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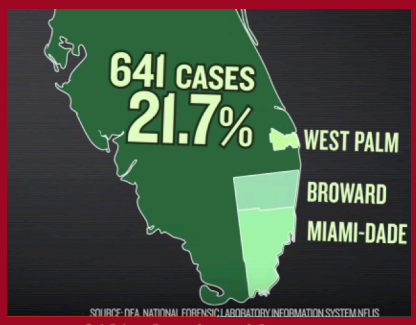
EM CASE OF THE WEEK

BROWARD HEALTH MEDICAL CENTER DEPARTMENT OF EMERGENCY MEDICINE



21% of nationwide cases
https://www.youtube.com/watch?v=12Tcq-i3oAE

Broward Health Medical Center is a veritable ground zero for patients with Flakka (alpha PVP) abuse. While the literature on Flakka intoxication is limited, it is important to recognize the Excited Delirium Syndrome that can result and to be ready to manage these challenging cases. This month we explore the facts about Flakka (alpha PVP), a cathinone amphetamine.

EM CASE OF THE WEEK

EM Case of the Month is a weekly "pop quiz" for ED staff. The goal is to educate all ED personnel by sharing common pearls and pitfalls involving the care of ED patients. We intend on providing better patient care through better education for our nurses and staff.

The Flakka Epidemic

A 35 year old Caucasian male is brought in to the Broward Health Medical Center Emergency Department by Emergency Medical Services after being found rolling on the ground in downtown Ft. Lauderdale with what appears to be an acutely psychotic state. He is shirtless, covered in dirt and presents agitated, thrashing violently and screaming threats at the medical staff. He has been physically restrained to the bed and continues to struggle against restraints. His vital signs are T 102.1, HR 125 and regular, RR 25, BP 130/84, O2 sat 94% on room air. His pupils are dilated, his skin is warm and he is diaphoretic. The patient insists that he be let go, remaining preoccupied with the FBI trying to apprehend him. Urine toxicology screen, EKG, electrolytes and comprehensive metabolic panel have been ordered. What is the next best step in management?

A. Administer haloperidol as the psychotic patient is at risk to harm himself and others

B. Administer benzodiazepines to decrease his risk for sudden death or seizures

C. Allow the patient to sign out AMA

D. Administer beta blockers as his heart rate is elevated and may be having an arrhythmia or MI

E. Administer bicarbonate to decrease his risk for long QT interval

BROWARD HEALTH MEDICAL CENTER

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Take Home Points

- Alpha PVP, otherwise known as Flakka or Gravel is a synthetically altered cathinone amphetamine in the same class as MDPV i.e. the "Bath Salts".
- Common complications include the sympathomimetic toxidrome with agitation, combative behavior, tachycardia, hallucinations, paranoia, confusion, chest pain, myoclonus, hypertension, mydriasis, CPK elevations, hypokalemia, and blurred vision.
- Risks include bizarre behavior at high doses, trauma, Excited Delirium Syndrome and sudden death, renal failure and electrolyte abnormalities.
- There is no commercially available laboratory assay for alpha PVP and clinical suspicion must be high.
- There is currently no antidote or reversal agent for alpha PVP. The recommended clinical approach is to treat as an amphetamine overdose with supportive care including IV fluid resuscitation, benzodiazepines, and/or antipsychotic therapy (Haldol or Geodon).

Flakka: Alpha PVP Cathinone Amphetamines

The correct answer is B.

The patient presents with the **sympathomimetic toxidrome of hypertension, tachycardia, tachypnea, fever, mydriasis, active bowel sounds and diaphoresis.** Furthermore, he appears to be in **Excited Delirium Syndrome**, likely from alpha PVP; alpha PVP is a cathinone amphetamine colloquially referred to in South Florida as "Flakka." In 2012, an American College of Emergency Physicians Task Force published their consensus regarding the existence of Excited Delirium Syndrome as its own diagnostic entity, characterized by **delirium, agitation, acidosis and hyperadrenergic autonomic dysfunction, typically in the setting of acute on chronic drug abuse** or serious mental illness or a combination of both (1). Excited Delirium is most often due to sympathomimetic toxicity from cocaine or amphetamines, such as alpha-PVP. It presents most commonly in patients with history of mental illness, a struggle with law enforcement and physical or noxious chemical control measures. Excited delirium presents a well-documented risk of a small percent of patients **progressing to cardiopulmonary arrest** and death in which autopsy fails to reveal a definite cause of death from trauma or natural cause. **Recommended treatment is through chemical and physical restraints**. The risk of administering haloperidol to a patient with unknown psychiatric medication history places him at risk for acute dystonia and neuroleptic malignant syndrome. Benzodiazepines do not present such a risk and are the safer first choice. Leaving AMA is not recommended as the patient is acutely delirious. His sinus tachycardia is likely part of the toxidrome and should be managed by treating the underlying cause, not by beta blockade. While bicarbonate may narrow a widened QRS from amphetamine abuse, it does not manage the toxidrome as do benzodiazepines.

