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To cite this article: Simonato Pierluigi, Bulsis Laura, Negri Attilio, Bansal Gurjeet K, Pessa Gloria, Mioni Davide, Giuseppe Borgherini, Martinotti Giovanni, Schifano Fabrizio, Giulia Perini & Corazza Ornella (2018) “Marvin, the Paranoid Android”: The Case of an Alpha-PVP User in the Expanding Galaxy of NPS, *Journal of Psychoactive Drugs*, 50:4, 306-313, DOI: [10.1080/02791072.2018.1447172](https://doi.org/10.1080/02791072.2018.1447172)

To link to this article: <https://doi.org/10.1080/02791072.2018.1447172>



Published online: 16 May 2018.



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“Marvin, the Paranoid Android”: The Case of an Alpha-PVP User in the Expanding Galaxy of NPS

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ABSTRACT

Alpha-PVP can be defined as a novel psychoactive substance (NPS)—more specifically, a novel synthetic cathinone with unpredictable stimulant effects in humans. “Marvin” arrived at a Dual Diagnosis Unit at Parco dei Tigli, Italy. He underwent a 30-day rehabilitation program to overcome his problematic Alpha-PVP use as a psychonaut. We conducted an online search to understand the properties of Alpha-PVP and its presence in scientific literature, reviewing official reports and the online drug market (e.g., fora, webpages). In the Dual Diagnosis Unit, Marvin completed the 30-day rehabilitation program that included assessments and group and individual cognitive behavioral therapy. Alpha-PVP is a synthetic cathinone with stimulant properties, available in the online market but with unpredictable effects in humans. The present case reports an important risk of psychosis in a psychonaut patient who arrived and declared its intense use before admission to our Unit. This article describes the psychopathological effects of the novel compound Alpha-PVP in a psychonaut patient. Patients attending clinics that have used Alpha-PVP pose a new challenge for traditional services of mental health and addiction.

ARTICLE HISTORY

Received 16 May 2017
Accepted 3 January 2018

KEYWORDS

Dual diagnosis; novel psychoactive drugs; psychiatric assessment; psychonaut; synthetic cathinones

Introduction

The rapid diffusion of novel psychoactive substances (NPS) represents an unprecedented phenomenon where synthetic drugs are reinvented and reintroduced with new and varied effects. Some NPS have been categorized in terms of their chemical structures and effects; several groups of substances have been identified by agencies (United Nations Office on Drugs and Crime; UNODC 2016) and literature (European Monitoring Centre for Drugs and Drugs Addiction; EMCDDA 2015a; Schifano et al. 2015): phenethylamines and novel stimulants, synthetic cannabinoids, cathinone derivatives, synthetic opiates/opioids, tryptamine derivatives, phencyclidine-like dissociatives, piperazines, GABA-A/GABA-B receptor agonists, a range of prescribing medications and psychoactive plants/herbs and “performance and image-enhancing drugs” (PIEDs), or “lifestyle drugs” (Mooney et al. 2017).

The European Union Early Warning System (EWS) has reported the rapid presence of more than one new NPS on the market every week. Regular online monitoring of the Recreational Drugs European Network

(ReDNet) and European-wide, Monitoring, Analysis and Knowledge Dissemination on Novel/Emerging Psychoactives (EUMadness) identified more than 750 new NPS and combinations. By July 2016, 102 countries and territories had reported over 540 NPS to the UNODC “Global Synthetics Monitoring: Analysis, Reporting and Trends (SMART) Programme,” far exceeding the 234 substances currently scheduled under the International Drug Control Conventions (UNODC 2016).

This “expanding galaxy” of NPS use poses a risk for the unaware health professionals (Simonato et al. 2013; Bowden-Jones 2014a, 2014b), facing NPS consequences in their clinical practice and meeting new populations of clients, like psychonauts (Bowden-Jones 2012; Orsolini et al. 2015).

