ALPHA-PVP: EXPLORING A NEW PUBLIC HEALTH CHALLENGE

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Abstract*. This study addresses the issue of the spread of synthetic cathinones, specifically Alpha-PVP, and their impact on public health. The paper thoroughly describes the chemical composition, metabolism, pharmacological, and toxicological aspects of synthetic cathinones. Issues of regulation and control over the distribution of these substances are discussed, as well as the role of the internet in their sale. The authors emphasize the need for further research to develop effective methods for prevention and treatment of dependencies caused by these dangerous substances.*

Keywords*: new psychoactive substances, synthetic cathinones; α-pyrrolidinovalerophenone, Alpha-PVP.*

1. Introduction

Drug abuse is currently a major public health problem. New psychoactive substances (NPS) are spreading at an unprecedented rate and are becoming a serious public health threat. Due to insufficient information about the harm of NPS to health and society, difficulties arise in the prevention and treatment of such cases [1].

The term "NPS" was coined by the United Nations Office on Drugs and Crime (UNODC). For the sake of terminological clarity, the term is defined as “substances of abuse, either in pure form or in preparation form, which are not controlled under the 1961 Convention as amended by the 1972 Protocol, or the 1971 Convention, but may pose a threat to public health." The word “new” in the name indicates not so much the novelty of such substances—some were synthesized 40 years ago—but rather their recent appearance on the market [1].

These substances are also known as “designer drugs.” They are created to imitate the effects of “classic” narcotic substances that fall under the strict legal control of government agencies and are included in the lists of the drug control conventions and these synthetic compounds, developed in illegal chemical laboratories, have a completely changed chemical formula to circumvent existing legal restrictions [2].

In fact, in parallel with the reduction or stabilization of the use of internationally controlled drugs, the market for NPS continues to grow, with the Internet playing a key role in this complex process [3].

The NPS market includes a large number of substances and is constantly being replenished with new compounds [4,5,6]. At the end of 2022, the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) was monitoring approximately 930 new psychoactive substances, 41 of which were reported for the first time in Europe in 2022. Synthetic cathinones (SC) are one of the most common classes of NPS on the underground market. According to the EMCDDA report, by the end of 2022, a total of 164 SCs were registered in Europe. In 2021, UK accounted for more

than half (over 4.3 tons) of the total NPS seizures, placing them at the top of the list of NPS seizures in 2021 [4].

SCs are spreading rapidly in the Republic of Uzbekistan. Thus, if in 2019 the law enforcement agencies of the Republic of Uzbekistan seized 194.1 grams of SC from illicit trafficking, then by 2022 this figure was more than 32 kg [7,8].

Synthetic cathinones are structural analogues of cathinone, a psychostimulant alkaloid present in khat (Catha edulis) [9]. In online stores they are sold under the guise of “bath salts,” although they are not such. The "salts" are usually a white or brown crystalline powder. These substances have nothing in common with true "bath salts" or Epsom salts, which are made from the mineral mixture of magnesium and sulfate and which people add to their bath water to relieve stress and relax muscles.

Chemically, synthetic cathinones are β-phenylethylamine (PEA) derivatives, including methamphetamine (N-methyl-1-phenylpropan-2-amine) and MDMA (3,4-methylenedioxy-N-methylamphetamine, “Ecstasy”). Cathinone (β-ketoamphetamine) compounds found in PEA derivatives include methylenedioxypyrovalerone (3,4-methylenedioxypyrovalerone, MDPV), 4-methylephedrone, mephedrone (4-MMC, Meph), methylone (3,4-methylenedioxy- N-methylcathinone, MDMC), as well as many others. The range of chemical structures of these compounds is very wide and constantly changing.

The use of SC can be very dangerous [10]. Their use sometimes causes severe poisoning and significantly affects human health. Typically, people become more anxious and aggressive after using SA and exhibit aggressive behavior at high doses (70–100 ng/ml) [11]. In some cases, these substances have caused death [12,13,14]. The abuse of synthetic cathinones is a serious public health problem. Abuse of SA mainly leads to sympathomimetic toxicity, which most often manifests as mania, tachycardia, increased blood pressure, and sometimes hallucinations, hyponatremia, chest pain and nausea. In severe cases, it can cause seizures, severe peripheral organ damage, and rhabdomyolysis [15]. Data are only available from consumers who have experienced these possible hazards [16]. The purpose of this study is to review expert information on these dangerous synthetic drugs in terms of their chemical composition, metabolism, pharmacology and toxicology.

