 17: e18743501297735. <http://dx.doi.org/10.2174/0118743501297735240510161825>



Received: December 09, 2023

Revised: March 17, 2024

Accepted: April 03, 2024

Published: May 30, 2024



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## 1. INTRODUCTION

Experimental data indicate diverse subgroups of individuals diagnosed with various severe psychiatric disorders, such as new-onset psychosis and substance-induced psychosis, frequently exhibit abnormalities. These

abnormalities commonly manifest in clinical practice [1]. Psychosis is one of the mind-related disorders that has been common in the new generation, and it has an increasing process [2]. Psychosis is an inconstant feature of mood that could be an outcome of substance use, which includes a few functionally psychiatric and neurologic

symptoms. In the initial version of the Diagnostic and Statistical Manual of Mental Disorders (DSM), psychosis was described as "abnormalities in one or more of the following five domains: *delusions, hallucinations, disorganized thinking speech, grossly disorganized or abnormal motor behavior, and negative symptoms*" or "gross impairment in reality testing" that interferes with the capacity to meet the ordinary demands of life [3] (Fig. 1). There are a few kinds of substances and drugs that can lead to psychosis; however, the reasons for this association. A clear connection between drug use and the appearance of psychotic symptoms has received considerable backing. Some studies indicate that drugs like cannabinoids, cocaine, amphetamines, methamphetamines, alcohol, methylphenidates, nicotine, Kratom, hallucinogens, and certain antibiotics possess psychotomimetic properties. [4]. Also, drug abuse has been one of the most popular behaviors in the new generation, and

the chemical formula of psychoactive drugs is progressing. Thus, it is probable that substance-induced psychosis may become a pandemic in the future [5]. This review aimed to find, analyze, and summarize the information on substances that could cause psychoses. In other words, it may cause temporary psychotic symptoms as a result of immediate intoxication and psychotic disorders [5, 6]. In another hand, it has been strengthened by teenagers [7-11]. The research gaps of recent articles are limited focus on specific substances, Insufficient research on longitudinal effects, variability in study methodologies, lack of research on specific populations, limited exploration of underlying mechanisms, and Sparse data on effective interventions. Therefore, these potential research gaps could provide avenues for future research to deepen our understanding of the relationship between substances and psychosis; the aim of this article is to resolve these research gaps.

According to the DSM-5, the Diagnostic and Statistical Manual of Mental Disorders fifth edition, the criteria for substance-induced psychosis include:

- A. Presence of one or both of the following symptoms
  - 1. Delusions
  - 2. Hallucinations

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication

2. The involved substance/medication is capable of producing the symptoms in Criterion A

- C. Differential Diagnosis

D. The disturbance does not occur exclusively during the course of delirium

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other areas of functioning

Fig. (1). The DSM-5, the Diagnostic and Statistical Manual of Mental Disorders fifth edition, the criteria for substance-induced psychosis.

Table 1. Data extraction.

Authors	Year	Title	Focus	Sample	Main Results
Fiorentini, Alessio; Sara Volonteri, Lucia; Dragogna, Filippo; Rovera, Chiara; Maffini, Michele; Carlo Mauri, Massimo; A. Altamura, Carlo [1]*	2011	Substance-Induced Psychoses: A Critical Review of the Literature	Drugs that may lead to psychoses	23	Most of the drugs, such as cannabinoids, may lead to psychoses.
Dharav Shah, Prabhat Chand, Mrunal Bandawar, Vivek Benegal, Pratima Murthy [75]*	2017	Cannabis-induced psychosis and subsequent psychiatric disorders	Cannabis and psychoses	38	Cannabis may lead to psychoses.

(Table 1) contd....

