

# Veterans' Use of Designer Cathinones and Cannabinoids

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Although not a new phenomenon, the use of designer drugs by veterans is rising, and health care providers need to understand their impact and how to diagnose their use.

**A**lthough the elevated risks and rates of veterans' substance abuse patterns are well documented, little has been written about veterans' use of designer drugs.<sup>1-6</sup> In recent months throughout Europe and the U.S., there has been a flurry of media attention for 2 classes of designer drugs: synthetic cathinones and synthetic cannabinoids.<sup>7,8</sup> In the U.S., the popularity of these drugs has surged, and a disproportionate amount of use of these 2 drug classes is coming from locations near military installations.<sup>9,10</sup>

The purpose of this article is to raise awareness regarding these 2 burgeoning designer drug classes and their impact on veterans. Designer drugs affecting vulnerable populations are not a new phenomenon, yet many providers are unfamiliar with the effects of these unique drugs of abuse on their veteran populations.<sup>11-13</sup>

Many designer drugs begin their existence as variations of other addictive or psychoactive drugs. Others begin in laboratories as investigative research compounds that

end up on the street, often promising a novel mind-altering experience as a "legal high."<sup>14-18</sup> The Designer Drug Enforcement Act of 1986 was an initial attempt in the U.S. to define and control the early rise of copycat drugs that appeared on the streets and mimicked the effects of other illicit substances. More recent legislation enacted in the U.S. has imposed Schedule I controls on the manufacture, distribution, possession, importation, and exportation of these types of drugs, including both synthetic cathinones and synthetic cannabinoids. State laws are perennially in flux trying to keep up with the latest drug trends.<sup>19-21</sup>

Similar efforts have been made by the European Union to control mephedrone, a synthetic cathinone, citing multiple fatalities, seizures, related crime, lack of medical use, and risk of dependence.<sup>22</sup> Although uniform levels of control do not exist in Europe for synthetic cannabinoids, many countries have independently acted to limit their use.<sup>23</sup>

In its recent World Drug Report 2013, the United Nations Office on

Drugs and Crime documents its growing concern about the "new psychoactive substances" category of illicit recreational substances (in which synthetic cannabinoids and cathinones are included) that has increased by 50% since 2009.<sup>24</sup> Alone, this category now outnumbered the total number of substances controlled by international drug conventions.

The novelty and variability of designer drugs causes difficulties with detection and regulation. Innovative chemists can legally manufacture new versions of known molecules intended for illicit use with a rapidity that outpaces bureaucratic control. Local law enforcement officials may be unaware of the latest designer drug trends, stifling efforts at public education or restriction. Designer drugs are often deceptively packaged and are available in convenience stores, tobacco outlets, gas stations, pawnshops, tattoo parlors, and truck stops.<sup>25-28</sup> The Internet may be the singular reason, however, that designer drugs continue to be widely available to veterans.<sup>11,18</sup>

Innumerable websites discuss, promote, and sell designer drugs or deceitfully market them as safe, legitimate household products ("not for human consumption"), which

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can be ordered online and shipped by commercial carriers.<sup>12</sup> Little accurate information is known about their effects or about the specific compounds they contain. When the recreational nature of the drugs is actually acknowledged, information on how the buyer can evade prosecution is often provided in tandem. The suppliers' inventory of the drugs has been shown to be variable and inconsistent, and the product ingredients can be similarly unpredictable despite comparatively more stable naming and labeling.<sup>14,29</sup>

In the clinical setting, a reliable patient drug history may not be available. This ensures that the diagnosis of designer drug use will be an exclusionary process involving routine laboratory work, physical examination, and at times electroencephalogram and/or neuroimaging. Psychiatric consultation is often useful in this setting. Routine immunoassay tests do not detect either synthetic cathinones or synthetic cannabinoids.<sup>30</sup>

Both cannabinoids and cathinones can be identified using gas chromatography-mass spectroscopy (GC-MS) or liquid chromatography-mass spectroscopy (LC-MS). However, this technology is limited to specialized laboratories.<sup>31,32</sup> The laboratory results often are not immediately available, potentially limiting the tests' use in emergency or inpatient settings, as the patient may have left the hospital by the time the results are available. Additionally, these drugs' prevalence of use, while increasing, often does not justify the cost of these tests.