Discussion:

Over the past half-decade, the use of α-Pyrrolidinovalerophenone (α-PVP), aka "Flakka," or "Gravel," has increased worldwide, with Broward County in South Florida as one of the most severely affected. Alpha-PVP is an amphetamine "designer street drug"

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of the cathinone class, usually found in the form of white powder or small candy-like objects supplied in small plastic containers or in Ziploc bags (2). Users generally snort, inject smoke, or orally consume synthetic cathinones. **Its low cost makes it readily available and available at high quantities, predisposing to abuse and toxicity.** It is often **combined with other stimulants** such illicit amphetamines, piperazines, cutting/binding agents, caffeine and topical anesthetics, **making its clinical presentation unpredictable as well as difficult to identify** (3). **The desired effects of cathinones by users include increased energy, alertness, focused mind and overall positive feeling, euphoria, empathy, openness, talkativeness, and increased libido/sexual arousal. Effects reportedly occur within 30-45 minutes, lasting several minutes to several hours while undesirable side effects persist from hours to days** (2, 4). Currently, Alpha PVP is a schedule 1 drug as designated by the DEA (5). As such, Alpha PVP presents as a challenge in the emergency department setting as patients are often reported by ER staff as violent and uncontrollable with paranoia and delusions, and patients frequently attack first responders (2). Due to the frequency of patients entering the BHMC ED, we will discuss the facts about the Alpha PVP ("flakka") epidemic.

Pathopharmacology

Alpha PVP, along with its structural analog "Bath Salts" (MDPV) is a synthetic cathinone amphetamine; cathinones are beta ketone amphetamines derived from the khat plant *Catha edulis* which has been used as a recreational stimulant for millennia in eastern Africa, the Arabian Peninsula and the Indian Subcontinent (4). Both alpha PVP and MDVP (Flakka and Bath Salts) are synthetic stimulants that **function as selective dopamine and norepinephrine reuptake inhibitors with weaker effects on serotonin reuptake.** **Both are more potent than cocaine and amphetamines as a dopamine reuptake inhibitors and norepinephrine reuptake inhibitors**, with Alpha PVP second only to MDVP in magnitude of effect (3, 6-10). Pharmacologic studies suggest that their greater dopaminergic effect is responsible for their **more profound psychomotor symptoms than those of methamphetamine or cocaine** (6-9). The cathinones' more rapid onset shorter acting pharmacokinetic profile along with the aforementioned dopaminergic effects suggest their increased risk for abuse and addiction (3, 6, 7, 9, 11, 12).

Clinical Presentation

The clinical presentation of cathinone amphetamines as a class is now well documented both in medical literature and in the media as similar to an amphetamine sympathomimetic toxidrome. Patients present with typical stimulant effects at lower doses most **commonly manifesting as agitation, combative behavior, tachycardia, hallucinations, paranoia**, **confusion, chest pain, myoclonus, hypertension, mydriasis, CPK elevations, hypokalemia, and blurred vision** (2, 4, 13, 17). Some drugs **produce bizarre behaviors at higher doses** (4, 6). In the cases of alpha PVP toxicity, these behaviors have been well documented on local newsreels and YouTube videos. Some cases have been noted from Ohio where patients attempted swimming in a snow bank to get away from snipers, believing people hide in walls, breaking into a home to decorate it with Christmas decorations and subsequently sitting down to watch TV (2). Sadly, severe morbidity and fatalities have been reported as a result of Excited Delirium Syndrome causing sudden cardiac death, renal failure and electrolyte abnormalities, (14,15).