Authors	Year	Title	Focus	Sample	Main Results
Vera L. Alves, João L. Gonçalves, Joselin Aguiar CQM - Centro de Química da Madeira, Universidade da Madeira, Funchal, Portugal; Helena M. Teixeira & José S. Câmara [74]*	2020	The synthetic cannabinoids phenomenon: from structure to toxicological properties. A review	Synthetic cannabinoids and psychiatric disorders	42	Synthetic cannabinoids can considerably lead to psychoses.
Anna Sunshine, Jon McClellan [3]*	2023	Practitioner Review: Psychosis in children and adolescents	Psychoses in children	58	Drug use by children can lead to psychosis.
F. Schifano, F. Napoletano, S. Chiappini, A. Guirguis, J. M. Corkery, S. Bonaccorso, A. Ricciardi, N. Scherbaum And A. Vento [4]*	2019	New/emerging psychoactive substances and associated psychopathological consequences	New drugs and psychiatric disorders.	66	Future drugs lead to psychotic symptoms.
Hannah E. Brown, Yoshio Kaneko & Abigail L. Donovan [6]*	2019	Substance-Induced Psychosis and Co-occurring Psychotic Disorders	Psychosis because of drug use such as cocaine, etc.	87	Amphetamine and cocaine considerably can lead to psychoses.
NEUFELD, NICHOLAS H. MD; MOHAMED, NOURHAN S. MD; GRUJICH, NIKOLA MD; SHULMAN, KENNETH MD [45]*	2017	Acute Neuropsychiatric Symptoms Associated with Antibiotic Treatment of Helicobacter Pylori Infections: A Review	Antibiotics as a risk factor for psychiatric patients.	91	Antibiotics may lead to psychoses.
Pedro Gurillo, MD, Dr. Sameer Jauhar MRCPsych, Robin M Murray FRS, James H MacCabe, FRCPsych [9]*	2015	Does tobacco use cause psychosis? Systematic review and meta-analysis	Smoking and psychosis	94	Nicotine may be a factor that increases the incur of psychosis
M.C. Cancino Botello, M.D.L.A. Canseco Navarro, A. Peña Serrano, F. Molina López and J.M. Hernández Sánchez [38]*	2020	Psychosis, cause or consequence of substance use disorder	Drug use and psychotic symptoms	102	Drugs lead to psychotic symptoms considerably.
M.C. Mauri a, C. Di Pace a, A. Reggiori a, S. Paletta a, A. Colasanti [12]*	2017	Primary psychosis with comorbid drug abuse and drug-induced psychosis: Diagnostic and clinical evolution at follow up	Substance abuse and psychiatric disorders.	108	Substance abuse lead to psychotic symptoms.
Corinne Cather, Gladys N. Pachas, Kristina M. Cieslak & A. Eden Ewins [21]*	2017	Achieving Smoking Cessation in Individuals with Schizophrenia: Special Considerations	Smoking as a risk factor for psychotic patients.	157	Smoking may lead to psychoses in a long-term use.
L. R. Valmaggia, F. L. Day, C. Jones, S. Bissoli, C. Pugh, D. Hall, S. Bhattacharyya, O. Howes, J. Stone, P. Fusar-Poli, M. Byrne And P. K. McGuire [76]*	2014	Cannabis use and transition to psychosis in people at ultra-high risk	Cannabinoids and psychoses	198	Cannabinoids may strongly lead to psychoses.
Khadija Pasha, Salomi Paul, Muhammad S. Abbas, Sondas T. Nassar, Tasniem Tasha, Anjali Desai, Anjana Bajgain, Asna Ali, Chandrani Dutta, Abeer O. Elshaikh [23]*	2023	Psychosis Induced by Methylphenidate in Children and Young Patients with Attention Deficit Hyperactivity Disorder	Methylphenidate and psychosis	202	Methylphenidate leads to psychotic symptoms.
G. Martinotti1, M. Di Nicola2, D. Quattrone1, R. Santacroce1, F. Schifano, R. Murray4, M. Di Giannantonio1 [64]*	2015	Novel psychoactive substances and induced phenomena in psychopathology: the lysergic psychoma	psychotic symptoms by drug use	212	Methamphetamine, Amphetamine, methylphenidates, etc., can lead to psychoses.

## 2. MATERIALS AND METHODS

The databases include PubMed, Scholar, Science Direct, PubChem, Scopus, and Web-Of-Science. The steps involved in conducting this systematic review are

1-Formulating the research question (Clearly defining

the research question “Which substances may lead to psychoses?” or hypothesis “Most of the usual drugs and some Antibiotics may lead to psychoses.” that the systematic review aims to address)