Synthetic cathinones and Alpha-PVP

Synthetic cathinones are a constellation of such an expanding galaxy. Since the late 1920s, synthetic cathinones have been developed from the natural compound occurring in the Khat plant, known as

cathinone; more recently, they have been diffused as an NPS via online drug markets beginning in the mid-2000s. Synthetic cathinones and their synthetic derivatives are closely related to the phenethylamine family (which includes amphetamine and methamphetamine), but with a lower potency than the latter (German, Fleckenstein, and Hanson 2014; Kelly 2011; Prosser and Nelson 2012).

The first identified synthetic cathinone, methylone, was reported to EMCDDA in 2005, while warnings of 4-methylmethcathinone (mephedrone) use emerged two years later (EMCDDA 2007, 2011, 2014; Winstock, Mitcheson, and Marsden 2010; Sedefov and Gallegos 2011). It took a few years to profile the effects of synthetic cathinones through international reports (UNODC 2013) and scientific literature, including mephedrone (Farré et al. 2016; Hockenhull, Murphy, and Paterson 2016; Schifano et al. 2011), methylone (Bossong, Van Dijk, and Niesink 2005; Corazza et al. 2014), naphyrone (Dunne, Jaffar, and Hashmi 2015) and 3,4-methylenedioxypyrovalerone (or MDPV) (Colon-Perez et al. 2016; Coppola and Mondola 2012).

According to the information collected by UNODC (2016), synthetic cathinones have increasingly been used as NPS from 2010 onwards, including the recent compound known as α -pyrrolidinopentiophenone (EMCDDA 2015; EMCDDA-Europol 2015; WHO 2015).

This article aims to: (1) gather reliable information on Alpha-PVP in scientific literature, governmental and international reports, and online websites/fora; and (2) provide a case study highlighting its presence in clinical practice and the clinical implications.

The case of Marvin originated from his admission to the Dual Diagnosis Unit of the Italian Clinic Parco dei Tigli, located in Padova in the northeast of Italy (www.parcotigli.it). The Dual Diagnosis Unit spans all regions of Italy, offering a 30-day rehabilitation program for alcohol, other classic substances (cocaine, cannabinoids, benzodiazepines), and NPS. The program includes: (1) a detoxification phase; (2) a psychopharmacological and psychiatric assessment; and (3) group and individual CBT psychotherapy.

Literature search methods

A literature search of Alpha-PVP was conducted using the following online databases: PsycINFO, Scopus, PubMed, and Google Scholar. The research team used key search terms such as " α -pyrrolidinopentiophenone" and its variations (e.g., "alpha-PVP," "A-PVP," "APVP"). Twenty-five peer-reviewed articles were found. A multi-lingual qualitative assessment of a range of websites, drug fora, and other online resources (i.e., e-newsletters, chat

rooms, mailing lists, e-newsletters, and bulletin boards) was also conducted. Between January 2013 and January 2017, exploratory qualitative searches of several websites in Europe were also completed by using key search terms, such as "Alpha-PVP" and its street names (e.g., "flakka," "gravel"). Thirteen websites were considered relevant and were monitored on a regular daily, weekly, or monthly basis, depending on their relevance. The remaining websites were considered not to bear any interest for the present study and were no longer monitored.

Overview of literature findings

Pharmacological profile

Alpha-PVP is a central nervous system (CNS) stimulant, chemically related to pyrovalerones (e.g., methylenedioxypyrovalerone; MDPV), belonging to the synthetic cathinones constellation (Katselou et al. 2016; Sauer et al. 2009). It was first synthesized approximately 50 years ago, but recently gained popularity as a recreational NPS. Due to its similarity to MDPV, this compound was suggested to be a norepinephrine-dopamine reuptake inhibitor (Kolanos et al., 2015; Smith et al. 2016), but with an unclear pharmacological profile. A recent study (Kaizaki, Tanaka, and Numazawa 2014) investigated the effects of Alpha-PVP in comparison to methamphetamine on the CNS of mice. The results concluded an earlier and stronger locomotor activity, and a rapid and shorter increase of dopamine in the striatum (D1 and D2 receptors). Further studies have suggested that Alpha-PVP acts as a dopamine-releasing agent (Aarde et al. 2015; Kaizaki, Tanaka, and Numazawa 2014; Smith et al. 2016), the main mechanism being responsible for CNS stimulation and psychopathological consequences.

