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The emerging threat of synthetic cannabinoids

By Jeffrey Phillips, BS, RN; Fidelindo Lim, DNP, CCRN; and Richard Hsu, BS

Globally, the use and abuse of synthetic cannabinoids increased alarmingly in the last few years.[1] Synthetic cannabinoids are drugs that possess some of the properties of delta-9-tetrahydrocannabinol (THC), the main psychoactive constituent of natural marijuana.[2]

In the 1980s, chemistry professor John Huffman developed a synthetic cannabinoid, known as JWH-018.[3] The original intent was to enhance understanding of the cannabinoid system. In what experts now call a classic case of research "hijacking," synthetic cannabinoids have been developed by unscrupulous manufacturers into a potent and potentially lethal drug of abuse sold under many names, including spice, K2, fake weed, Yucatan fire, skunk, moon rocks, black mamba, and crazy clown.[2] When consumed (smoked or ingested), these products elicit psychoactive effects similar to those of marijuana.[4] We provide an overview of this emerging public health threat, illustrated by a case report.

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From lab to consumer

The active ingredient in synthetic cannabinoids is a lab-produced liquid that's sprayed over dried plant matter to provide a natural appearance and aesthetic similar to that of natural marijuana.[5] The plant matter itself can potentially be poisonous or hallucinogenic, creating an enhanced or more dangerous product.[1] Often packaged into small, attractive colored bags, the product is sold in drug paraphernalia shops, novelty stores, gas stations, bodegas (small corner grocery stores), and through the Internet.[4] Based on the latest data from the CDC, inhalation by smoking is the most common means of consumption (about 80%), followed by ingestion (20%) by eating or drinking the product in the form of a cookie or brewed as tea.[6] Rectal absorption has been reported in the literature as well.[5] (See *The rise of synthetic cannabinoids*.)

Unbeknownst to the consumer, many of these products are laced with substances ranging from simple flavors to more dangerous components, including other drugs, rat poison, and even embalming fluids.[7] Such was possibly the case with Mr. G.

Mr. G, 53, was brought to the ED by emergency medical services after bystanders observed him walk into traffic and harass pedestrians. Arrival vital signs were stable: heart rate, 103 beats per minute (bpm); BP, 118/74 mm Hg; Spo_2, 100% on room air; respiratory rate, 20 breaths per minute; and a temporal temperature of 98.2˚ F (36.8˚ C). Mr. G was alert and oriented to person, place, and time, but refused to answer questions about the events preceding his arrival. In triage, he denied any significant health history or use of prescription medications. However, he did report smoking an unknown quantity of "K2," a common name for synthetic cannabinoids, earlier in the day.

Mr. G was verbally abusive to staff immediately upon his arrival. In a loud voice, he claimed he felt fine and demanded release. Due to the patient's inability to participate in an interview and discuss risks of his departure from the ED, the ED physician deemed Mr. G to be lacking decision-making capacity, making discharge from the ED unsafe.

Pathophysiologic effects

Cannabicyclohexanol, one of the many known types of synthetic cannabinoid, is approximately five times more potent than THC, natural marijuana's main psychoactive component.[8] Because synthetic cannabinoids may be misleadingly labeled and marketed as "safe" and "natural," users like Mr. G may be falsely reassured about their safety and underestimate the dangers.

Like THC, cannabicyclohexanol, acts as an agonist of cannabinoid receptors—mostly CB1 receptors, which cause the psychoactive effects.[7] CB1 receptors are present in the central nervous system, but both CB1 and CB2 receptors are found in certain peripheral tissues.[8]

CB1 activation decreases the activity of cyclic adenosine monophosphate, which in turn inhibits neurotransmitters, such as acetylcholine, dopamine, norepinephrine, glutamine, and gamma-aminobutyric acid, which explains some common psychoactive adverse reactions such as agitation.[9] (See *Clinical manifestations of synthetic cannabinoid use*.) Synthetic cannabinoids have a stronger affinity for cannabinoid receptors than natural marijuana.[2]