2-Developing inclusion and exclusion criteria (Setting

specific criteria for including or excluding studies based on relevance and quality. The inclusion criteria include all clinical studies concerning adult (more than 17 years old) patients, published in English, content directly relevant to substance-induced-psychosis, report original patient, and studies defining drugs that can be related to psychosis. Exclusion criteria include studies with less than 10 participants, case reports, animal studies, articles that were not available in English, content related to other disorders like schizophrenia, not concerned with the field of substance-induced-psychosis, repeated research, unavailable full research (Tables 1 and 2), 3-Systematic search for studies (Conducting a comprehensive and systematic search across multiple databases such as PubMed, Scholar, and Science Direct, PubChem, Scopus, and Web-Of-Science to identify all relevant studies), 4-Screening and selecting studies (Reviewing titles, abstracts, and full texts of potentially relevant studies to determine which ones meet the inclusion criteria. We focused on review articles for our results. If the database did not have that filter, we looked for search terms related to reviews (like Review, systematic review, and meta-analysis) in our search strategy. Our main search topics were 'substance use and psychosis' and 'psychological intervention' (including psychological symptoms and behavior therapy, for instance) (Fig. 2). 5-Data extraction (Extracting relevant data from each included study using a predefined data extraction form), 6-Quality assessment (Assessing the quality of included studies to evaluate their risk of bias and methodological rigor), 7-Data synthesis (Analyzing and synthesizing the findings of the included studies using narrative synthesis which involves summarizing and qualitatively analyzing the findings of individual studies to identify patterns, themes, and discrepancies and qualitative thematic analysis methods to identify and interpret recurring themes, patterns, or discrepancies across the included studies. This can enrich the understanding of complex phenomena), 8-Interpreting results (Drawing conclusions based on the synthesized evidence and discussing implications).

### 3. RESULTS

#### 3.1. Eligible Reviews

The search of the databases has returned 213 references. After excluding 116 duplicates based on title, we screened the titles of 97 studies. After excluding 79 duplicates based on abstract, we screened abstracts of 18 studies. We managed to obtain 14 complete texts. Fig. (1) summarizes the screening process described above. The reviews that were included had differences, as outlined below. Our research has found 14 studies examining the relationship between substance use and psychosis. Although the methodologies of studies and substance use psychosis criteria have varied, there was a considerable consistency between substance use and psychosis.

#### 3.2. Conceptualization of Substance-induced Psychosis (SIP) in the Eligible Reviews

The current research findings have provided insight into the intricate connection between psychotic symptoms

and the utilization and misuse of illegal substances. Moreover, there are instances where chronological factors alone are inadequate to establish a clear cause-and-effect connection between the substances and psychosis. To determine if psychotic symptoms in individuals with a history of drug use are truly independent of the drugs, these symptoms must persist even after a prolonged period of abstaining from psychoactive substances. It's worth noting that drug-induced psychosis is generally expected to resolve during a period of abstinence. People with drug-induced psychosis, in contrast, had a higher tendency to abuse multiple drugs and appeared to experience prolonged hallucinations even after stopping drug use [12].

**Table 2. Inclusion and exclusion criteria refer to the requirements for being included or excluded from a particular group or study.**

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>All clinical studies concerning adult (more than 17 years old) patients               <ul style="list-style-type: none"> <li>Published in English</li> <li>Content directly relevant to substance-induced-psychosis</li> <li>Report original patient</li> </ul> </li> <li>Studies defining drugs that can be related to psychosis</li> </ul>	<ul style="list-style-type: none"> <li>Studies with less than 10 participants               <ul style="list-style-type: none"> <li>Case reports</li> <li>Animal studies</li> </ul> </li> <li>Articles which were not available in English</li> <li>Content related to other disorders like schizophrenia, not concerned with the field of substance-induced-psychosis               <ul style="list-style-type: none"> <li>Repeated researches</li> <li>Unavailable full researches</li> </ul> </li> </ul>

#### 3.3. Cannabinoids

In 2019, cannabinoids were the most commonly used illegal substance, with 22.2 million adults in Europe having used cannabis [13]. The point is that the effect of cannabis is related to its tetrahydrocannabinol (THC) content. THC causes negative effects associated with cannabis, such as cognitive impairments and the promotion of psychosis and anxiety [14]. This receptor is mainly found on peripheral nerve terminals. Cannabidiol (CBD) appears to be the second most prevalent cannabinoid that does not seem to cause any signs of psychosis. Marijuana includes 20% THC, and its concentrates include hash oil, wax, and edibles containing 60% THC [15-18] (Table 3).

#### 3.4. Alcohol

Alcohol has a main role in substance use disorder, and alcohol-use disorders are associated with a considerable burden in terms of morbidity and mortality [19]. Psychotic symptoms can occur in several clinical conditions that are related to alcohol use and can lead to first-episode psychosis as well ref. Despite the main role of alcohol in substance use disorders, recent studies on substance-induced psychotic disorders have generally shown psychoses are usually induced by illicit drug use. Alcohol-induced psychotic disorder is a severe mental disorder with poor outcome [20]. However, the point is that it can be cured by behavior therapy with considerable outcomes (Table 3).

