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Flakka (α -PVP): Mode of Action, Side Effects and Treatment

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Abstract: Newly introduced psychoactive substances (NPS) are being used as drugs and are becoming enormously popular. The most common components in these novel medications are synthetic cathinones. One of the most well-known cathinone-designed drug is α -pyrrolidopentadione (α -PVP), commonly known as "Flakka". α -PVP, like other synthetic cathinone medications, has the ability to block norepinephrine and dopamine transmitters. Mania, tachycardia, and hallucinations are the most common side effects of α -PVP. In this review a brief history, mechanism of action, and effects of the strong synthetic cathinone α -pyrrolidinovalerophenone, as well as therapeutic possibilities of α -PVP or flakka or zombie drug have been discussed.

Keywords: Flakka, Bath salts, Synthetic cathinone, α -pyrrolidinopentiophenone

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Introduction

Misuse of various drugs is currently a significant global issue of public health, particularly among recreational users of so-called designer drugs or research chemicals. Since 2014, roughly 540 different medications have been classified as new psychoactive substances (Patocka *et al.*, 2020). These compounds are mimic created and used as alternative to the banned drugs such as cocaine, methylenedioxymethamphetamine (MDMA, ecstasy), and methamphetamine, which are still not under control even after so many international laws have been implemented (Karila, 2012). Bath salts are compounds of -phenyl-ethylamine (PEA), such as methamphetamine (N-methyl-1-phenylpropan-2-amine) and MDMA

(3,4-methylenedioxy-N-methylamfetamin, Ecstasy, or Molly), 4-methylephedrone, mephedrone (2-methylamino-1-(4-methylphenyl)propan-1-one, 4-methyl-methcathinone (4-MMC), Drone, Meph, or Meow Meow), methylone (3,4-methylenedioxy-N-methylcathinone, MDMC, Drone, Meph, or Meow Meow), and methylone (3,4-methylenedioxy-N-methylcat). The chemical structures of these molecules are constantly changing (Mas-Morey *et al.*, 2013).

History of Synthetic Cathinones:

The stimulant alkaloid cathinone is extracted from the leaves of the 'khat' shrub. Chemically, cathinone is comparable to ephedrine, cathine,

and other amphetamines. It has psychostimulatory properties (but with low potency) similar to amphetamine, such as euphoria, alertness, and psychomotor hyperactivity (Krikorian, 1984). Many designer medications have been developed by researchers working on chemical and pharmaceutical aspects of these drugs and looking for novel ways to treat various related diseases (Griffiths *et al.*, 2010). Synthetic cathinones such as mephedrone, exhibit chemical characteristics similar to cathinones and were first produced in 1920s (Winstock *et al.*, 2011). The term cathinone was first used 40 years ago, and the synthetic cathinone is newly introduced term (Glennon, 2014). However, due to legal loopholes, Clandestine chemists began to use these drugs to create some novel medications (Gibbons and Zloh, 2010; Spiller *et al.*, 2011; Fass *et al.*, 2012). Use of cathinone has been increased again before ten years. It was first reported from the United Kingdom and then spread over the other regions of Europe and United States (Prosser and Nelson, 2012). The use of cathinones has skyrocketed in the last few years (Bronstein *et al.*, 2011; Gummin *et al.*, 2017). Many synthetic cathinones have recently gained popularity, particularly among young generations (German *et al.* 2014).

The majority of synthetic cathinones are produced in China and India and are reaching very fast to other parts of the world (Sauer *et al.*, 2009; Marinetti and Antonides, 2013). Figure 1 explains the chemical structures of key synthetic cathinones (Patocka *et al.*, 2020).

Flakka:

In the United States, a synthetic substance which is a chemical relative to MDPV called as "Flakka" (α -pyrrolidinovalerophenone, α -PVP) has gained much popularity; commonly known as bath salt. This salt is linked to a number of cases of intoxication and agitation mostly from the United States (Patocka *et al.*, 2020).