Table 2 User reported clinical effects of synthetic cathinones [17, 25, 28, 30, 62]

Cardiovascular	Palpitations, shortness of breath, chest pain
ENT	Dry mouth, epistaxis, nasal pain, "nose burns", oropharyngeal pain, tinnitus
Gastrointestinal	Abdominal pain, anorexia, nausea, vomiting
Genitourinary	Anorgasmia, erectile dysfunction, increased libido
Musculoskeletal	Arthralgias, extremity changes—coldness, discoloration, numbness, tingling, muscular tension and cramping
Neurologic	Aggressiveness, bruxism, dizziness, headache, lightheadness, memory loss, tremor, seizures
Ophthalmologic	Blurred vision, mydriasis, nystagmus
Pulmonary	Shortness of breath
Psychological	Anger, anxiety, auditory and visual hallucinations, depression, dysphoria, empathy, euphoria, fatigue, formication, increased energy, increased and decreased concentration, loquaciousness, panic, paranoia, perceptual distortions, restlessness
Other	Body odor "mephedrone stink", diaphoresis, fever, insomnia, nightmares, skin rash

These are self-reported symptoms by users of synthetic cathinones. It is possible that these effects are not all related to cathinone use as many users take these substances simultaneously with other drugs and ethanol. Additionally due to lack of reliability and consistency of products, users may not be aware of what drug they have actually taken. Please see text for more information

Table 4 Medical provider (including emergency department and poison center data) reported effects associated with use of synthetic cathinones [1, 13, 30, 35, 38, 70–72]

Cardiovascular	Chest pain, hypertension, palpitations, myocarditis, tachycardia
ENT	Epistaxis, oral and pharyngeal effects, tongue disorder
Gastrointestinal	Abdominal pain, abnormal liver function tests, nausea, liver failure
Musculoskeletal	Elevated creatinine kinase, peripheral vasoconstriction, rhabdomyolysis
Neurologic	Agitation, aggression, altered mental status, collapse, confusion, dizziness, drowsiness, dystonia, headache, hyperreflexia, myoclonus, paraesthesias, seizures, tremor
Ophthalmologic	Abnormal vision, mydriasis
Pulmonary	Shortness of breath, tachypnea
Psychological	Anxiety, confusion, delusions, hallucinations, paranoia, psychosis
Renal	Abnormal renal function, acute renal failure
Other	Diaphoresis, fever, hyponatremia, rash

It is possible that these effects are not all related to cathinone use as many users take these substance simultaneously with other drugs and ethanol. Additionally due to lack of reliability and consistency of products, users may not be aware of what drug they have actually taken. Please see text for more information

Prosser J, Nelson L (2012) The toxicology of bath salts: a review of synthetic cathinones. J Med Toxicol 8:33–42

Diagnosis: The diagnosis of alpha PVP intoxication is **clinical and one of exclusion, with a high index of clinical suspicion for patients presenting with sympathomimetic toxidrome or Excited Delirium Syndrome**. At the current time, alpha PVP is not detectable by routine tox screens in urine or blood, which adds to its popularity. Gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry have discovered up to six metabolites of alpha PVP although they are unreliable and have limited clinical utility; further studies are warranted (16, 17).

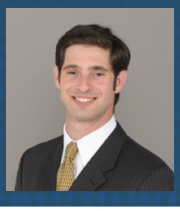
Management:

Routine laboratory evaluation of the poisoned patient is indicated in all cases. In cases of significant toxicity, which should be suspected in all patents with Excited Delirium, testing should focus on the common complications of Excited Delirium Syndrome. As stated previously, these complications include sudden cardiac death, renal failure, electrolyte abnormalities, hemodynamic instability and hyperthermia (14, 15). Management of these complications is the focus of acute management. (20)

- EKG and cardiac monitoring to assess for cardiac dysrhythmias.
- Basic serum electrolytes; If hyponatremia is present, a serum osmolality is recommended
- Creatinine kinase and urine myoglobin, to evaluate for rhabdomyolysis
- Serum creatinine, to assess for renal injury
- Serum aminotransferase concentrations, to assess for hepatic injury
- Coagulation studies (ie, aPTT, PT, INR, platelet count, d-dimer), to assess for disseminated intravascular coagulation.

Treatment: Unfortunately, there is no antidote or reversal agent for cathinone amphetamine intoxication. Recommended treatment is supportive as in an amphetamine overdose: **benzodiazepines are best for agitation and seizures to counteract excessive catecholamine release and reuptake inhibition**; Treat hyperthermia with aggressive cooling; Treat hyponatremia with water restriction or hypertonic saline as for MDMA, although further research is needed (4). The most common treatments include benzodiazopenes (diazepam, lorazepam, midazolam), antipsychotics (Haldol, ziprasidone) propafol, diphenhydramine (13).

Disposition: There are no published guidelines on how long these patients need to be observed. Many suggest following the recommendations for amphetamine overdose or MDMA overdose. Patients can be discharged if hemodynamically and psychiatrically stable.



ABOUT THE AUTHOR:
This month's case was written by Sam Kohrman. Sam is a 4th year medical student from FIU HWCOM. He did his emergency medicine rotation at BHMC in September of 2015. Sam plans on pursuing a career in Psychiatry after graduation.

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