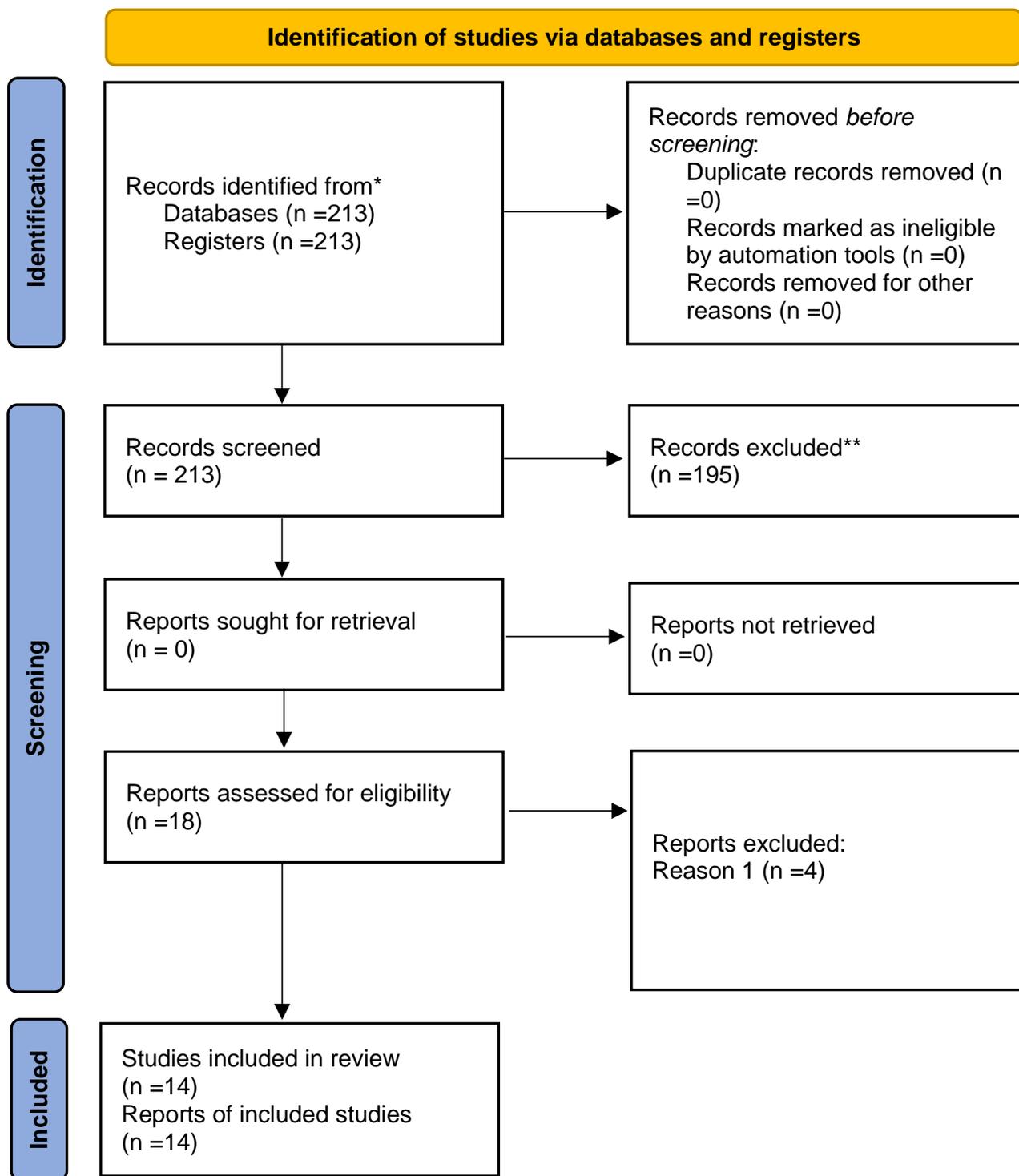


Fig. (2). PRISMA 2020 flow chart.

### 3.5. Nicotine

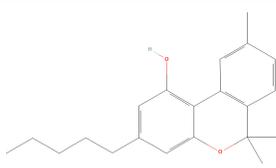
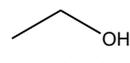
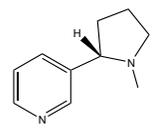
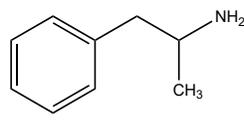
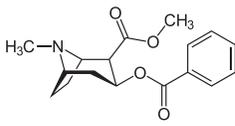
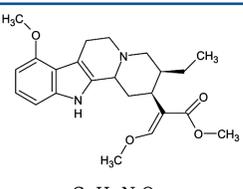
Nicotine is one of the most popular substances that has been used by a large group of people, especially young

generations. It is the basic substance used to make cigarettes, and it comes from tobacco, which is a plant. Usually, people smoke cigarettes during adolescence, so there can be a huge misuse by individuals, and it has been