Full and potent CB1 agonist

Seven major structural groups of synthetic cannabinoids have been identified, including naphthoylindoles such as JWH-018, a cannabimimetic aminoalkylindole.[10] In vitro studies have demonstrated that although THC acts as a partial agonist on the CB1 receptor, JWH-018

The rise of synthetic cannabinoids

In April 2015, the National Poison Data System reported to the CDC an alarming 330% increase in adverse reactions to synthetic cannabinoids over a 3-month period.[6] Nationwide, cases reported to the American Association of Poison Control Centers peaked in April 2015, with 3,572 calls related to synthetic cannabinoids, a 229% increase from the same period in 2014.[29] Experts are unsure about the reasons for this exponential increase in use.

Males comprised 80% (2,882) of reported cases, with a median age of 26 years old (range, 7 months to 72 years old).[6] Among 12th graders, twice as many males reported use of "synthetic marijuana" as females in the same age group.[4]

For reasons not fully understood, reported cases have gone back to 2014 levels since May 2015. This decrease is likely explained by a decline in reporting rather than a drop in actual use.[29]

New York and Alabama by far outpaced the rest of the states in most reported cases.[29] Since 2015, over 6,000 synthetic cannabinoid-related ED visits have been reported in New York City, with 2,300 cases in July and August alone.[27]

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acts as a full and potent CB1 agonist. Compared with THC, JWH-018 possesses a fourfold higher affinity for the CB1 receptor and 10-fold higher affinity for the CB2 receptor, accounting for the higher prevalence of adverse reactions and toxicity.[3]

Rearchers have provided a comprehensive list of facts about synthetic cannabinoids.[7] They emphasize that synthetic cannabinoids shouldn't be confused with marijuana or the legal synthetic cannabinoid receptor agonists such as dronabinol, an appetite stimulator for patients with AIDS and an antiemetic for patients with chemotherapy-related nausea and vomiting, or nabilone, an antiemetic for oncology patients who haven't responded to conventional antiemetics.[11-12]

Potentially serious adverse reactions

Research related to clinical presentation is largely powered by case reports. A 4,000-case systematic review of 106 synthetic cannabinoid studies revealed major complications, such as myocardial infarction, ischemic stroke, acute kidney injury (AKI), generalized tonic-clonic seizures, and cannabinoid-induced hyperemesis syndrome.[1] Among all etiologies, 26 deaths were reported; however, most patients required only supportive care for less than 8 hours to manage signs and symptoms, including, but not limited to, tachycardia, agitation, and nausea.[1] Users may experience subjective intoxication and conjunctival erythema in addition to psychiatric manifestations, such as first-episode psychosis, paranoia, aggressive behavior, and self-harm or suicidal ideation.[1,2] Some patients may transition between a depressed mental state and seemingly unprovoked aggressive behavior in seconds.[13]

In 3,572 calls to poison centers nationwide from January to April 2015, the most commonly reported adverse reactions were agitation (35%), tachycardia (29%), drowsiness or lethargy (26%), and vomiting (16%).[6] Individuals over age 30 were more likely than those ages 10 to 19 to report a severe outcome. For reported incidences with known medical outcomes, only 0.5% of cases resulted in death; patients in 11% of cases suffered life-threatening signs and symptoms that resulted in residual disfigurement or disability.[6] Reports of serious exposure to synthetic cannabinoids (35 patients in a 2-month period) identified delirium and seizures in 24 and 14 cases respectively, with 5 patients requiring mechanical ventilation and admission to the ICU.[14]

Cardiovascular effects

Case reports indicate that synthetic cannabinoid poisoning can cause cardiovascular complications, notably prolongation of the QTc interval.[15] Drug-induced delayed ventricular repolarization resulting from potassium channel blockade may lead to a lethal dysrhythmia, such as torsades de pointes (TdP), a form of polymorphic ventricular tachycardia that occurs in the setting of QTc prolongation.[16] Monitoring for TdP is warranted, especially when the patient is also taking medications that are known to prolong the QTc interval, including some antiemetics such as ondansetron, benzodiazepines, and first-generation antipsychotics such as haloperidol—drugs that may be prescribed for relief of physical and psychiatric manifestations of synthetic cannabinoid poisoning.

