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Mechanisms of psychiatric disorders induced by amphetamines: A comprehensive review

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Abstract

Objectives: Amphetamines are stimulants and addictive drugs. Saudi officials announced in 2023 a huge campaign against abused drugs. Numerous studies have shown that amphetamines abuse may affect the functions and structures of the brain and result in damage and psychiatric disorders. Nothing evidence was gathered and summarized for all available mechanisms to induce psychiatric disorders. Therefore, we summarized the alterations that cause psychiatric disorders.

Methods: We are accessed the studies included in our scope by conducting a literature review involves using engines of the health database such as APA, PubMed, Cochrane Review, Scopus, Google Scholar, Medline, and EMBASE to collect the data and identify the materials that describe the topic by using multi-key words including amphetamines, methamphetamine, ecstasy which known as (MDMA) 3,4-Methylenedioxymethamphetamine , mechanisms of psychiatric disorders; substance-induced psychiatric disorders; psychosis; abuse mechanisms; cognitive-behavioral abnormalities.

Results: Psychiatric Disorders induced by amphetamines is a result of direct mechanisms such as abnormalities in the levels of dopamine, glutamate, and GABA, in addition to high dopamine in the midbrain and forebrain, neuronal network dysregulation, and ultimately, cortical and subcortical damage. Indirect mechanisms are confirmed, such as long-term use, high doses, sleep deprivation, genetics, and reactive oxygen species. Dopamine functions and sensitization are confirmed in schizophrenia and drug-induced psychiatric disorders.

Conclusion: Mechanisms that induce psychiatric disorders are complex and interrelated. Research focuses on alterations of dopaminergic, sensitization, glutamatergic, neuronal inflammation, cortical GABAergic neurons, apoptosis following neurotoxicity, and mediators of protein kinases. Amphetamine-induced psychiatric disorders could be avoided by early prevention and detoxification.

Keywords: Amphetamine; Psychiatric Disorders; Schizophrenia; Cognitive-behavioral abnormalities

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1. Introduction

Amphetamine and its derivatives, such as ecstasy or 3,4-Methylenedioxymethamphetamine (MDMA) and methamphetamine, can extend insomnia, focus, energy, and decrease fatigue feelings. Adverse effects include hyperactivity, tachycardia, anxiety, paranoia, reduced appetite, aggression, dilated pupils, insomnia, and cardiac profiles such as elevated breathing rate, high blood pressure, cardiac palpitations, and arrhythmia. Psychotic disorders are among the most harmful side effects linked to amphetamines abuse. Complications involving dangerous impacts on the community, people, family, and healthcare system. Amphetamine addiction is considered the second most widely abused drug in the world (1,2). Amphetamines are considered highly addictive drugs. These drugs act on the mesolimbic dopaminergic system by reward system through direct way, and inducing the release of dopamine, norepinephrine, acting on nucleus accumbens (NA) in the synaptic clefts, and reporting that other terminal areas may excite a euphoric state, ultimately causing addiction (3).

Amphetamines could trigger psychiatric disorders that may be similar to spectrum psychosis, which has been seen in acute schizophrenia. The differentiation between the two types of psychosis depending on the acute symptoms is difficult, but it is distinguished that acute psychosis induced by amphetamines tends to recover faster and appears to be resolved more fully in comparison with schizophrenic psychosis (3,4,5).

Substance-induced psychosis has been reported in 8–46% of amphetamines abusers, and around 30% of psychosis triggered by amphetamines may end with a primary psychosis lasting for a long time (5,6,7). Accompanied symptoms may last hours to days, depending on dosage, strength, abuse duration, and elimination of the drug. Experts examined the consumption of high doses and daily usage and found an elevated risk of substance-induced psychosis (7). Old studies manifested that amphetamines may trigger acute psychosis in healthy people by giving simultaneously high doses until psychosis precipitates is often induced by 100 mg to 300 mg of amphetamine, and symptoms stabilize within 1 week (4).

The variation in psychosis incidence may be due to populations, gender, abuse methods, duration, and type of instrumental diagnostic tools. Abnormal brain functions were seen in temporal cortices, prefrontal, and abnormal integrity of white and gray matter tissue, which were triggered by amphetamines (8).

1.1. Psychiatric Disorders Associated with Amphetamines According to DSM-5

The fifth edition of DSM, known as the diagnostic and statistical manual of mental disorders, has been released by American Psychiatric Association and describes 11 psychiatric disorders induced by amphetamines, which are anxiety disorder, bipolar disorder, depressive disorder, psychotic disorder, sexual dysfunction, sleep deprivation, intoxication induced by amphetamine, intoxication delirium, amphetamine withdrawal, obsessive-compulsive and related disorder, and unspecified stimulant-related disorder.