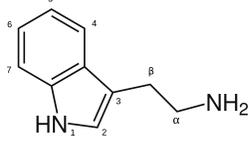
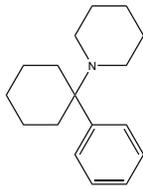
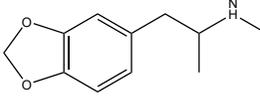
associated with an increased risk factor of psychosis REF. Also, genetics may influence this association as genes associated with psychosis have been shown to overlap with those for cigarette smoking ref. It also increases

cytochrome CYP1A2 enzyme activity, so it increases metabolism in a way [21]. Behavioral therapy can be useful even more than medicine in quitting smoking (Table 3).

**Table 3. The main features of the canonical of substances led to psychosis.**

Substance	Antidote	Exposure	Treatment	Symptoms	Neurotransmitter/pathways/receptors Implicated	Chemical Structure
<b>Cannabinol</b>	Naloxone (97)	Oral, inhaled. (35)	Decreasing THC levels in cannabis leads to decreasing the risk factor of psychotic disorder even for daily users(34)	Reducing the level of THC in cannabis lowers the likelihood of developing a psychotic disorder, even for individuals who use it daily. (36)	They influence the endocannabinoid system, specifically by fully activating CB1 and CB2 receptors.	 C <sub>21</sub> H <sub>26</sub> O <sub>2</sub>
<b>Alcohol</b>	Metadoxine, Fomepizole	Drink(self-use and used by moms)	Behavioral therapy	Visual illusion, nauseous, loss of regular movements	-	 C <sub>2</sub> H <sub>6</sub> O
<b>Nicotine</b>	Benzodiazepines, Atropine, Ventilator, Intravenous fluids	Inhalation, insufflation, oral, rectal.	Medical care, behavioral therapy	-	-	 C <sub>10</sub> H <sub>14</sub> N <sub>2</sub>
<b>Amphetamine (psychostimulant)</b>	Benzodiazepines (98)	Oral (self-used by youth)	Medical care and do not misuse	Serotonergic syndrome, Psychosis, Paranoid ideation, Impulsivity, Mania, Agitation,	Mood disorders like serotonin syndrome (Serotonergic syndrome), psychosis, paranoid thoughts, impulsive behavior, manic episodes, and agitation are commonly associated with the use of psychostimulants. These drugs traditionally focus on activating the monoaminergic systems, resulting in higher levels of serotonin (5-HT), dopamine (DA), and/or norepinephrine (NA) C9H13N Cocaine (psychostimulant) Benzodiazepines in the brain.	 C <sub>9</sub> H <sub>13</sub> N
<b>Cocaine (psychostimulant)</b>	Benzodiazepines (98)	Oral, inhaled (used by mouth mostly)	Do not misuse medical care	90% of the participants exhibited paranoid delusions, while 96% reported experiencing hallucinations, paranoia, and suspicious beliefs.	Psychostimulants, in the traditional sense, mainly focus on the monoaminergic systems, resulting in elevated levels of SER, DA, and/or NA in the extracellular space.	 C <sub>17</sub> H <sub>21</sub> NO <sub>4</sub>
<b>Kratom</b>	Naloxone	commonly used by chewing, as a tea, powdered in capsules and pills, or extracted for use in liquids	Medical care	-	-	 C <sub>23</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub>

(Table 3) contd....

Substance	Antidote	Exposure	Treatment	Symptoms	Neurotransmitter/pathways/receptors Implicated	Chemical Structure
<b>Hallucinogens</b> (Tryptamines)	Naloxone	Inhalation, Intravenous, Oral	The main chemical is in a kind of mushroom, so do not misuse	Perception will be interrupted, and alteration in the perception, spontaneous reoccurrence of perceptual disturbance, and the illusion of movement will exist.	All three subgroups share a common mechanism in the serotonergic system, represented by the agonism/partial agonism at the 5-HT <sub>2A</sub> receptor (activation), 5-HT <sub>1A</sub> , and 5-HT <sub>2C</sub> . However, Various hallucinogenic/psychedelic substances might have distinct interactions with various neurotransmitters, such as NMDA receptors, $\sigma$ -receptors, $\mu$ -opioid receptors, and muscarinic receptors, in addition to their ability to inhibit serotonin and dopamine reuptake at their respective transporters.	 C <sub>10</sub> H <sub>12</sub> N <sub>2</sub>
<b>Phencyclidine</b>	Diazepam, haloperidol, chlorpromazine	Smoking, by mouth, snort, injection.	Medical care	PCP exhibits more intense psychotic effects, such as hallucination and delusion, especially illogical thinking (79). Apathy (lack of interest), decreased talking, repetitive speech, and catatonic posturing (unusual body movements).	-	 C <sub>17</sub> H <sub>25</sub> N
<b>Entactogens,</b> (MDMA)	Medical care	delusions (96%), hallucinations (96%), disorganization (96%). Feeling down (90%) with reduced emotional expression (81%), (77).	-	-	-	 C <sub>11</sub> H <sub>15</sub> NO <sub>2</sub>
<b>Antibiotics</b>	Use them in a limited amount.	-	-	-	-	-