However, data also suggest that Alpha-PVP acts on monoamine uptake receptors (Marusich et al. 2016; Sauer et al. 2009), but with a specific pharmacological profile, different from amphetamine, cocaine, and other synthetic cathinones (Negreira et al. 2015; Kolanos et al., 2015; Smith et al. 2016). Alpha-PVP neurotoxicity in humans is unknown.

The EMCDDA (2015b; EMCDDA-Europol 2015) summarize *in vitro* Alpha-PVP properties: (1) inhibition of dopamine uptake at the dopamine transporter; and (2) norepinephrine uptake at the norepinephrine transporter, similar to MDPV. An important pharmacological feature is that Alpha-PVP does not inhibit serotonin uptake at the serotonin transporter. Specific information about the pharmacology of the individual enantiomers of Alpha-

PVP has not been published, and other pharmacological targets are not described.

Alpha-PVP appearance in the drug scene

Alpha-PVP was developed in the 1960s as a synthetic derivate in the cathinones family, and was later identified in peer-reviewed literature in 2009 (Sauer et al. 2009). The European EWS formerly notified its availability in 2011, and a specific risk assessment was issued by EMCDDA (2015b; EMCDDA-Europol 2015). Its presence on the online drug market was later confirmed (Grifell et al. 2016; Umebach et al. 2016) and its use linked to cases of impaired driving (Knay, Peterson, and Couper 2014), acute intoxications (Beck et al. 2016; Dumestre-Toulet, Brault, and Penouil-Pucheu 2016; Umebach et al. 2016; Wright and Harris 2016), and psychiatric disturbances (Crespi 2016; Klavž, Gorenjak, and Marinšek 2016). Furthermore, the EMCDDA (2015b) reported 116 deaths related to Alpha-PVP between 2012 and 2015.

Alpha-PVP has many street names, such as α -PVP, O-2387, β -ketone-prolintane, prolintanone, gravel, and flakka (Steinberg 2015); it is sold online as a white crystal or in a blue variant form. Since 2011, more than 750 kg of Alpha-PVP have been seized in powder and tablet form (EMCDDA-Europol 2015). It is important to note that some of the seizures of tablets by law enforcement showed a range of colors, markings, and logos consistent with ecstasy tablets, suggesting a misleading design in the illicit drug market.

The online price of Alpha-PVP is USD 1–6/gram; it is available through international websites and laboratories based mostly in China (EMCDDA 2015b). Sites on the European online drug market deliver the product for 16.5 Euros/gram with a discount in case of high-dosage orders. Similarly to other NPS, online sellers appear to be able to send the product anonymously and internationally.

Legal status

Although the EMCDDA reports that the majority of EU member states have a prohibition (four member states) or a control measure (16 member states) regarding Alpha-PVP, it is still legal and not subject to regulation in seven states (Belgium, Bulgaria, Croatia, Denmark, Luxembourg, Malta, and Spain).

In the U.S., Alpha-PVP has been temporarily categorized as a schedule I drug under the temporary scheduling provisions of the Controlled Substances Act (DEA 2014). Other countries with legislative

control include Japan (“Designated Substance”), China, and other United Nation member states (WHO 2015).

Clinical evidences on Alpha-PVP

No published data exist on the psychological and behavioral effects of Alpha-PVP in humans. Animal studies suggest that its effects might bear some similarities to other psychostimulants (e.g., MDPV, cocaine; Sauer et al. 2009; Smith et al. 2016). Moreover, no clinical studies have identified the health effects of Alpha-PVP and/or its metabolites in humans.

Between 2011 and 2015, eight EU member states have reported 205 acute intoxications associated with Alpha-PVP. Half of these cases also involved other drugs (e.g., alcohol, benzodiazepines) and their clinical features were generally consistent with sympathomimetic toxicity (tachycardia, mydriasis, anxiety, tremor, hyperthermia, hallucinations, hypertension, diaphoresis, restlessness, convulsions, and seizures; EMCDDA 2015b; WHO 2015).