2. Methods

We used numerous methods to access the studies included in our scope. Conducting a literature review involves using engines of the health database such as PubMed, Scopus, Google Scholar, APA, Psych-Info, Cochrane Review, Medline, and EMBASE to collect the data and identify the materials that describe the topic or are related to it by using multi-key words such as amphetamine, methamphetamine, ecstasy 3,4-Methylenedioxymethamphetamine (MDMA), mechanisms of psychiatric disorders; substance-induced psychosis; psychosis; abuse mechanisms; cognitive and behavioral abnormalities.

3. Results

3.1. Mechanisms of amphetamine-induced psychiatric disorders

We made a conclusion from the studies that investigated the mechanisms of psychiatric disorders in amphetamine abusers, and we concluded that the incidence of psychiatric symptoms experienced by amphetamine abusers is a result of direct mechanisms such as toxicity and sensitization of the dopaminergic system, toxicity of glutamate, GABA, neuronal networks, and damage in the cortical and subcortical areas. Indirect mechanisms are involved to induce psychosis such as long-term use, high doses, sleep deprivation, genetic factors, and reactive oxygen species (ROS) (see Figure 1).

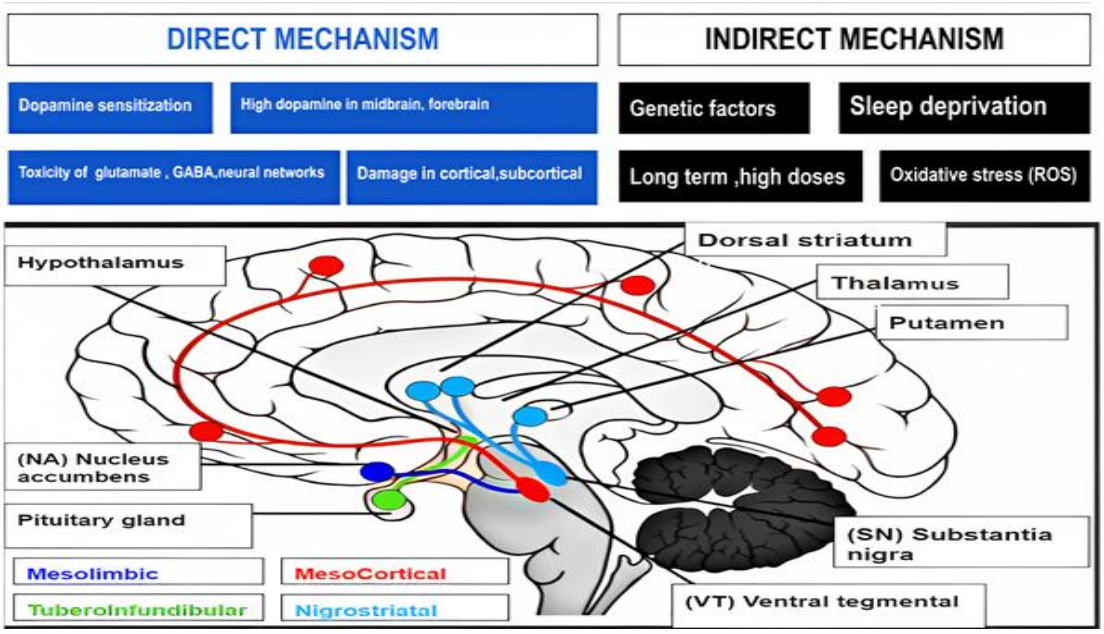

Figure 1 The possible mechanisms of amphetamine to induce psychosis (direct and indirect).

Many mechanisms have been investigated to state the main cause of psychosis among amphetamine abusers such as dopaminergic hypothesis, dopamine sensitization, glutamate alterations, neuronal inflammation, apoptosis following neurotoxicity, and mediators of protein kinases.

The function and sensitization of dopamine, confirmed in the pathology of schizophrenia and elsewhere can manifest in psychotic status triggered by drugs (9,10)..