**Note:** MDMA: 3,4-Methyl enedioxy methamphetamine, commonly known as ecstasy.

### 3.6. Amphetamine

Amphetamine is a strong central nervous system stimulant. Amphetamines, such as methamphetamine and 3,4-methylenedioxyamphetamine (MDMA), belong to a class of compounds called phenethylamines that induce catecholaminergic effects in the CNS and peripheral circulation. Nowadays, amphetamines are clinically used to treat short-term obesity, narcolepsy, and attention deficit disorder with hyperactivity [22]. Due to recent studies, psychosis following amphetamine use is characterized by delusions, visual hallucinations, and symptoms resembling acute psychosis most commonly observed in schizophrenia. There is an obvious pattern of high dosage and daily usage correlating with higher risks of substance-induced psychosis. Amphetamines impair the cognitive thought process and precede acute psychosis. This shows that continued impairment due to amphetamine use is a precursor to psychosis. (Table 3) [23, 24].

### 3.7. Cocaine

Cocaine is one of the most common substances that leads to transitory paranoia [25]. Cocaine is widely recognized to be associated with several mental disorders, and its use develops psychotic symptoms. Cocaine works as an inhibitor of serotonin and noradrenaline reuptake. The majority of psychotic symptoms are related to cocaine use within 24-48 hours [26, 27]. In sum, it is one of the most favorite drugs among teenagers and can be a serious risk factor and increase the possibility of psychoses in the future [28, 29] (Table 3).

### 3.8. Kratom

Kratom (*Mitragyna speciosa*) is a psychoactive plant preparation that has medicinally been used for its stimulant effects and as an opioid substitute [30]. It can cause psychosis and even death. But the difference is that kratom's effect for causing psychosis is stronger than

other opioids. It can lead to addiction, sleeping and eating disorders as well. Also, neuropsychiatric side effects such as hallucinations, delusions and paranoia are usual after kratom intake [31] (Table 3).

### 3.9. Cathinone

Cathinone is related to the phenethylamine family but its potency is much lower than others [32]. It starts to have effects on consumers within 15 minutes at least and 45 minutes at most after injection. By inhaling, the sensations can be experienced within minutes and reach a higher intensity and stronger effect, but the effects last for 2-3 hours in oral and nasal use [33, 34]. This group consists of substances similar to the ones naturally occurring in *Catha edulis* (Khat) known as cathinone [35] (Table 3).

### 3.10. Hallucinogens

Hallucinogens include a wide group of natural and synthetic substances. As hallucinations are the intended toxidrome, these substances may cause psychosis. Currently, classic hallucinogens are seen as those that have a psychopharmacological profile similar to mescaline, psilocybin, and lysergic acid diethylamide (LSD) [36]. Classical hallucinogens (psychedelics) can be divided into three main chemical classes: tryptamines (*e.g.*, psilocin), ergolines (*e.g.*, LSD), and phenethylamines (*e.g.*, mescaline). Tryptamines closely resemble serotonin chemically. Psilocybin and mescaline are natural, but LSD and LSD-like are synthetic drugs. It affects the visual cortex, which leads to illusions and open-eye dreams, which is one of the most important psychotic symptoms *ref.* There are two kinds of perception disorders by using hallucinogens: *short-term*, in which users do not experience significant impairment; psychiatric care is rarely sought; and *long-term*, which reflects chronic severe syndrome [37, 38] (Table 3).

### 3.11. Phencyclidine and Ketamine

These effects can be attributed to dopamine level increment in the prefrontal cortex, which can be understood by considering the binding of ketamine and PCP to the dopamine receptor 2 (D2) [[39, 40]. Beck and coworkers discovered a noteworthy increase in temporary

mental health issues related to ketamine usage [38, 41-43] (Table 3).

### 3.12. Antibiotics

Surprisingly, some kinds of antibiotics can lead to psychotic disorders (*e.g.*, fluoroquinolones) [44-47] (Table 3).