2. History of synthetic cathinones

Some SAs (for example, mephedrone) were first synthesized back in the 20s of the last century and have chemical properties similar to cathinones [17]. However, the term “cathinone” did not appear until the 1970s, and the term “synthetic cathinone” appeared even later [18]. Until recently, they were almost forgotten. However, due to legal loopholes, underground chemists have started using them in designer drugs [19,20,21]. 15 years ago, cathinone use began to rise again. They initially began to spread in the UK, then in other parts of Europe and finally in the USA [22], where SCs appeared in 2010 and were registered by US poison control centers [20]. There has been a dramatic increase in the use of cathinones [23,24]. The UK National Poisons Information Service has collected telephone reports of the toxicity of mephedrone and other cathinone-related recreational drugs used in the UK. Until 2009, there were no reports of these compounds in the UK. Between 2009 and 2010, 188 telephone messages related to cathinone were recorded, and the majority of these (157 calls) were related to mephedrone. However, after 2010, the number of calls related to cathinone became equal to the number of calls involving both MDMA (“ecstasy”) and cocaine. Moreover, there has been an alarming increase in the availability of these substances, as

well as an increase in their use and hospitalizations in the United Kingdom and across Europe [25]. By mid-2015, α-PVP was responsible for 105 fatal poisonings in Europe [26]. In Europe, these drugs were mainly purchased on websites or in small packages as souvenirs.