The inability to routinely detect metabolites in urine may increase the enticement of these drugs given the likelihood that active-duty personnel could use them surreptitiously. Further, these compounds

**Table 1. Common Street Names**

<b>Synthetic cathinones</b>	Blue Silk, Charge+, Ivory Snow, Ivory Wave, Ocean Burst, Pure Ivory, Purple Wave, Snow Leopard, Stardust, Vanilla Sky, White Knight, and White Lightening
<b>Synthetic cannabinoids</b>	Spice, Yucatan Fire, Smoke, Sence, ChillX, Highdi's Almdröhner, Earth Impact, Gorillaz, Skunk, Genie, Galaxy Gold, Space Truckin, Solar Flare, Moon Rocks, Blue Lotus, Aroma, Scope, Spice Diamond, XXX, K2, K2-Blond, Black Box, and Smoke 'n' Skulls

are evolving and seemingly limitless in their variability, and there is often a paucity of pure reference materials. As such, it is impossible to guarantee reliable test results.

The following profiles of each of these drug classes will be accompanied by clinical cases depicting the drugs' effects and how an affected veteran might present clinically. The severe effects of these novel agents illustrate the value in maintaining a functional knowledge base about emerging drug trends. The accuracy of diagnosis as well as the outcome of a veteran's treatment may depend on the provider's ability to identify the presence of a drug and manage its effects.

### SYNTHETIC CATHINONES

*Mr. H is a 28-year-old Iraq War veteran with a history of posttraumatic stress disorder (PTSD), alcohol abuse, and opioid dependence who presented for inpatient psychiatric admission after making suicidal statements to his wife in the context of 2 weeks of "bath salts" use. A family member initially introduced him to the drug. His first drug purchase had been 1 gram (\$30) at a local movie rental store.*

*After discharge from the hospital, Mr. H began purchasing increasing amounts online with a credit card. Although he initially had been insufflating and inhaling the substance, he later began injecting it (dissolving it in tap*

*water and loading it through a cotton filter in a syringe). The patient admitted to finding the drug significantly more addictive than any others he had used, and his use resulted in leaving his job and abandoning his family.*

*Severe cravings and depression were present between episodes of use. He spent \$40,000 over 6 months of use. Insomnia lasted for several days, his appearance changed dramatically (including persistent skin infections), and he became paranoid, believing that everyone around him was an undercover police officer. He remained on medications for persistent anxiety. His daily drug cravings continued, although he remained uncertain about the actual ingredients of bath salts.*

Cathinone is a naturally occurring stimulant from the khat plant (*Catha edulis*), which grows indigenously in Egypt and on the Arabian Peninsula. The recreational and religious use of this plant has occurred for thousands of years, though it is not without risk: The chewing of the leaves containing natural cathinones has been associated with esophagitis, gastritis, oral keratosis, myocardial infarction, dilated cardiomyopathy, hypertension, cerebral ischemia, thromboembolism, diabetes, sexual dysfunction, duodenal ulcer, and hepatitis.<sup>33,34</sup>

The stimulants known colloquially as bath salts are synthetic cathinones, which have become

**Table 2. Intoxication and Withdrawal Symptoms**

	<b>Intoxication Symptoms</b>	<b>Withdrawal Symptoms</b>
<b>Synthetic cathinones</b>	Energy increase, mood elevation, empathy, openness, increased libido, diaphoresis, headache, nausea and vomiting, muscle twitching, dizziness, vertigo, short-term memory difficulty, anxiety, hallucinations, delusions, insomnia, nightmares, tremor, tachycardia, paranoia	Intense cravings, dysphoria, depression, anxiety, fatigue, paranoia, restlessness, irritability, insomnia, poor concentration
<b>Synthetic cannabinoids</b>	Disorientation, anxiety, tremulousness, palpitations, tachycardia, agitation, injected conjunctivae, hyperreflexia, nausea, vomiting, nystagmus, myoclonus	Irritability, anxiety, tremor, palpitations, diaphoresis, insomnia, headache, diarrhea, nausea, vomiting

more widely available within the past 10 years: first in the Middle East, then Europe, and now in the U.S.<sup>5,9,10,14,19,25,35-41,44</sup> Although the current rise in use has occurred in the past few years, the first documented abuse of synthetic cathinones in the U.S. dates to the early 1990s in Michigan.<sup>42</sup>

Bath salts is the most common of the many names used to denote synthetic cathinones. The compounds have no utility when used as such but often are marketed as research chemicals, plant fertilizer, or shoe polish. It is this deliberate counterfeit of household product names that allows many distributors to avoid classifying the compounds according to the true, intended use. More appealing brand names may also be used to entice the user (Table 1).<sup>25</sup>

Synthetic cathinones owe their popularity to similarities with cocaine and methamphetamine. They are sympathomimetic with synaptic increases of monoamines after use: Surges in norepinephrine and dopamine account for the stimulant qualities, and serotonergic changes mediate distinct psychoactive effects (Table 2).<sup>40</sup> Users are interested in

the drugs for many of the same reasons that other recreational stimulants have appeal: euphoria, energy, empathy, heightened sexuality, sociability, and an overall intensification of senses. Synthetic cathinones have become preferred to cocaine for some users.<sup>43</sup>