In a three-year span from 2012 to 2015, eight EU member states reported a total of 116 deaths related to the analytically confirmed presence of Alpha-PVP. However, in most of these cases, toxicology tests confirmed the simultaneous use of a variety of other substances (i.e., benzodiazepines, opioids, alcohol, antidepressants, and anticonvulsants), in addition to Alpha-PVP (EMCDDA 2015b).

There is only limited literature that describes the specific psychopathological features of Alpha-PVP, including agitation, delusions, paranoia, hallucinations, delirium (Beck et al. 2016; Wright and Harris 2016), psychosis (Crespi 2016), and suicide attempts (Klavž, Gorenjak, and Marinšek 2016).

Subjective users’ self-reports

Online fora in different languages (e.g., English, Italian, Spanish, French) (CannabisCafe.net 2014; Drugsforum.com 2012–2016; Erowid.org 2013; Psychonaut.com 2013; Psyvault.net 2011) describe the effects of Alpha-PVP, and users’ online reports declare analogies with stimulants like cocaine, amphetamines, and other synthetic cathinones (like MDPV).

Alpha-PVP in crystal form can be ingested, sublingually administrated, smoked, insufflated, vaporized (Erowid.org 2013; EMCDDA 2015b; World Health Organization 2015; Katselou et al. 2016), and even injected with severe health risks (Marusich et al. 2016). According to online reports, the most common modalities of intake are insufflation and smoking

(Drugsforum.com 2012–2016). Users suggest a very low dosage of the compound, particularly during the first consumption (0.1–0.2 mg/kg), to avoid allergic reaction, reaching 10–50 milligrams per dose (Drugsforum.com 2012–2016). Although the average insufflated or smoked dosage is considered 10–25 mg (EMCDDA 2015b), users describe a powerful stimulant effect also at a lower dosage (Drugsforum.com 2012–2016; Erowid.org 2013). Some online experiences and clinical cases describe abuse of Alpha-PVP at higher dosages, representative of the case study discussed in this article.

The average dose of Alpha-PVP is 10–25 mg administered via insufflation or smoking. The experiences that follow are often shared online, and describe the process of use as outlined: (1) 2–5 minutes after intake, a mild euphoric effect; (2) 20–40 minutes proceeding euphoric and sexual stimulation; (3) one hour after a peak of stimulant effect; (4) two hours after intake, a decrease in the effects of the substance; and (5) the comedown begins at approximately three hours.

This compound is suggested as an alternative to amphetamines, cocaine, methamphetamines, and methylphenidate, due to its stimulant properties (Drugsforum.com 2012–2016; Erowid.org 2013; Psychonaut.com 2013). Specifically, this compound can induce: euphoria (in 15 seconds, with maximum effect in one hour, lasting for 3–4 hours; 20 mg); sexual arousal reported in many experiences as an important effect: this effect is in common with 2C-B, 4-FA, 4-DMAR (Reddit.com 2014); tachypsychia; alertness.

Although most self-reports by users have described Alpha-PVP's powerful effects, according to the evidence from animal assays, some psychonauts report consuming other substances in conjunction with it (Psyvault.net 2011; Drugsforum.com 2012–2016; Psychonaut.com 2013; Erowid.org 2015). These poly-substances include energy drinks, Lidocaine, Percocet (oxycodone), Baclofen, pyrazolam, visteril, cannabis, olanzapine, and theanine.

Some compounds appear to support psychonauts during their comedown phase, such as Kratom and Lyrica (Pregabalin), while some users noted that Tetrahydrocannabinol (THC) could increase psychotic symptoms. Nevertheless, several online records suggest a high psychopathological risk as a consequence of Alpha-PVP use (Drugsforum.com 2012–2016), such as: anxiety and panic attack; insomnia (for almost eight hours with a single dosage);

paranoia, delusions and hallucinations—both auditory and visual hallucinations reported with high dosage (1200 mg, re-dosing the compound in a single night) in the form of delusional parasitosis (Drugsforum.com 2012–2016); a compulsion to re-dose reported by many users (Erowid.org 2015); depressive feelings (during the comedown).