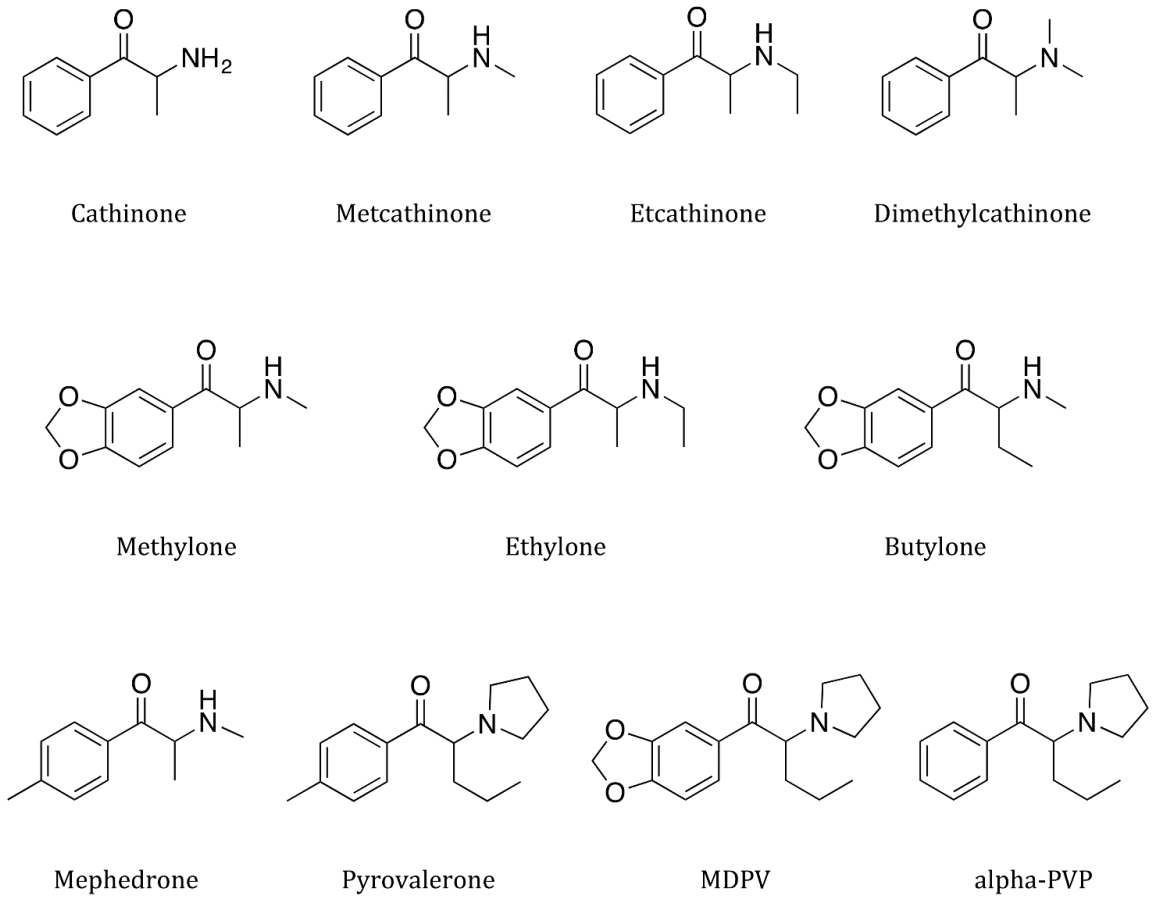

Figure 1. Chemical structures of some important synthetic cathinones.

Since then, many new cases of designer drug use have been reported. In the short term, many SCs have become popular, especially among the younger generation [27]. Since the re-introduction of recreational drugs into the market in several countries, there have been many reports of abuse, addiction and deaths associated with the use of SA [28,29,30].

Synthetic cathinones are chemical derivatives of cathinones, natural monoamines, and have been used for centuries by the indigenous people of the Horn of Africa and the Arabian Peninsula for their psychostimulant properties [31]. Most synthetic cathinones are produced in China or India and are rapidly spreading throughout the world [32,33]. The chemical structures of important synthetic cathinones are presented in Figure 1.

3. "Speed"

The synthetic cathinone α-pyrrolidinovalerophenone, α-PVP is known in Uzbekistan as “Speed”. Other slang names for α-PVP are also common in Uzbekistan, such as “salt”, as well as the abbreviation “SK”, which stands for “salt crystal/speed crystal”. It is chemically similar to MDPV, which was responsible for an increase in bizarre cases of intoxication and agitation in the United States several years ago [34]. Although people use α-PVP to achieve euphoria, symptoms can easily develop into terrifying hallucinations, paranoid psychosis, extreme agitation, and many other altered mental states. α-PVP causes a condition called excited delirium, in which there is an

excessive influx of sympathetic activation [35]. This condition causes mental status changes including strange/inappropriate behavior, anxiety, agitation, aggressive behavior, confusion, myoclonus and seizures [36,37]. Clinical signs of excited delirium include tachycardia, hypertension, pyrexia, diaphoresis, and mydriasis [38]. Although α-PVP is a very dangerous drug, this new SA is beginning to dominate the drug market in the USA and Europe [39].

3.1. Pharmacology

Studies have shown [40,41] that, as one of the synthetic cathinones, α-PVP can increase the levels of extracellular neurotransmitters by inhibiting the monoamine transporters NET and DAT, corresponding to norepinephrine and dopamine, or by inhibiting the vesicular monoamine transporter (VMAT). α-PVP appears to have effects similar to MDPV, which is similar to the norepinephrine and dopamine reuptake inhibitor [42]. Metzler and colleagues showed that α-PVPs have selective uptake activity at dopamine and norepinephrine receptors, with little effect on serotonin transport/reuptake (SERT) [43].

α-PVP stimulates a significant increase in locomotor activity, which occurs much more rapidly than the locomotor activity stimulated by methamphetamines [44]. Following administration of α-PVP (25 mg/kg orally), the extracellular concentration of dopamine in the striatum increases. This suggests that α-PVP triggers dopamine delivery [45,46], leading to increased locomotor activity; thus, it influences, at least in part, α-PVP activity in the central nervous system (CNS) through D1 and D2 receptors [45,47].

There is growing evidence that α-PVP has a stimulant effect similar to cocaine. In fact, it is more effective than common psychostimulants such as cocaine and amphetamine [48,49]. Gannon and colleagues [48] used an absorption inhibition assay in rat brain synaptosomes to directly compare the efficacy of MDPV, 3',4'-methylenedioxy-α-pyrrolidinobutiophenone (MDPBP), 3',4'-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP), α-PVP, α-pyrrolidinopropiophenone (α-PPP) and cocaine on DAT, NET and SERT. The results showed that α-PVP had the strongest selectivity for DAT and the lowest selectivity for SERT among the above-mentioned substances. Collins and colleagues [49] used four adult male rhesus monkeys to study MDPV and α-PVP self-administration and directly compared the results to the effects of cocaine and methamphetamine. The results confirmed that the synthetic cathinones MDPV and α-PVP can maintain high levels of response over long periods of time and that they are more effective than cocaine or methamphetamine.