Although α -PVP are used for its euphoric effects but the symptoms can quickly increase into

terrifying delusions, paranoid psychosis, acute agitation, and a variety of other mental disorders. α -PVP induces agitated delirium, which is characterized by an overabundance of sympathetic activity (Patocka *et al.*, 2020). Bizarre behavior, anxiety, agitation, aggressiveness, disorientation, myoclonus, and seizures are some of the other symptoms of this illness (Gómez-Arnau *et al.*, 2015; Gussow, 2015).

Some more symptoms of agitated delirium are tachycardia, hypertension, heat, diaphoresis, and mydriasis (Beck *et al.*, 2016). α -PVP is a novel synthetic cathinone dominated in the medicine market of United States and Europe, despite the fact that it is a risk associated drug (Katselou *et al.*, 2016). α -PVP usually consumed orally, snorted, smoked, vaporized in e-cigarette devices and injected intravenously. Among all the other synthetic cathinone and traditional stimulants, vaporizing drugs in e-cigarettes are one of the most popular method of drug administration. Vaporization of this drug gives more exposure to a cocktail of parent compounds and thermolytic degradants resulting into differing toxicological and pharmacological effects (Banks *et al.*, 2014; Marusich *et al.*, 2016). This method of administration causes a quick absorption of the drug into the blood stream increasing the danger of overdosing. When α -PVP is orally administered, develop a range of symptoms (Patocka *et al.*, 2020).

Mechanism of action:

Flakka (α -pyrrolidinovalerophenone, α -PVP) has structural similarities to 3,4- methylenedioxypyrovalerone (MDPV), which is one of the synthetic cathinone that is widely misused. α -PVP acts like cocaine, activating the Central Nervous System (CNS) by inhibiting the reuptake of dopamine and norepinephrine and had no effect on the serotonin (SERT) transport as compared to the cocaine. The pyrrolidine ring in α -PVP is responsible for the highly potent dopamine reuptake inhibiting action (Glennon and Young, 2016).

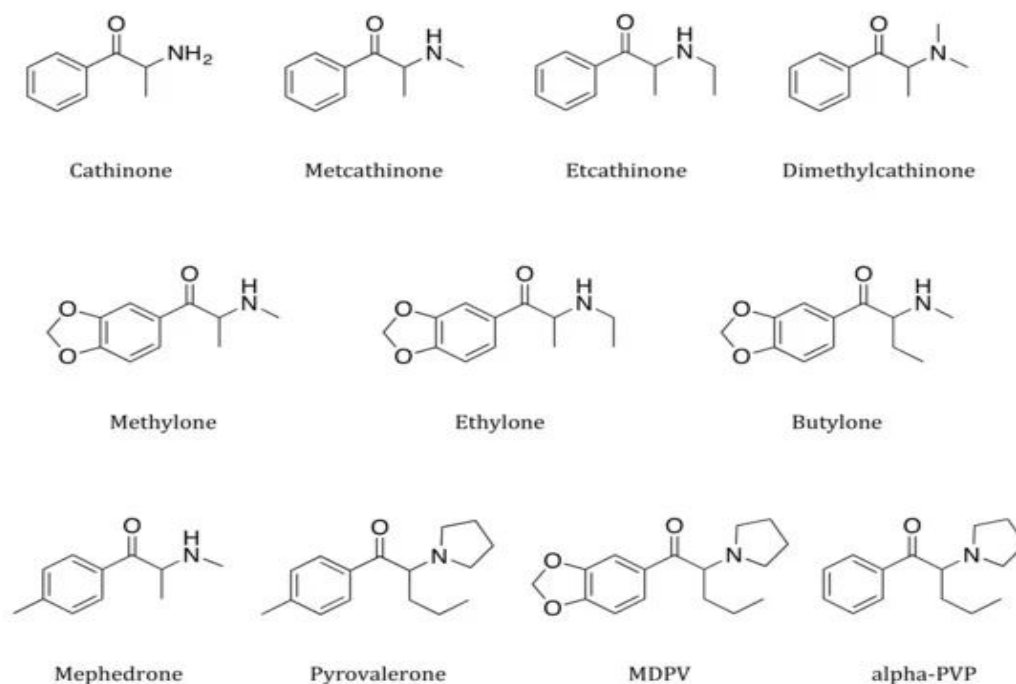


Fig. 1: Chemical structures of some important synthetic cathinones (Patocka *et al.*, 2020).