3.2. Direct Mechanisms: (See Figure 2)

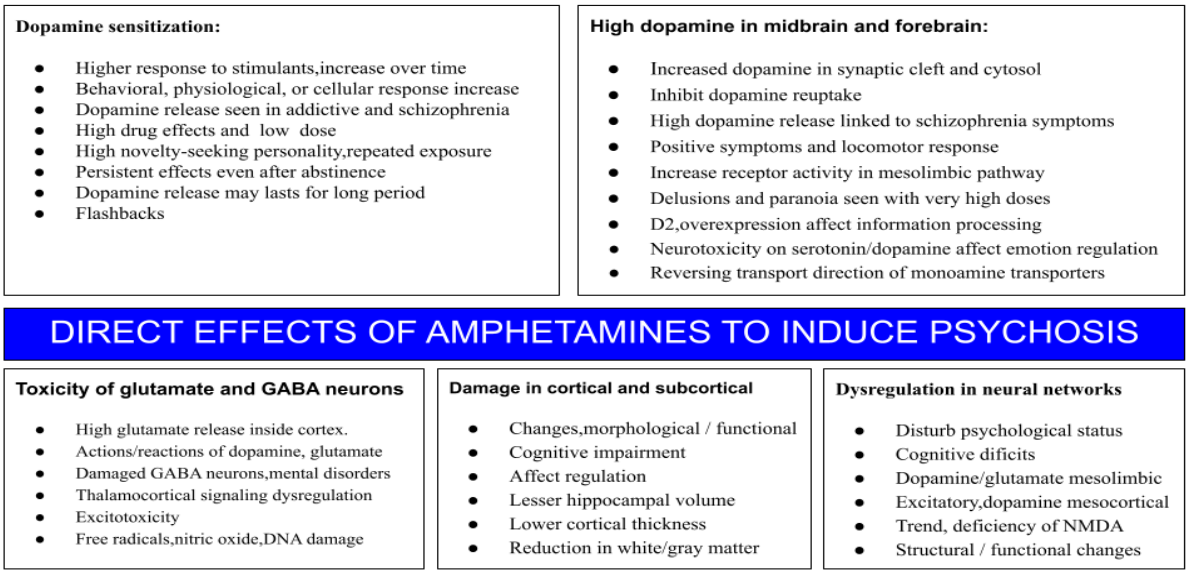

Figure 2 Direct mechanisms of amphetamines to induce psychosis.

3.2.1. Dopamine sensitization

Schizophrenia is thought to be an endogenous pathological sensitization and a potent behavioral response. In schizophrenia, increased dopamine release is observed after amphetamine abuse or stress exposure (11). Sensitization is a neurological and behavioral process; repeated exposure to a stimulus results in enhancing the response to the stimulus. Dopamine, a neurotransmitter, is involved in the expansion of neuronal and behavioral responses to

environmental stimulants and abused drugs. Dopamine release is considered necessary for addictive behavior and may cause psychotic symptoms in schizophrenia patients (11). Schizophrenia patients are sensitive to amphetamines despite having no history of drug abuse, indicating that schizophrenia may have a natural sensitization to amphetamines (11).

Pharmacologically, sensitization results in a rise in drug effects and a reduction in the dose causing half-maximal response (ED50), the opposite of tolerance, which occurs when a drug's efficiency decreases and the abuser requires a higher dose. People sensitized to low doses of amphetamine reported an increase in alertness, euphoria, and extended focus following drug administration (12).

A one-year follow-up of repeated administrations of amphetamines in ten healthy male volunteers was conducted. On days 1, 3, and 5, they were given three single doses of (dextroamphetamine sulfate, 0.3 mg/kg orally) (13). Positron emission tomography has been used, and [11C] raclopride, which is sensitive to changes in dopamine release in the striatum area, has been observed to monitor the response to amphetamine on day no. 1 to assess the first exposure, 14 days, and 1 year following the third exposure of stimulant. The initial amphetamine dose resulted in dopamine release in the ventral striatum (a reduction in [11C] raclopride binding). Later, after the third amphetamine dose, there was a greater psychomotor response and elevated dopamine release (greater reduction in [11C] raclopride binding) in the ventral striatum, which gradually extended to the dorsal caudate and putamen. It is indicating that a trait of high novelty-seeking personality, impulsivity, shows a predicted susceptibility to sensitization. The phenomenon is linked to increased dopamine release and lasts at least one year (13). Higher dopamine levels in ventral striatum(VS) and post commissural DP(PDP) are associated with increased energy, possibly reflecting the close interaction of striatal subdivisions with the anatomical arrangement of the striatum, which promotes a hierarchical flow of information within the brain from the limbic to motor systems (see Figure 3) (13). Flashbacks, known as the spontaneous occurrence of hallucinatory psychosis by amphetamines, noticed a concurrent elevation in plasma norepinephrine and 3-methoxytyramine in the frontal cortex, which are metabolites of dopamine (14).