The drugs can be used via oral and anal routes. Using methods known as “bombing” or “keystercing,” users deliver boluses of the powder wrapped in cigarette paper, which they swallow or insert into the rectum. Insufflation and IV injection are also common methods of administration with a quicker onset of action expected.<sup>40</sup> The prices of the drugs range from \$25 to \$50 per 500-mg packet (though the cost is increasing with more regulation). Users typically use 500 mg to 2 g in one session.

The 2 most commonly abused synthetic cathinones are mephedrone and MDPV (methylenedioxypropylvalerone). There is some regional variability about which ingredient is present; mephedrone tends to be more prevalent in Europe, whereas MDPV is noted to be more common in the U.S.<sup>10,44</sup>

When ordering a laboratory test to evaluate for the presence

of these drugs, a specific request should be given to the technicians to look for signals of MDPV (most common metabolite is dimethylenyl-methyl-MDPV), mephedrone (4-methylmethcathinone), 3-bromomethcathinone (3-BMC), or 3-fluoromethcathinone (fluphedrone).<sup>45-48</sup> The study testing (both in VA and civilian settings) for Mr. H was done by a commercial laboratory several states away where patented techniques can screen for more than 30 compounds via LC-MS. The laboratory offered bath salts panels for urine, serum/plasma, and blood samples.

Synthetic cathinones are dangerous, and as the body of medical literature continues to expand, reports of significant morbidity and death related to their use are appearing. The harmful effects of recreational synthetic cathinone use has been documented across the globe in the form of serotonin syndrome, intoxication delirium, hyperthermia and multi-organ failure, myocarditis, hypo-osmotic hyponatremia with encephalopathy, agitation, psychosis, and death after cardiac arrest.<sup>5,12,38,39,49-53</sup> Published treatment methods are largely supportive with

the available literature, suggesting that benzodiazepines, antipsychotics (both typical and atypical), restraints to maintain safety, and IV fluids may be indicated.<sup>5,9,50</sup>

## SYNTHETIC CANNABINOIDS

*Mr. W is a 58-year-old veteran with a history of alcohol dependence and PTSD who reported use of the synthetic cannabinoid "Spice" during intake assessment for treatment of alcohol dependence. He reported using Spice about 4 times over a 2-month period. He purchased a small jar of the substance from a party store for \$15 per gram and understood its contents to be synthetic marijuana, which he appreciated for its low cost and assumed legality. He denied having any understanding of the package's contents beyond "synthetic marijuana."*

*The patient ingested the drug by smoking and inhaling from a pipe. For the first 3 times that he used the substance, Mr. W reported feeling a pleasant sensation that started quickly and lasted about 30 minutes. The fourth time that he used synthetic cannabis he felt nauseated and vomited several times, had auditory hallucinations, and increased anxiety; he also reported a hangover effect after this use. He identified that the effects may have been different the fourth time "because the brands were changing."*

*Mr. W also reported that his neighbor—a daily user of synthetic cannabinoids for several months—became paranoid, suspicious, and developed incomprehensible speech. His neighbor's symptoms and his own unpleasant experiences prompted a discontinuation of use.*

Synthetic cannabinoids are a diverse group of agents numbering in excess of 100 artificial compounds that act as agonists at cannabinoid receptors, mimicking the effects of

tetrahydrocannabinol (THC), an active ingredient in marijuana.<sup>28,54</sup> The availability of these drugs online and in specialty shops has been documented since the mid-2000s.<sup>27,28,32</sup> Their packaging often describes the contents as incense or herbal blends, using various names. Spice is a common name, but these products are also known by a myriad of other designations (Table 1).<sup>28</sup> A single packet usually contains several grams of the drug and costs about \$30.<sup>55</sup>

To the user, who may already be familiar with marijuana, the contents intentionally appear similar to the dried buds of cannabis.<sup>30,56</sup> In reality, the drug has just been sprayed onto inert plant material.<sup>57</sup> The drug is smoked, and the psychoactive dose can be as little as 1 mg.<sup>30</sup> Users describe potent drug effects (Table 2). There is a rapid onset of action, and duration of effects last 1 to 2 hours.<sup>58</sup>