Case report: Marvin, the paranoid android

Marvin was a Caucasian man, 28 years old, with no past or ongoing organic illness. The patient came from a healthy family, he was single, he studied at Liceo Scientifico (high school), and for two years attended university, in the faculty of herbal techniques. He was admitted to the Dual Diagnosis Unit (Casa di Cura “Parco dei Tigli”) in 2014 due to symptoms suggestive of a depressive episode that occurred in the previous four weeks. When hospitalized, his reality testing was not impaired by active hallucinations or delusions; at arrival, he was compliant with prescribed therapy but complained of a generalized “lack of energy.”¹ The blood panel did not show significant features except for elevated levels of cholesterol (220 mg/dl) and triglycerides (226 mg/dl); electrocardiography indicated normal activity. Toxicological tests and urine sample were positive for benzodiazepines (delorazepam 246 ng/ml, was previously prescribed) and negative for cocaine, cannabis, alcohol, methadone, barbiturates, and opioids.

At the time of Marvin's arrival to the Dual Diagnosis Unit, he was already known to the local mental health service (CSM) due to a psychotic episode when he was 16 years old, induced by cannabis and skunk (Di Forti et al. 2009; Hall and Degenhardt 2015). He received a diagnosis of substances induced psychosis (DSM IV-R) and was treated with antipsychotic and antidepressant medications: risperidone (4 mg/day), venlafaxine (75 mg/day), biperiden (4 mg/day), and delorazepam (2 mg/day). Marvin was also briefly followed by a local drug service (Ser. D) for his past THC misuse, but he never disclosed his problematic NPS use, which began when he was 18 years old. He then became a “psychonaut.” In the Dual Diagnosis Unit, Marvin revealed his misuse of drugs in detail. He explained that the majority of his experimental substance use occurred over several years (Table 1), though during the last eight months prior to his admission into the Dual Diagnosis Unit the frequency of his Alpha-PVP use intensified. In parallel, he experienced a

¹This symptom reminded us the fictional character in the book *The Hitchhiker's Guide to the Galaxy*, the depressed robot called Marvin.

Table 1. Previous compounds consumed by Marvin during his activity as psychonaut.

Substance	Frequency	Dosage*
Classic Compounds:		
THC	Constantly during years	Variable
Alcohol	Inconstantly during years (weekly)	Variable
Classic compound/Novel psychoactive substance:		
Ephedrine + Caffeine	5–6 times	
Novel psychoactive substances:		
JWH 210	Several times	25 mg
DMT [N,N-Dimethyltryptamine]	Once	
4 HO Met [4-hydroxy-N,N-ethyl-methyltryptamine]	Once	15–20 mg
2 C-E [4-ethyl-2,5-dimethoxyphenethylamine]	Once	18 mg
MDPV [3, 4- methylenedioxypyrovalerone]	Twice	
Kratom	Once	
Salvia divinorum	5–6 times	
Ketamine	3–4 times	
Methoxetamine	Once	50 mg
Pentedrone (α-methylamino-valerophenone)	2–3 times	
Ethyl-phenidate	Once	
25 C and I NBOMe	Twice	
Oxycodone	Once	
AH-7921 and MT-45 (doxilam)	Once	

*Dosage provided when available.

worsening of his depressive symptoms until his last episode, in which he suffered visual hallucinations, leading to his referral to the Dual Diagnosis Unit from the CSM.