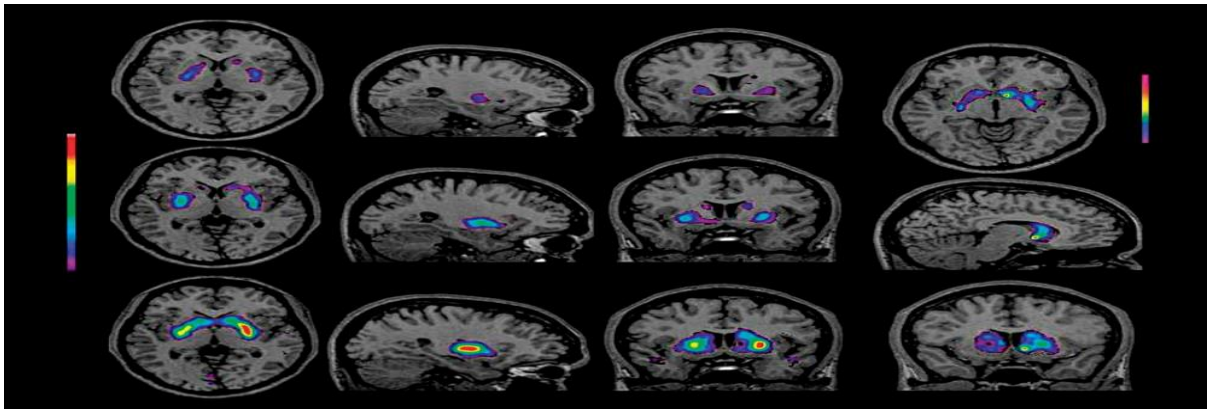

Figure 3 *t*-Statistical maps of [11C]raclopride binding potential (BP) change illustrating a decrease in [11C]raclopride BP after dose 1 (A), dose 4 (B), and dose 5 (C) amphetamine administrations (0.3 mg/kg by mouth) relative to the drug-free control condition (x, y, z=28, 2, 0). D, General linear model with dose as a regressor illustrating the progressive decrease in [11C]raclopride BP as a factor of repeated amphetamine doses (x, y, z=9, 7, -6). Colored *t*-maps are overlaid on an averaged T1-weighted magnetic resonance image of all the participants (see ref. 13).

3.2.2. High dopamine levels in the midbrain and forebrain

Increased dopamine concentration in the synaptic cleft and cytosol is one of the mechanisms known to cause psychosis and may be due to amphetamine neurotoxicity. Amphetamines inhibit dopamine reuptake and increase dopamine release by interacting with dopamine transporter and vesicular monoamine transporter VMT2. Elevated synthesis in subcortical dopamine and release capacity in patients is substantially linked to positive symptoms, particularly in the associative striatum (14,15). Amphetamines can cause similar symptoms of psychosis in healthy people, and schizophrenics are more susceptible (15).

Positive symptoms of schizophrenia are directly related to amphetamine-induced dopamine release in patients with schizophrenia's striatum (11,16). Amphetamine-induced locomotion is primarily driven by limbic dopamine release, which could be inhibited by blocking dopamine transduction in the nucleus accumbens (15). Ultimately, dopamine levels in the midbrain and forebrain are affected by amphetamines via the reversing transport direction of monoamine

transporters, which is linked to a variety of schizophrenia symptoms, including positive symptoms and locomotor responses.

Amphetamine alters the use of monoamines as neuronal signals in the brain and tends to increase dopamine receptor activity in the mesolimbic pathway, which produces a significant contribution to motivational salience-promoting effects (17). The elevated concentrations of dopamine and norepinephrine induce euphoria and locomotor stimulation (18). Amphetamine has emotional effects such as euphoria at therapeutic doses, but at higher doses, it impairs cognitive function, and very high doses can cause delusions and paranoia (19). Amphetamines provoke dopamine receptor subtype 2 (D2) overexpression, which may impact information processing, as well as dopamine dysregulation in the ventral subiculum, which can disrupt emotional regulation (20). Finally, the neurotoxicity of amphetamine on serotonin and dopamine can play a serious role on emotional regulation in the long-term side effects and even on the information processing in drug abusers by producing alterations in a complex way (21).

3.2.3. Toxicity of glutamate and GABA neurons

The elevation of dopamine in the striatum area through the mesolimbic pathway may cause an elevate in glutamate release and else inside the cortex. The actions and reactions of dopamine, glutamate, and finally, GABA neurons demonstrate that systems are linked together through complex neural circuits that are involved in mental disorders (22). The overflow of cortical glutamate damages the interneurons of GABA neurotransmitter (23). The loss of cortical GABA functionality initiates thalamocortical signaling dysregulation, which might result in the onset of psychosis. It is unclear whether this damage plays a direct role in psychosis or only in cognitive impairment. (22). Amphetamines cause excitotoxicity, which has characteristics including excessive glutamate release, increased levels of intracellular calcium, activation of a number of calcium-dependent enzymes, activation of GLU receptors, generation of free radicals and nitric oxide (NO), and activation of apoptotic pathways that lead to failure of cellular organelles like mitochondria, breakdown of cytoskeletal proteins, endoplasmic reticulum, and DNA damage (24). The primary inhibitory neurons in the central nervous system (CNS) are GABA interneurons, which are involved in a number of pathophysiological processes such as modulating cortical, hippocampal neural circuitry, organizing activity, cognitive function-related neural oscillations (such as gamma oscillations), processing information, and integration. Excitatory/inhibitory balance in the cortex may be upset by dysfunctional GABA interneuron activity, which is a key pathophysiological mechanism of cognitive dysfunction in schizophrenia. In schizophrenia, neural oscillations are impaired due to deficiencies in the GABA inhibitory circuit (25).