Adverse Effects of Flakka:

Synthetic cathinone's negative and harmful effects:

(1) Somatic Effects:

Chest discomfort, hypertension, tachycardia, myocarditis, and cardiac arrest are the common somatic effects on cardiovascular system. Dizziness, sleeplessness, headache, seizures, disorientation, tremor, unstable mental status, system collapse, confusion, drowsiness, anemia, thrombocytopenia and disseminated intravascular coagulation are also the symptoms of somatic effects of this drug. Emesis, nausea, abdominal discomfort, abnormal liver function tests, and liver failure are symptoms of the gastrointestinal and hepatic systems. Shortness of breath, tachypnea, respiratory failure and arrest, are the other symptoms showing effects on the cardiovascular system (Karila *et al.*, 2015).

(2) Psychiatric Effects:

Aggression, agitation, Anorexia, Paranoia, paranoid delusion, visual and auditory halluci-

nations (typically in the form of frightening individuals), psychosis, Anxiety depersonalization/derealization panic attacks, self-harm such as gunshots, self-stabbings, repetitive self-mutilations and risk behavior without evidence of psychosis or depression comorbidity long-term cognitive impairments, confusion to names, places, and times are few other examples of cognitive disorders due to Flakka's addiction (Karila *et al.*, 2015).

Some case studies on the effects of Flakka:

(1) Ischemic Stroke Caused by Alpha-Pyrrolidinopentiophenone (Flakka):

A 60-year-old Finnish man suffering from hepatitis C and osteoarthritis in both knees was admitted to the emergency with acute right-sided hemiparesis, that was started before a day but clinical neurological examination revealed the right-sided hemiparesis without any visual impairments and aphasia or dysarthria. Through the CT scan in head region infarctions in the left sulcus centralis was observed. An urine

examination revealed the presence of benzodiazepines. An occupational therapist observed that the patient started with the rehabilitation process. The patient on the other hand, left the hospital on his own will on the fifth day without completing a full physiotherapy evaluation. The patient had a mild right-sided hemiparesis at the time of discharge, but was able to walk using forearm crutches that he was already using due to osteoarthritis. The patient was prescribed aspirin 100 mg and atorvastatin 10 mg once in day and advised to continue occupational therapy at any local healthcare facility to rehabilitate his right arm (Heinonen *et al.*, 2021). Although the exact mechanism is unclear, but we believe that the patient's stroke was possibly due to the use of α -PVP. Other possible causes of stroke were ruled out throughout the complete investigation as the stroke occurred shortly after injecting α -PVP. In the urine investigation for presence of any drug, only benzodiazepines were detected, ruling out the possibility of other confusing medications (Heinonen *et al.*, 2021). The synthetic cathinones are structurally and pharmacologically similar to amphetamine. The physiological effects include arrhythmia, hypertension, and vasoconstriction, all of them have been found linked with strokes (Prosser and Nelson, 2012).