To investigate whether synthetic cathinones have direct myotoxicity, Zhou et al. [50] examined the potential toxicological effects of synthetic cathinones on C2C12 myoblasts (a mouse skeletal muscle cell line). After exposure of C2C12 myoblasts to α-PVP and other substances for 1 or 24 h, the integrity of cell membranes, ATP content, mitochondrial oxygen consumption, and the production of mitochondrial superoxide anion radicals were measured. The results showed that α-PVP consumes ATP, causes loss of cell membrane integrity, and increases superoxide radical anion levels in C2C12 myoblasts in a concentration-dependent manner. In addition, as a pyrrolidone derivative, α-PVP also impairs cellular respiration, indicating abnormal mitochondrial function. Thus, in addition to effects on the sympathetic nervous system, direct effects of α-PVP on skeletal muscle mitochondria may result in myotoxicity in susceptible cathinone users.

In a rodent study, acute administration of α-PVP at doses of 1–10 mg/kg via vapor or injection produced significant dose-dependent hyperlocomotion, likely associated with increased signaling at dopamine D1 and D2 receptors [51]. The psychopharmacological effects of α-PVP in

humans occur within 10 minutes of a single dose (usually 15 to 300 mg), peak within 10 to 40 minutes, and last for 2 to 3 hours.

3.2. Toxicology

Kolesnikova et al characterized the behavioral effects of α-PVP in adult zebrafish following short-term (1, 5, 25, and 50 mg/L for 20 minutes) and long-term (1, 5, and 10 mg/L for seven days) interventions [52]. Overall, acute exposure to α-PVP produced psychostimulant (but not anxiolytic) effects in this new zebrafish test, with characteristic and stereotypical side-to-side swimming along the bottom at concentrations of 5, 25 and 50 mg/L. Analysis of zebrafish brains by high-performance liquid chromatography/high-resolution mass spectrometry showed detectable levels of α-PVP following acute administration, which likely underlies the observed behavioral effects. α-PVP signal peaks in the brain corresponded to systemic concentrations of the administered drug. Although acute two-day cessation of administration after chronic seven-day administration of α-PVP at doses of 1, 5, and 10 mg/L did not produce any effects, after seven days of chronic administration, hypolocomotion and repeated withdrawal were observed, reminiscent of the effects of some psychostimulants. Taken together, these results confirm the sensitivity of zebrafish to α-PVP and show some parallels with its effects in mammals. This study also suggests that aquatic models based on zebrafish may help further study the CNS effects induced by α-PVP and the search for associated new synthetic psychoactive drugs. However, no experimental studies have been conducted to examine the chronic effects of α-PVP on human health. In fact, knowledge about the long-term effects of α-PVP use in humans is limited.

3.3. Metabolism

Understanding the metabolism of synthetic cathinones is valuable not only for anti-doping and forensic purposes, but also for helping to identify metabolites that have the potential for further abuse and that require additional pharmacological evaluation. For example, several synthetic cathinones, including α-PVP, have been added to the list of prohibited substances at sporting events [53]. The metabolism of α-PVP and MDPV has been studied, but only phase I metabolism will be described here. Many of the metabolites can form sulfates or, more commonly, glucuronides or other conjugates as phase II metabolites. The metabolism of α-PVP has been studied mainly in rats [32,54]. Eleven α-PVP metabolites were detected in rats as well as in consumer urine samples. In phase I it is recommended to include metabolic stages, i.e. hydroxylation of the side chain followed by dehydrogenation to the corresponding ketone and hydroxylation of the 2-position of the pyrrolidine ring followed by dehydrogenation to the corresponding lactam.

Another way is to decompose the pyrrolidine ring to the corresponding primary amine by hydroxylation of the phenyl ring, most likely at the 4-position, and open the pyrrolidine ring to the corresponding carboxylic acid. Phase II metabolic steps include glucuronidation [55] (Fig. 2). However, there is insufficient knowledge about whether these metabolites are pharmacologically functional.

When Shima and others [56] analyzed 19 urine samples from α-PVP abusers, the main metabolic pathways were reduced ketone recruitment and oxidation of the pyrrolidine ring. Urinary 2"-OH-α-PVP levels were higher than 2"-oxo-α-PVP levels. This information revealed interindividual differences in human α-PVP metabolism due to decreased ketone recruitment or oxidation at the 2′ position of the pyrrolidine ring. Extremely high concentrations of α-PVP and its metabolites (2"-OH-α-PVP + 2"-oxo-α-PVP) in urine (11,200 and 5,300 ng/ml), as well as

relatively excessive concentrations in the kidneys (1,580 and 972 ng/g, respectively) showed that α-PVP is rapidly excreted in the urine through the kidneys [57]. There are no experimental studies of the chronic effects of α-PVP and/or its metabolites on human health.