3.2.4. Damage in cortical and subcortical areas

The morphological and functional changes inside the cortical and subcortical areas are linked with cognitive impairment in abusers of methamphetamine, whether diagnosed with psychosis or not, which were identified in neuroimaging studies through fMRI (functional magnetic resonance imaging). Evidence raised concerns about the cortical and subcortical, which are affected by methamphetamine and psychosis, implying amphetamine addicts with or without psychosis may impair regulation, cortical variations such as lesser hippocampal volume, and lower cortical thickness among people with together variables, and it is completely compatible with findings of neuroimaging in different psychotic disorders (26). Schizophrenia and methamphetamine-induced disorders are linked to changes in the integrity of white matter. Abnormality in the frontal white matter may be responsible for the impulsive behavior related to drugs abuse, alcohol, and ultimately, psychosis (14).

Chronic methamphetamine abuse induces neurotoxicity, which could result in a reduction in the affected volume areas. Older research has identified reductions in frontal and temporal volume as markers of neural function in psychosis (27). MRIs have been taken from 20 patients with methamphetamine psychosis compared to 20 control subjects to assess the variations in regional brain volume. Methamphetamine psychosis revealed important reductions in gray matter volume in left perisylvian structures and even in white matter volume in the orbitofrontal region. The reductions in volume of left perisylvian structure reflected a pathophysiologic similarity to schizophrenia (28,29).

The neuroimaging found a reduction in volume of gray matter and ventricular enlargement in people with schizophrenia. They found abnormalities including hypoactivation, reduced connectivity, which may be raised according to thalamo-cortical connections, hubs of cortico-striatal-limbic, amygdalostriate pathways, and defaults in the mode network and salience network (30). Diffusion weighted and diffusion tensor imaging indices exhibited aberrations in white matter according to diagnosed schizophrenia (30).

3.2.5. Dysregulation in neural networks

The brain's neural networks are responsible for organizing thoughts, concepts, cognitive abilities, memory, attitude, behavior, and those networks are linked together by complex pathways. Any dysregulation following amphetamine neurotoxicity may cause disturbances in psychological status. Dopamine pathways are regulated by glutamate pathways, and the descending glutamate pathway connects to the dopamine mesolimbic system through the interneuron of GABA, and any disruption can result in psychotic symptoms (31). The glutamate descending pathway has an excitatory effect on dopamine mesocortical pathway, and disruptions may result in cognitive deficits (31). However, the trend of research focuses on dysfunctional networks and NMDA receptor deficiency as a primary element, which may lead to psychosis (32,33,34).

Chronic methamphetamine abuse and psychosis induced by substances have been linked to dysfunction in several neural networks, with reports of deficits in psychosis after the exclusion of acute effects from methamphetamine (10,35). They found evidence that structural and functional abnormalities of affected neuronal networks are linked to the development of psychosis induced by abuse of methamphetamine when compared to the control group after evaluating several fMRIs for the brain structures, functional connectivity maps in methamphetamine addicts, methamphetamine-accompanied psychosis, and schizophrenia (10,36).