(2) *Stevens-johnson syndrome/Toxic epidermal necrolysis overlap:*

Inhaling flakka through cigarette smoking before 5 days, a 24-year-old male patient was referred to the clinic with some widespread rashes all over his body and there were no other ailments. The patient's substance abuse therapy was started but he refused. No other drugs or substances he had in combination. The patient's vital signs were normal throughout the physical examination. Dark purple decayed patches extending from the scalp to the back of the neck, eroded areas on the ears and nose were observed. Dermatological examination such as typical target sites, attached to the trunk, extremities, and bark areas were performed. Erosion was observed on oral mucosa, scrotum,

penis, and some other body parts. The patient was admitted to the dermatology clinic and Stevens-Johnson syndrome/interfering toxic epidermal necrolysis (SJS/TEN) was diagnosed. Intravenous immune globulin (IVIG) and methylprednisolone were given to the patient. After 12 day's treatment an improvement in skin's health was recorded. (İlhan *et al.*, 2019)

Treatment of flakka:

α -PVP has been linked to multidrug usage for the treatment of drug addiction as well as an outbreak of the human immunodeficiency virus (HIV) (Giese *et al.*, 2015; Heikman *et al.*, 2016; Sundström, *et al.*, 2016). The drug's average dose was determined by the route of administration. Despite the dose 100 mg α -PVP, it has been observed that the oral dose of 1–2 mg can provide psychoactive effects, whereas 20–25 mg showed substantial effects (Nelson, 2021). Oral administration of 1–25 mg, nasal administration of more than 20 mg, smoked administration of 10 mg and vaporized administration of 400 mg have been reported in the literature (Karila *et al.*, 2018). This vaporized α -PVP is absorbed more quickly than other routes, thereby increasing the risk of overdosing.

Monitoring of side effects of Flakka can minimize its addiction. For hyperthermic addiction, treatment is done by lowering the body temperature to avoid any other ailment associated with high body temperature. Likewise, hyperthermia puts the patient at risk due to loss of fluids which makes rehydration therapy necessary. A comfortable environment around the patient also helps in the treatment. Few clients must be pharmacologically asphyxiated who are with robust behavior and mechanical constraints. Medications used to treat brutal or violent practices may include administration of intravenous (IV) benzodiazepines such as midazolam (2 mg) or diazepam (5 mg). Ketamine (250 mg IM) or haloperidol (5 mg IM) can also be the optional medications. The use of antipsychotics to treat the side effects of flakka is controversial and concerned with the feasibility.

Addiction of flakka is almost incurable and there is nothing that can counteract its belongings. During the treatment, all frameworks of the body which are affected by the drug must be adhered to, and for the patient it is the phase of difficulties. When the patient becomes stable, suspicion can persist and regular medications with antipsychotics are required (Abbott and Smith, 2015).

Methylone (a structural analogue of MDMA was prepared in 2010 by mixing with mephedrone and is the second most popular drug) showed euphoric effects similar to MDMA. Effects of methylone include anxiety, calmer euphoria, alertness, a strong sense of empathy, and gentle stimulation at 100 to 200 mg doses of this drug. Methylone can lead to depression and many other serious side effects, and even can cause deaths, especially when combined with other illicit substances (McIntyre *et al.*, 2013).

Conclusion

α -PVP is a novel synthetic cathinone which is dominating to similar drugs of this family. Synthetic cathinones and traditional stimulants, vaporizing drugs in e-cigarettes are becoming the most popular methods of drug administration. Although α -PVP is used for its euphoric effects but the symptoms can quickly enhance into paranoid psychosis, terrifying delusions, acute agitation, and a variety of other mental disorders. Flakka (α pyrrolidinovalerophenone, α -PVP) has structural similarities to 3,4- methylenedioxypyrovalerone (MDPV), which is one of synthetic cathinone and common in use. Synthetic cathinones are well known for their negative and harmful effects. Synthetic cathinones are similar to amphetamine in structure, physiology and pharmacology. Some of the physiological effects include arrhythmia, hypertension and vasoconstriction, all of them can lead to a stroke. From the review of literature and various case studies it can concluded that a dose of 1-2 mg of α -PVP showed psychoactive affects, however, a dose of 20-25 mg cause substantial effects, whereas oral dose of 1–25 mg, nasal dose of more than 20 mg, smoked dose of 10 mg, and

vaporized dose of 400 mg all are reported to cause the similar effects.

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