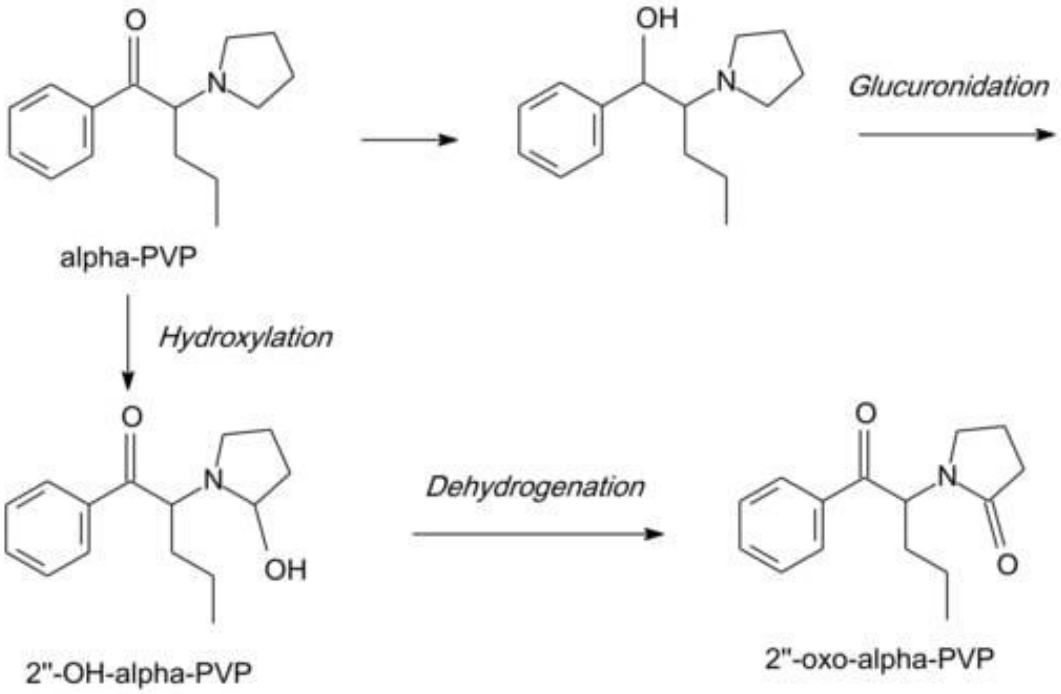

Figure 2. Metabolism of α-PVP.

Thus, further integration of human and animal models (including humans, rodents and aquatic organisms) is still needed to understand the biological lifespan of α-PVP metabolites and the presence of any biological activity in major species.

3.4. Clinical course and health risks

The public health risks associated with α-PVP depend on several factors: frequency and route of administration, availability and properties of the substance, and the level of knowledge among users about adverse health effects. There is no adequate information on episodic and chronic use that could help prevent the risks associated with α-PVP. The resurgence in the use and abuse of illicit drugs poses challenges for clinicians in terms of screening, diagnosis and treatment, and also makes it difficult for various drug monitoring agencies to determine appropriate regulations.

α-PVP can be taken orally, smoked, inhaled, used parenterally, and vaporized in e-cigarettes. Vaporization of drugs in electronic cigarettes is becoming a common method of administering SCs and classical stimulants. Heating during evaporation may expose the user to a mixture of parent compounds and thermolytic degradation products, which may result in different toxicological and pharmacological effects compared to administration of the parent compound alone via injection or nasal inhalation [58,59]. The latter route of administration results in rapid entry into the bloodstream, resulting in a high risk of overdose. α-PVP causes various symptoms when consumed. The drug has been reported to cause depression, panic attacks, chest pain, paranoia, hallucinations, aggressive behavior, self-harm (including suicide) and chronic psychosis [35]. The rate at which new psychoactive drugs are emerging is alarming. New structures have new properties and thereby create unique behavioral characteristics during intoxication. It can be assumed that the trend towards the use of new drugs will increase and the number of cases in

clinical practice will increase. Doctors must take this into account to prescribe appropriate treatment and minimize unwanted damage.