3.3. Indirect mechanisms: (See Figure 4)

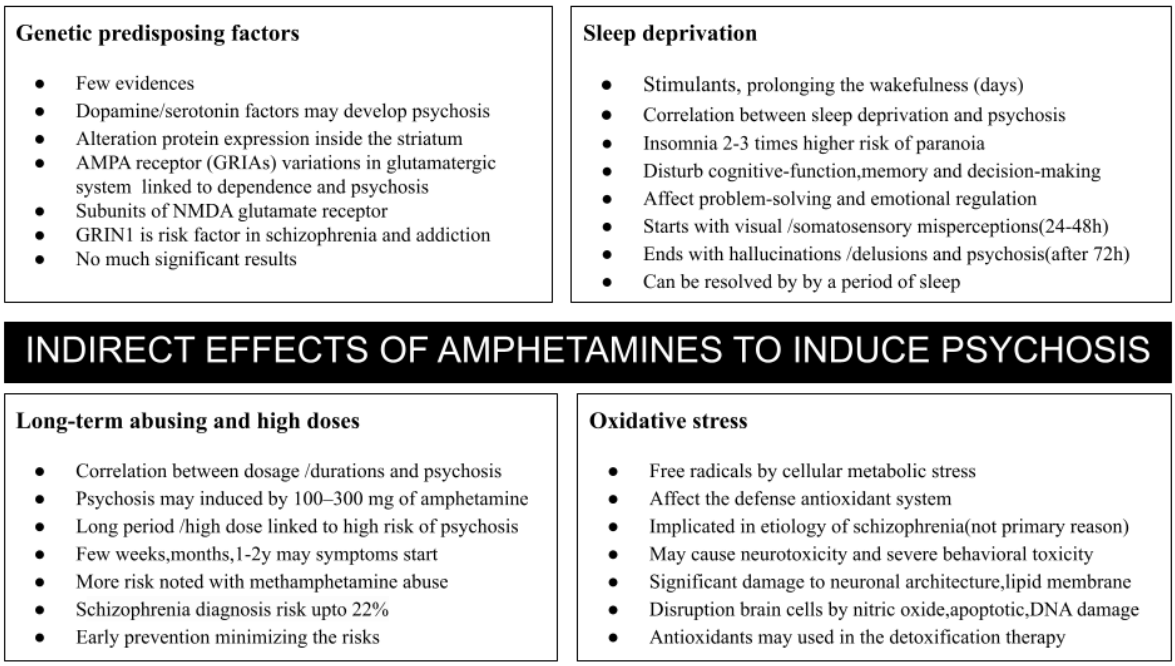

Figure 4 The indirect mechanisms of amphetamines to induce psychosis.

3.3.1. Genetic predisposing factors

Genetic predispositions related to the dopamine and serotonin systems might participate in the development of psychosis following methamphetamine abuse (10,37). According to the serotonin system, two studies claimed that induced neurotoxicity due to drug abuse impaired brain regions of this system, such as limbic structure and the basal ganglia, especially among methamphetamine addicts (38,39). Furthermore, there is a report that methamphetamine exposure might trigger an alteration in the expression of proteins inside the striatum that are important for neural regulations such as energy regulation, neuroprotection, neuroplasticity, synaptic vesicle maintenance, and cellular cytoskeleton maintenance (10,40). Genes encoding AMPA receptor subunits (GRIAs) have variations in the glutamatergic system that have been linked to chemical dependence and psychosis (40). The relationship between the found variations and psychosis induced by methamphetamine is under investigation; until today, there have been no significant results (40). Another study was conducted in addict's men on methamphetamine; they were genotyped for two single nucleotide polymorphisms of GR1NI and claimed responsibility for encoding the subunits of NMDA glutamate receptor. Variants in GRIN1 have been known as risk factors in schizophrenia and drug addiction, lending support to the theory that dysfunction in the glutamate may play a role in the evolution of psychosis (41). However, findings are insignificant; further research may help to understand the relationship (10).

3.3.2. Sleep deprivation

Sleep deprivation and amphetamines are frequently linked; chronic amphetamine consumers regularly experience prolonged periods of wakefulness due to stimulant effects (42). According to a global study that included 261,547 people, aged 18 years, from 56 countries to investigate sleep deprivation, there was a strong correlation between sleep deprivation and symptoms of psychosis (44). Insomnia was linked to a 2-3 times higher risk of paranoia (45,46). Psychotic experiences may be predictable after a long period of sleep disorders (47). Wakefulness due to amphetamines has a variety of negative consequences, including mood disturbances, cognitive impairment, and ultimately, psychosis (43). Cognitive dysfunction such as attention, alertness, impaired performance, memory consolidation, decision-making, problem-solving, emotional regulation, learning, creativity, moodiness, and difficulty coping with the daily-live activities.

Study carried out to investigate the relationship between psychosis induced by methamphetamine and sleep deprivation. The sample size was 78 patients; addicts were compared to 49 patients in the control group with no past history or current amphetamine-induced psychosis. The addicted group revealed higher regular and daily doses of amphetamine and experienced further durations of sleep deprivation, particularly with elevated doses of amphetamine. Participants reported that sleep deprivation was the reason that may have encouraged them to start or end their psychotic status, regardless of amphetamine doses (48).

A systemic review claimed that psychosis symptoms may range from visual and somatosensory misperceptions until experiencing hallucinations, delusions, and acute psychosis in healthy people, which can be resolved by a sleep period (49). Symptoms developed faster after staying awake for one night, progressing in a nearly time-dependent way. Anxiety, irritability, perceptual distortion, depersonalization, and temporal disorientation may start during 24 and 48 hours of sleep loss, and hallucinations and disordered thinking have been seen between 48 and 90 hours, and delusions starting after 72 hours. Ultimately, the clinical presentation of the case may have been identified due to toxic delirium or acute psychosis (49).

Neurobiological modifications in adolescents, such as abnormal circadian rhythm, could be a mechanism for the development of psychiatric illness because a brain undergoes numerous modifies in a concise time due to neurobiological changes combined with environmental and psychosocial factors **(**47**)** (50). The deepest brain areas, like the limbic and reward systems such as the ventral striatum and amygdala, may increase their neural activity. This temporary overactivity of dopamine circuits can result in emotional dysregulation, increasing the risk of developing psychological malaise (51). Furthermore, delayed melatonin secretion might occur with circadian rhythm modifications which in conjunction with environmental and psychosocial factors such as over-social encounters and cellphone usage at night, can result in disturbances such as sleep deprivation, circadian rhythm disorders, and insomnia (52, 53). Sleep absence can disrupt and minimize functional connectivity in the prefrontal cortex and the amygdala, exactly between the regions of top-down control (54).