The compounds' mechanism of action and appeal are derived from their high affinity for the cannabinoid receptors. The CB1 receptor is located primarily in the central nervous system and is responsible for the psychoactive component of the drugs' actions.<sup>27,30,58,59</sup> Two particular synthetic cannabinoids, cannibicyclohexanol and JWH-018, are potent cannabinoid CB1 agonists with affinity exceeding their natural counterparts.<sup>27,30, 32,56,58,59</sup>

Chemically, these drugs are varied. The largest structural family of these compounds is the JWH group, which includes JWH-018.<sup>60</sup> Also common are CP 47,497 and other CP compounds.<sup>58</sup> HU compounds, such as HU-210, have also been identified and have been shown to be 100 to 800 times more potent at the CB1 and CB2 receptors than is THC.<sup>60,61</sup> A final group includes

the benzoylindoles, such as AM-964 and RCS-4, which also bind strongly to CB1 and CB2.<sup>60,62</sup>

Constitutional symptoms of synthetic cannabinoid intoxication include disorientation, anxiety, tremulousness, palpitations, tachycardia, agitation, injected conjunctivae, hyperreflexia, nausea, vomiting, lateral gaze nystagmus, and myoclonic jerks, which have been mistaken for seizure activity.<sup>27,30,55</sup> Pupils are often normal sized.<sup>55</sup> Withdrawal phenomena are similar to those of cannabis withdrawal: irritability, anxiety, tremor, palpitations, diaphoresis, insomnia, headache, diarrhea, nausea, and vomiting.<sup>59</sup>

Given the established link between cannabis use and psychosis, synthetic cannabinoids may stand as a precipitant of psychotic symptoms, which may include visual hallucinations, auditory hallucinations, disorganized speech, paranoia, grandiose delusions, disorganization, or bizarre behavior.<sup>58,63-66</sup> These symptoms may represent a relapse of a primary thought disorder or, for some unfortunate individuals, a de novo psychotic illness.<sup>58,65,66</sup> Symptoms can linger for months after drug use.<sup>65</sup>

A key risk in the use of synthetic cannabinoid moieties may involve the absence of cannabidiol. Cannabidiol naturally occurs in many strains of cannabis and is thought to have antipsychotic, neuroprotective properties.<sup>67</sup> The absence of this molecule in synthetic cannabinoids may at least partially explain their severe psychoactive effects. Treatment for synthetic cannabinoid intoxication and related psychosis is largely supportive and may include the use of antipsychotic medication.<sup>66</sup>

Detection of synthetic cannabinoids in urine is difficult, yet many

compounds can be detected via GC-MS or LC-MS. Molecules of significance include JWH-018, JWH-073, JWH-015, JWH-250, CP-47497, HU-210, cannabicyclohexanol, and oleamide; however, these compounds are rarely excreted in urine in their pure form. The many hydroxylated or dealkylated metabolites of these compounds, mostly unnamed, are more consistently detected in urine.<sup>68,69</sup> One author has noted that the pentanoic acid metabolite of JWH-018 seems to appear most reliably in urine specimens.<sup>68</sup>

Many synthetic cannabinoid herbal mixes also contain a detectable compound called tocopherol, seemingly added as an antioxidant.<sup>69,70</sup> Synthetic cannabinoids are an evolving drug class, and reliable detection will require that laboratories stay up-to-date in their detection methods. As stated earlier, a commercial laboratory in the region accepted the civilian and veteran patient samples for these case studies. The synthetic cannabinoid panels offered evaluation of the drug itself (GC-MS), an oral fluid screen (LC-MS), and isolation of metabolites in urine (enzyme-linked immunosorbent assay).

## CONCLUSION

Designer drugs will remain a challenge for providers caring for veterans for several key reasons: (1) Veterans are a vulnerable population who abuse substances at higher rates than do their civilian counterparts; (2) Chemists are able to manufacture variations of known habit-forming substances; (3) Modern technology facilitates the purchase and wide distribution of addictive substances; (4) Many designer drugs are deceptively packaged and marketed; (5) The effects of the drugs are often severe; (6) No standardized treatment guidelines exist; and (7) Detection of the drugs

is difficult, and new versions of the molecules may evade even cutting-edge techniques.

Due to the high cost of detecting synthetic cathinones and synthetic cannabinoids in body fluids, screening should be considered only in settings where severe symptoms are accompanied by reasonable clinical suspicion of use and an otherwise negative toxicologic workup. As more designer drugs inevitably emerge, research will be needed on their pharmacology, toxidromes, and detection. Military and civilian practitioners must remain abreast of the dynamic trends in designer drugs to ensure that their patients receive the highest level of medical care. ●

### Author disclosures

*The authors report no actual or potential conflicts of interest with regard to this article.*

### Disclaimer

*The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, Frontline Medical Communications Inc., the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

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