Heikman et al [60] indicated that frequent use of multiple substances may be common in patients taking α-PVP. It is estimated that about 0.8% of high school students in 2016/2017 used α-PVP in the past year [61]. Students whose parents had less than a high school education had higher odds of use. α-PVP users report a high prevalence of other drug use, especially synthetic cannabinoids (85.6%), ketamine (72.3%), marijuana (59.1%), and GHB (47.5%). α-PVP use is also associated with higher amounts and frequency of other drug use, with 51.7% of users using 4 to 12 other drugs.

3.5. Poisonings and deaths

In 2012, α-PVP poisoning was particularly identified in the Scandinavian countries, Denmark and Iceland. In Finland in 2012, 162 cases of use of various illicit drugs were registered, which was confirmed by positive test results. Among them, the incidence of α-PVP poisoning was 4.9%. In Sweden, 255 cases of use of various illicit drugs have been reported, confirmed by positive test results. Among them, the incidence of α-PVP poisoning was 0.4%. In most cases, we were talking about other NPS and/or "classical" substances [62]. From April 2013 to November 2015, 31 patients with α-PVP intoxication were registered in Sweden, of which 73% were dependent [63]. In all cases, other NPS and/or "classic" drugs were also detected. Among the surfactants in cases of intoxication, α-pyrrolidinobutiophenone (α-PBP) and other pyrrolidone analogues were the most common NPS, and benzodiazepines were the most common CNS inhibitors. Of the 14 cases requiring intensive care unit monitoring, eight were considered severe poisonings. No deaths were reported.

3.6. Forensic toxicology

There have been two fatal poisonings in Finland: suicide and accidental death. In cases of suicide due to doxepin poisoning, α-PVP (70 ng/ml) was identified in the blood, as well as doxepin, citalopram, quetiapine, MDPV, buprenorphine and temazepam. In cases of death from multiple injuries due to an accident, α-PVP (60 ng/ml), amphetamine and ketamine were identified in the blood [64]. In addition, Richards-Waugh et al [65] described three cases of α-PVP-related deaths in three adults aged 31, 35 and 51 years. Toxicological analysis revealed blood concentrations of 29, 52 and 10 ng/ml. All three men showed typical signs of using these drugs: aggressive behavior and suicidal tendencies in the first case and seizures in the second case. Toxicological analysis also revealed the presence of sertraline, oxycodone and 7-aminoclonazepam. In all three cases, α-PVP contributed to their deaths; however, this substance was not a major factor [65].

Similar fatal cases have also been reported in Ohio [33]. Four women aged 32 to 44 years and two men aged 34 to 51 died from fatal poisoning. α-PVP was found in their blood and urine at autopsy. Other drugs were also confirmed (morphine, codeine, hydrocodone, and 6-monoacetylmorphine) in four cases, cocaine and its metabolites in one case, and synthetic cathinones (MDPV, pentylone, and methedrone) in three cases. Quetiapine was detected in one case, and amitriptyline, citalopram, venlafaxine and norvenlafaxine in three cases [33]. In one of the first reports of fatal α-PVP poisoning in humans, where α-PVP was the only reported cause of death [66], the drug concentration in cardiac blood was 486 ng/ml.

In Japan, a fatal case of sudden death due to heart failure was reported in 2014 in a 41-year-old man taking α-PVP [67]. Toxicological analysis identified other substances, but α-PVP was detected (411 ng/ml) in post-mortem blood samples, as well as in blood samples from the

right and left ventricles and the femoral vein [57]. α-PVP levels were detected at concentrations of 597, 635 and 580 ng/ml in blood from the right and left ventricles and femoral vein, respectively [68]. α-PVP was also detected in urine. There are an increasing number of other cases of α-PVP poisoning. In the United States, 18 deaths were reported in just one county in south Florida [69].

4. Conclusions

The study highlights the significant increase in the use of synthetic cathinones, especially α-PVP, which pose a serious threat to public health due to their high toxicity and potential for addiction. The main difficulty in combating the spread of synthetic cathinones lies in their high adaptability and ability to circumvent existing legal frameworks, which requires increased international cooperation and updated legislative measures.

There is a critical need for more research into the pharmacology and toxicology of synthetic cathinones to better understand their effects in humans and to develop effective treatments and rehabilitation for addictions.

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