Visual issues following a sleep loss may result in early participation of the occipital cortex. The regions of visual-sensory and visual-attention are described as the premier brain regions, which are impacted by sleep deprivation, according to neuroimaging studies. According to research, these degrade the accuracy of perceptual representations (55, 56, 57). The metamorphopsias caused by migraine auras, which induce visual distortions brought on by cortical spreading mechanisms that start in the occipital cortex and move toward the prefrontal regions (58). Gradual change in brain processes among posterior-anterior directions , may contradict neurophysiological findings, and during pre-sleep and early stages of sleep deprivation, the direction of neuronal activity starts out in the anterior areas prior extending to the posterior ones (59, 60).

3.3.3. Long-term abuse and high doses

Research shows a connection between dosage and durations and the onset of acute psychosis at doses up to 300 mg or more (4). In one published cohort study, 528 chronic methamphetamine users were followed for 2 years post-discharge to determine the relationship between length of methamphetamine abuse and risk of psychosis (61). It starts with a baseline appointment and then 4 follow-up visits, 6-months' post-baseline, and then 12,18, and 24 months' post-baseline. Methamphetamine abuse over the past 6-months has been investigated at each assessment. Abusers who completed at least one follow-up were 340 methamphetamine addicts, and they are included in the study. At a 6-month interval, they found that methamphetamine use had a two-fold elevated risk of psychosis in comparison with non-methamphetamine abusers (odds ratio [OR] = 2.15). The effect of dose response was found between the interval of methamphetamine use and risk of psychosis (continued 12-month methamphetamine use versus no use: (OR=2.84); 18-month methamphetamine abuse versus no use: (OR= 9.93). They found that extended periods of methamphetamine

abuse were linked to further higher risk of psychosis, and early prevention of drugs minimized the risk of getting psychosis (61).

Based on a 10-year retrospective cohort study to assess the psychosis risk, 74,601 amphetamine abusers versus 298,404 control group, median age 33 and 84% male, amphetamine abusers versus nonusers: depression (2% vs. 0.4%), anxiety (0.9%vs. 0.3%), ischemic heart disease (1.3% vs. 0.8%), cardiovascular disease (0.8% vs. 0.45%), and stroke risk (1.3%vs. 0.7%) (62). After adjusting for age, sex, duration of use and health history, amphetamine abusers are five times more likely to develop psychosis than nonusers. The rates for psychosis in annual cumulative incidence among control vs. abusers were 77 and 468 per 100,000 people, respectively (62).

High levels of abuse in the past month have linked to risks reaching five times higher among chronic methamphetamine users than nonusers, with strong dose response effects, and the risk of symptoms increasing from a low baseline level during a few months of stoppage from 7% to 48% when addicts were abusing methamphetamine heavily for 16 days (1,63).

The diagnosis of schizophrenia according to cumulative risk in an 8-year approach is 30% following primary amphetamine-induced psychosis (64). A six-year follow-up study, following initial hospitalization due to methamphetamine psychosis, showed 22% had been diagnosed with schizophrenia (65).

3.3.4. Oxidative stress

Free radicals produced by cellular metabolic stress affect the defense antioxidant system and result in reactive oxidative stress, which is implicated in etiology of schizophrenia, despite not being the primary reason (66,67). One mechanism is the release of reactive oxygen species, followed by neurotoxicity due to high doses of amphetamines, which are linked to severe behavioral toxicity such as stereotypic, self-injurious behavior, and psychoses similar to schizophrenic illness (68). Increased extravehicular dopamine levels cause oxidative stress through reactive oxygen species, dopamine quinone, and ultimately neuronal damage (68). Depletion in antioxidant levels and high levels of reactive oxygen species (ROS) may lead to significant damage to neuronal architecture, leading to cognitive decline and behavioral abnormalities (69). Schizophrenia symptoms may lead to damage to the neuronal lipid membrane, triggered by excess reactive oxygen species (70). Generation of free radicals by amphetamines may cause disruption of brain cells, then release of nitric oxide, activation of apoptotic pathways, failure of cellular organelles such as cytoskeletal proteins, mitochondria, endoplasmic reticulum, and ultimately DNA damage (24). Finally, this mechanism alleviates the need to insert antioxidant supplements as adjunctive therapy in the detoxification of amphetamines in rehabilitation centers. Actually, these supplements are used in multi-study that focus on the therapy of substance use disorder (SUD) but are still not confirmed on a large-scale basis.