Marvin decided to try Alpha-PVP because of its: (1) stimulant properties; (2) availability on the online market; and (3) legal status. Marvin explained that Alpha-PVP was easily purchasable in powder form through online websites, and in a few days the compound arrived in an anonymous package. Marvin insufflated or smoked Alpha-PVP every day for 3–4 days for a period of 5–6 months. The dosage was progressively higher, until he administered 300–400 mg in a day. Marvin was aware that the suggested dosage in online fora was 25–30 mg, but he desired a stronger stimulation and sexual arousal, since he was prescribed antipsychotic medications that appeared to dull its effect. Marvin reported the effects as: stimulation with mental euphoria, high levels of physical energy, insomnia, sexual arousal, “panic attacks” with anxiety and tachycardia, hyperpyrexia (with a body temperature reported of 40°C), and delusions (with both visual and auditory hallucinations), especially at high dosage (from 100 mg to 300 mg). Ekblom’s syndrome and a severe persecutory delusion were reported by the patient after the re-dose of the compound that required the most recent hospitalization.

Marvin did not reveal the ingestion of Alpha-PVP to the CSM where he received treatment for his mental health, in order to avoid police or legal consequences. As a result, his symptoms were treated as an expression of a primary mood disorder with psychotic features until his arrival at the Dual Diagnosis Unit.

Assessment and treatment

During his recovery in the Dual Diagnosis Unit, after discontinuing the use of Alpha-PVP, he was assessed and evaluated with clinical interviews, a Structured Clinical Interview for DSM-IV I and II, The Symptom Checklist 90 (Carrozzino et al. 2016), and The Minnesota Multiphasic Personality Inventory (Graham 1990; Greene 2000; Rouse, Butcher, and Miller 1999; Sawrie et al. 1996). The final diagnoses assigned to the case were:

- Stimulant and cannabis dependences: cannabis addiction diagnosis was anamnestic;
- Psychotic episode induced by substances;
- Schizoid personality disorder.

Marvin’s hospitalization in the Dual Diagnosis Unit lasted 40 days, during which he engaged in a rehabilitation program that included: individual (biweekly) and group (2–3 times a day) psychotherapy, and psychopharmacological assessment and psychomotor rehabilitation. A significant change in Marvin’s recovery occurred when he was given bupropion (150 mg/day). This antidepressant (O’Byrne et al. 2014) was chosen because of its chemical structure (it is the only synthetic cathinone with medical use); it improved his depressive symptoms. However, a review of the scientific literature has identified that there is no suggested treatment for psychonauts using Alpha-PVP (Costa et al. 2014; Oppek et al. 2014).

Discussion

Alpha-PVP is a synthetic cathinone which appeared in the online market in recent years, with only limited

scientific literature and international reports. The compound was only recently banned in Europe, despite the clinical impact of its effects. Alpha-PVP is a powerful dopamine-releasing agent, which induces CNS stimulation (amphetamine-like effect), sympathomimetic symptoms, and severe psychopathological disturbances.

This article elucidates the lack of peer-reviewed literature concerning this emerging NPS, its psychopathological effects, and its risk of erratic symptoms that can present in clinical activity. Healthcare professionals are called to treat NPS in their everyday activity, where the misuse of novel compounds involves specific new populations of users such as clubbers (Parrott et al. 2014), psychonauts (Davey et al. 2012; Orsolini et al. 2015), and the young adult psychiatric population (Martinotti et al. 2014).

This article highlights the difficulties faced by healthcare professionals in detecting NPS users and assessing their symptoms, especially when patients have a psychiatric history. Marvin reported the presence of psychotic symptoms indicative of his use of Alpha-PVP at a high dosage while he was taking his antipsychotic medications.

This prompts further study of the psychopathological effects of this substance, while informing clinicians of the possible clinical impact of Alpha-PVP in their patients. Future research needs to: (1) better and more rapidly define, from a pharmacological and toxicological point of view, the nature and effects of new NPS; and (2) exhaustively describe the psychopathological profile and personality of these emerging groups, in order to guide a specific treatment for these patients (Novel Psychoactive Treatment UK Network 2015).

Limitations

The clinical case was not confirmed by any laboratory testing; therefore, the previous or more recent use of any NPS was only spontaneously self-reported by the patient during his recovery in the Dual Diagnosis Unit. The documented history of psychosis symptoms and his reported consumption of NPS could be problematic to establish a meaningful association between Alpha-PVP and paranoid delusions, suggesting that more studies are needed in this direction.

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