### 3.13. Miscellaneous Compounds

Although, these are not the only substances that may lead to psychosis. There are other substances that can lead to psychosis; Dissociative, Sedatives or analgesics, New synthetic opioids (NSOs) (*e.g.*, U-47700, U-49900, AH-7921, U-50488, U-51754, MT-45, Acetylfentanyl, Carfentanyl, Furanylfentanyl) [48], Desomorphine ('krokodil'), Mitragynine ('Kratom', 'kakuum', 'thang', 'ketum', 'biak') [49], Salvinorin A (*Salvia divinorum*, *hierba de Maria*, 'Maria pastora', 'Sally-D', 'magic mint') [50], Ketamine-like dissociatives; Ketamine ('ket', 'special K', 'super K', 'kit-kat') [51], Phencyclidine (PCP, 'angel dust', 'supergrass', 'boat') and PCP-type substances (*e.g.*, 3-MeO-PCE, 4-MeO-PCP) [52], Methoxetamine ('mexxy', 'special M'), Novel Stimulants and novel psychedelics [53]; Synthetic cathinones (*e.g.*, mephedrone, 'm-cat', 'meow') [54], Psychedelic/empathogenic phenethylamines (*e.g.*, 2C series; D series, such as DOI, DOC; benzodifurans, such as 'bromodragonfly'; others, such as PMA/PMMA) [55], Piperazines (*e.g.*, BZP, mCPP, 'party pills', 'smileys') [56], Tryptamines (*e.g.*, DMT, 5-MeO-DMT, 'magic mushrooms'), Prescription drugs with a misusing potential: 1. ANTIDEPRESSANTS; (Bupropion, Amitriptyline, Venlafaxine ('baby ecstasy')) [57], 2. ANTIPSYCHOTICS: (Quetiapine ('Susie Q', 'Quell', and 'baby heroin'); 'Q ball' (quetiapine with cocaine); 'MaQ ball' (quetiapine and marijuana), Olanzapine ('Lilly')) [58], 3. GABAPENTINOIDS (pregabalin and gabapentin), 4. Z-DRUGS (zaleplon, zolpidem and zopiclone) [59], DESIGNER BENZODIAZEPINES (*e.g.*, clonazolam, etizolam, flubromazepam, phenazepam ('Zinnie') and pyrazolam [60], 5. OVER-THE-COUNTER DRUGS: (Codeine [61] ('Purple drank' is a mix of codeine and promethazine), Loperamide [62], Dextromethorphan (DXM) [63] for instance [64-72] (Tables 3 and 4).

**Table 4. Psychoactive substances or medications causing secondary psychosis.**

Medical Section	Category (type)
Psychoactive Substances	Alcohol Withdrawal and Hallucinosis, Amphetamine Intoxication, Cocaine Intoxication, Hallucinogen Intoxication, Phencyclidine Intoxication, Sedative Hypnotic Withdrawal
Cardiology	Digitalis, Beta-blockers, Antiarrhythmics
Oncology	Asparaginase, Cytarabine, Fluorouracil, Ifosfamide, Methotrexate, Vincristine
Infectious diseases	Ciprofloxacin, Antitubercular agents, Antimalarials, Antivirals
Neurology	Dopamine agonists (amantadine, bromocriptine, and levodopa)
Psychiatry	Antidepressants (bupropion, tricyclic antidepressants), Anticholinergics (benztropine, diphenhydramine)
Gastroenterology	Cimetidine, Ranitidine
Analgesia	Pentazocine, Meperidine, Indomethacin
Genera	Corticosteroids, Metrizamide, Methysergide, Baclofen Ephedrine

#### 4. DISCUSSION

In the last two decades, plenty of research has been dedicated to psychosis induced by cannabinoids, psychostimulants such as methamphetamine, amphetamine, methylphenidate and cocaine, hallucinogens and so on. Despite the apparent connection to psychotic symptoms, the scientific community is still unable to give definitive proof on this specific subject. The main point about the subject is that there has been a notable rise in both the quantity and diversity of newly developed psychoactive drugs. Over time, more powerful have been formulated and circulated, resulting in more harmful side effects and more severe impacts on the body. This surge in new drug misuse has greatly expanded the occurrence of secondary psychoses.

For example, synthetic cannabinoids and synthetic cathinone may lead to serious clinical syndrome with a high risk of a fully structured psychotic disorder [73, 74]. Clinicians still face a difficult task in differentiating SIP and primary psychotic illnesses. Nonetheless, we hold optimistic expectations that this research could assist in overcoming the challenge [75, 76].