4. Discussion

Amphetamines are considered highly addictive drugs, and have an essential role in the development of psychosis. Addicts may experience withdrawal symptoms after a few doses. Mechanisms to induce negative impacts on pathological, physiological, and psychological status have been studied for years through different methods and theories. Psychosis following addiction is a result of direct and indirect pathways that start after the initiation of neurotoxicity. Sensitization induced by dopamine stimulants, known as repeated exposure to a drug, results in an advance enhancement in the response (71). Thought disorders in schizophrenia may be less notable in psychosis induced by amphetamines (4). People with schizophrenia and traits of schizotypal personality are more vulnerable to psychotic effects from amphetamines. The development of psychosis may occur with less or even no exposure, while others may not develop psychosis even with high exposure (4).

The neurotoxicity effects of amphetamines may lead to the loss of dopamine fibers and cell bodies (72). Disruption in the mesolimbic pathway by ultra-high doses leads to delusions and paranoia. A long period of addiction to amphetamines is linked to a higher risk of psychosis due to extended toxic exposure to neurons, ultimately leading to neurodegenerative disease. Excessive cortical glutamate may lead to damage to GABA neurotransmitters (6). Function loss within cortical GABA may lead to dysregulation in thalamocortical signaling and the onset of psychosis. Changes in cortical and subcortical areas are linked to cognitive dysfunction with or without psychosis (10,73). Lower cortical thickness and hippocampal volume have been shown in other psychotic disorders (26). The dysfunction in several neural networks induced by amphetamines abuse may disrupt brain functions through the induction of abnormalities in the structural and functional networks, which are linked to psychosis.

Chronic methamphetamine abuse may affect the striatum; researchers discovered decreased levels of dopamine terminal markers, including dopamine, tyrosine, hydroxylase, and dopamine transporter (74). Positron emission tomography found decreased levels of dopamine transporter, vesicular monoamine transporter 2, and D2 (75,76,77). Single photon emission computed tomography found a reduction in cerebral blood flow in chronic methamphetamine abusers (78,79). According to magnetic resonance spectroscopy, a reduction in N-acetylaspartate (NAA) was discovered within the basal ganglia, frontal lobe, and anterior cingulate, indicating a reduction in neuronal integrity in these zones (80,81,82). Alteration of GABA function following addiction may be the result of multiple factors, including alterations in neuronal firing or synaptic connectivity (83).

The sleep disturbances found in people with schizophrenia usually share the trigger of psychosis (85). Narcolepsy patients are improved by 65%-85%, when they used amphetamines medically as wakefulness-promoting agents (84,86). Although medicinal usage may disturb sleep habits for addicts. Sleep deprivation following amphetamine abuse is interrelated (42). Wakefulness has a range of negative consequences, including cognitive impairment, mood disturbances, and elevating the risk of psychosis due to sleep habit disturbances (86,87). Extended wakefulness can produce misperceptions, hallucinations, and delusions. Later, it may induce acute psychosis after 48 to 90 hours following sleep deprivation (47,48,49,88). Sedative agents to induce sleep, such as alcohol, cannabis, or benzodiazepines, may be abused to prevent psychosis by ending wakefulness (4) (48) (89).

Genetic predictive biomarker studies claim that some people are more susceptible to psychosis if they have the DAOA/G72 gene, which encodes an activator of N-methyl D-aspartate (NMDA), which describes why schizophrenics are more susceptible (90). People with the DTNBP1 dysbindin gene are 2.6 - 7.1 times more presumably to suffer from psychosis induced by methamphetamine than people without the gene, according to 197 Japanese patients examined and compared to 243 healthy controls (91).

Current study carried out a comparison, ranked the most harmful drugs among the class of amphetamines. They found that methamphetamine is the most harmful, followed by amphetamine, then ecstasy, and the least harmful is methylphenidate, which is still used clinically to treat some diseases (92).

5. Conclusion

Amphetamines induce psychosis in abusers through direct mechanisms such as sensitization of the dopaminergic system, high levels of dopamine in the midbrain and forebrain, toxicity to glutamate and GABA systems, damage to cortical and subcortical areas, and dysregulation of neuronal networks in the brain. The involvement of indirect mechanisms to induce psychosis is proven in literature, such as long-tern abuse, high doses, genetic factors, sleep deprivation, and reactive oxygen species (ROS). Mechanism of psychosis following amphetamines abuse is complex and interrelated.

Compliance with ethical standards

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Disclosure of conflict of interest

No author has a conflict of interest in this study.

Author contributions

Conceptualization, Saud D AlOtaibi (S.A) and Ashraf M. Emara (A.E); methodology, S.A and A.E; validation, S.A, A.E and Hossam Abdelkader Elsisi (H.E); formal analysis, S.A, A.E and H.E; data curation, S.A; writing—original draft preparation, S.A; writing—review and editing, S.A, A.E and H.E; supervision, A.E and H.E; project administration, A.E and H.E. All authors have read and agreed to the published version of the manuscript.

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