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REVIEW ARTICLE

α-PVP ("flakka"): a new synthetic cathinone invades the drug arena

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Abstract "Flakka" is the street name for the synthetic cathinone α-pyrrolidinopentiophenone (α-PVP). Although it was developed by Boehringer Ingelheim as a central nervous system stimulant and pressor agent in the 1960s, it entered in the drug arena at an accelerated rate during the last 4 years causing intoxications, fatal or not. α-PVP is abused in Europe, as well as in the United States and Japan, as a substituent of 3, 4-methylenedioxypyrovalerone, and recently scheduled by the United States Drug Enforcement Administration, possessing similar pharmacological action to that of the latter. It can be easily manufactured and purchased through the Internet or in retail shops and is usually sold as "bath salts". The aim of this review is to summarize the current knowledge of this drug concerning its chemistry, synthesis, metabolism, pharmacology, and toxicology. "Flakka" related cases, published or reported, including fatalities or intoxications, as well as seizures are reviewed. The existing analytical methodologies for the determination of α-PVP in biological and postmortem samples are summarized, and its current legal status is reported.

Keywords Flakka · α-PVP · Synthetic cathinone · Pharmacology · Toxicology · Legal status

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Introduction

During the last decade, a number of substituted cathinone stimulants have appeared on the drug markets worldwide and are available for purchase through the Internet or in retail shops. They are labeled as "bath salts", "plant food", "fertilizer", "insect repellants", "research chemicals", "jewelry cleaner", and "stain remover". In their labels, phrases like "not for human consumption" or "for research purposes only" are usually included [1–4]. Synthetic cathinones are chemical derivatives of cathinone, a natural monoamine, amphetamine-like alkaloid found in the shrub *Catha edulis* (khat) that has been used for centuries by indigenous peoples of the Horn of Africa and Arabian Peninsula for its psychostimulant properties [5]. Most of the synthetic cathinone supply originates in China or India and spreads worldwide [6, 7].

Because of their high abuse liability, cathinone and some of its synthetic derivatives have been driven by legal control actions for specific compounds resulting in their replacement by closely related designer drugs. For instance, cathinone is classified as a Schedule I controlled substance in the United States since the early 1990s, while 3,4-methylenedioxypyrovalerone (MDPV) (Fig. 1) was temporarily scheduled by the United States Drug Enforcement Administration (US DEA) in 2011 [8] and permanently scheduled by Congress in 2012. As a response to MDPV scheduling in the United States, the closely related α-pyrrolidinopentiophenone (Fig. 1) (α-PVP or "flakka" or "gravel"), a "second-generation" cathinone, made a sudden and explosive entrance into illicit drug market as a "legal" alternative not only to MDPV, but also to cocaine, methamphetamine, and MDMA, particularly in poor neighborhoods, due to its low price [4, 9].

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α-PVP chemically is a pyrrolidine-type cathinone derivative that was developed by Boehringer Ingelheim as a central nervous system stimulant and pressor agent in the 1960s [10]; however, it is not currently used for medical purposes. Although it appeared in the drug markets only during the last decade, it has already been associated with human fatalities [11, 12]. The US DEA temporarily scheduled α-PVP as a Schedule I substance in 2014 [4], despite the fact that there are only few data attesting to its abuse liability. The aim of this review is to summarize the current knowledge about this drug concerning its chemistry, synthesis, metabolism, pharmacology, and toxicology. "Flakka" related cases, published or reported, concerning fatalities or intoxications, as well as seizures are reviewed. The existing analytical methodologies for determination of α-PVP in biological and postmortem samples are summarized and its current legal status is reported.

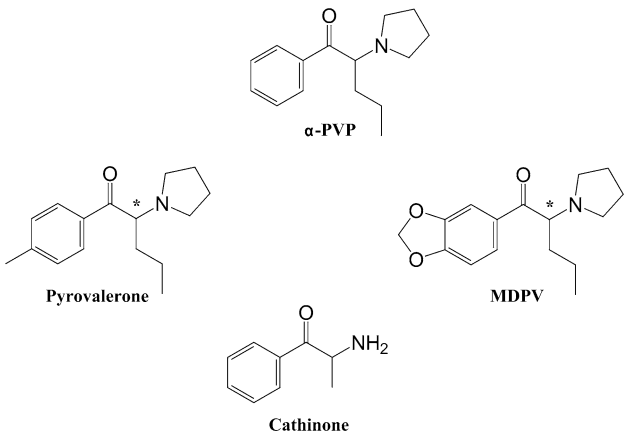

Fig. 1 Structures of α-PVP, pyrovalerone, MDPV, and cathinone

Chemistry

α-Pyrrolidinopentiophenone [commonly referred as α-PVP, alpha-PVP, O-2387, β-ketone-prolintane, prolintanone, or 1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one] is chemically related to pyrovalerone (Fig. 1) and is the ketone analogue of prolintane. It has the molecular formula $C_{15}H_{21}NO$ (or $C_{15}H_{22}NOCl$ in the case of its hydrochloric salt), a molecular weight of 231.33 g/mol, and a melting point of 161.3 °C. Its hydrochloric salt is a white powder at room temperature [13–16]. α-PVP as a free base is soluble in phosphate buffered saline (10 mg/mL in pH 7.2), ethanol (~20 mg/mL), dimethyl sulfoxide (~10 mg/mL), and dimethylformamide (~3 mg/mL) [17].

Synthesis of α-PVP

The laboratory synthesis of α-PVP (Fig. 2) is achieved via a three-step synthetic procedure; however, exact experimental details are not provided. The Grignard reaction of pentanenitrile or else valeronitrile with phenylmagnesium bromide in an acidic environment led to the formation of 1-phenyl-1-pentanone that was then brominated to form the respective α-bromoketone. The latter reacted with pyrrolidine to give α-PVP, which was finally converted to the HCl ion pair [15, 18, 19]. Alternative synthetic routes that could be also used clandestinely were not found in the scientific or grey literature.

Prevalence and use

α-PVP has recently emerged as a "legal high" and is sold via the Internet or at retail shops, smoke shops, adult book stores, and gas stations [4] as "bath salts" or "plant food".

Fig. 2 Synthesis of α-PVP