But despite considerable variation in how substance exposure and psychosis were elicited or defined, there is a notable consistency across the population groups studied in different research. As has been said before, young ages play a big role in drug abuse. The most common reasons are fun or parents' attitudes. On the other hand, drug abuse may have real side effects on the body and especially the brain as time passes and may lead to psychosis in the future. Although none of these variables, alone or together, can recognize the etiology of psychosis accurately. A combination of approaches is the best management for substance-induced psychosis, which includes medication management, psychological treatment (individual therapy or group therapy), and family engagement in some cases. After all, we have collected as much information as we could about different drugs that may lead to psychosis, psychotic symptoms, and similarities and differences between such substances. Finally, this article has been based on limited evidence, and further study of both pharmacologic and psychological interventions is needed to find out how to provide the best care to vulnerable youth and adults who have experienced such symptoms of psychosis and substance use. Systematic literature reviews are crucial in research articles for several reasons. For example, they provide a comprehensive overview of existing research on a particular topic, helping researchers understand the current state of knowledge. By following a systematic approach, researchers can ensure that the review is unbiased and based on all available evidence, reducing the risk of cherry-picking data. Systematic reviews help identify gaps in the existing literature, highlighting areas where further research is needed. They allow for the evaluation of the quality of individual studies, helping to assess the reliability of the findings. Also, systematic reviews can facilitate meta-analysis, where data from multiple studies are combined to provide more robust conclusions. The results of systematic reviews can inform policy-making, clinical practice, and future research

directions. Overall, using systematic literature reviews in articles enhances the credibility and reliability of the research by providing a structured and rigorous synthesis of existing knowledge. The research includes most of the substances that can lead to psychoses, and it is a comprehensive article that can help to identify these substances conveniently. Psychoactive substances and some medications can cause secondary psychosis. For example, Digitalis, Beta-blockers, Antiarrhythmic in cardiology, Asparaginase, Cytarabine, Fluorouracil, Ifosfamide, Methotrexate, Vincristine in oncology, Dopamine agonists (amantadine, bromocriptine, and levodopa) in neurology, Cimetidine, Ranitidine in gastroenterology and Antidepressants (bupropion, tricyclic antidepressants), Anticholinergics (benztropine, diphenhydramine) in psychiatry can cause secondary psychosis (Table 4).

#### 5. LIMITATIONS AND FUTURE DIRECTIONS

This systematic review has some limitations. There are few scientific research and articles about substance-induced psychoses, and it is difficult to say with certainty that these substances lead to psychoses definitely, and these are all of the substances that may lead to psychoses. First of all, this article has been written about humans, and there is nothing certain about humans, and the effects of substances differ from one another. Secondly, there are lots of substances that are undetermined and uncharted. Also, there will be more human-made substances in the future. Further studies and investigations are required to verify these substances and to find antidotes and cures for substance-induced psychotic patients as well. Finally, this research can only represent the situation of a single part of the whole world population.

#### CONCLUSION

A few studies indicate that there are a few substances and even medicines that may lead to psychoses with high possibility. Numerous psychological intervention strategies for SIPs show promising treatment results, indicating the potential for customizable interventions that can meet individual needs. It can be concluded that the etiology of psychoses is different. Psychoses can develop because of sad experiences in childhood, available genes, depressing experiences and accidents, some medicines for a long time, or drug misuse. However, the most common reasons are available genes and substances that have been discussed. Unfortunately, these substances change the chemical structures of genes and can lead to other disorders and diseases besides psychoses. However, additional research is needed to effectively put these strategies into practice in interventions that are supported by a reliable mechanism of change and to verify the effectiveness of those interventions.

#### AUTHORS' CONTRIBUTIONS

**Research design:** Isaac Karimi

**Data collection:** Nioosha Pooyanmehr

**Writing the manuscript:** Nioosha Pooyanmehr

**Primary revision:** Isaac Karimi

**LIST OF ABBREVIATIONS**

DSM	=	Diagnostic and Statistical Manual
SIP	=	Substance-induced Psychosis
THC	=	Tetrahydrocannabinol
CBD	=	Cannabidiol
LSD	=	Lysergic Acid Diethylamide

**CONSENT FOR PUBLICATION**

Not applicable.

**STANDARDS OF REPORTING**

PRISMA guidelines have been followed.

**AVAILABILITY OF DATA AND MATERIALS**

All the data and supporting information is provided within the article.

**FUNDING**

None.

**CONFLICT OF INTEREST**

Hereby, it has been announced that the authors have no conflict of interest.

**ACKNOWLEDGEMENTS**

Declared none.

**SUPPLEMENTARY MATERIAL**

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

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