Pathophysiologic explanations for all adverse reactions are unclear. In two cases of acute ischemic stroke, magnetic resonance

Leading users include high school and college students, and those who may have psychosocial, mental health, and physical comorbidities.

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imaging revealed an infarction without a definite cause; another patient's computed tomography (CT) scan showed a likely embolic infarction, but the patient had no identified thromboembolic risk factors.[17]

Rhabdomyolysis and AKI in a single case have been reported.[18] However, in a 2013 report of 16 cases of AKI, tubular necrosis was identified on biopsy with no pigmented deposits or urine myoglobin found, suggesting rhabdomyolysis wasn't the primary cause of the AKI. Ultimately, the etiology of the AKI is unclear, but a direct toxic effect of synthetic cannabinoids or its contaminants has been proposed.[19]

Caring for Mr. G

In Mr. G's case, clinicians couldn't objectively confirm that a synthetic cannabinoid was the cause of his altered behavior. His treatment would be empiric, based on his history, presenting signs and symptoms, and ruling out use of other drugs via urine and blood testing.

Because synthetic cannabinoid use is associated with a wide variety of presentations, Mr. G was placed on continuous cardiac monitoring and assessed frequently. Initially, the cardiac monitor revealed sinus tachycardia at 110 to 120 bpm. Other vital signs remained within normal parameters. However, Mr. G repeatedly tore off his cardiac monitor electrodes, so accurate monitoring was a challenge.

Mr. G's continued refusal to cooperate with ED staff, escalating agitation, and attempts to leave the ED despite being deemed to lack the decision-making capacity to do so safely, resulted in the need for chemical sedation to protect his own safety and that of the staff. He was given an I.M. injection of haloperidol and lorazepam, and placed in 2-point physical restraints. He continued to attempt physical assault on staff before being subdued by hospital security. Only after these interventions, as Mr. G calmed down, could any testing be performed.

Peripheral venous access was obtained and blood specimens were collected for complete blood cell count, basic metabolic profile, and ethanol levels. An ECG revealed a normal sinus rhythm of 94 bpm and a normal QTc measurement. A urine specimen was also sent to the lab for a toxicology panel.

Two hours after his arrival, Mr. G's heart rate decreased to 30 to 40 bpm (sinus bradycardia), with a QTc interval within normal range. BP, Spo2, and temperature remained within normal parameters. All previously collected lab test results were within normal limits and the drugs-of-abuse urine (DAU) screen was negative for toxicology.

Mr. G remained lethargic but arousable to verbal stimuli, consistent with his level of consciousness before the appearance of bradycardia. Transcutaneous pacing pads were applied as a precaution.

After an additional 8 hours of observation, Mr. G's heart rate increased to 50 to 55 bpm (sinus bradycardia) and remained in this range for over 3 hours. Now alert and oriented to person, place, and time; calm and cooperative; ambulatory with steady gait; and with a normal cardiovascular exam, Mr. G was deemed to have recovered his decision-making capacity. He was discharged from the ED after a total of 15 hours. At discharge, Mr. G was encouraged to seek treatment at a local substance abuse program and told to return to the ED for concerning symptoms, such as palpitations, chest pain, or trouble breathing. However, he left the ED without waiting to see an in-house social worker.

Diagnostic and legal challenges

As Mr. G's case illustrates, the lack of readily available drug testing for synthetic cannabinoids complicates assessment and treatment. Standard rapid urine toxicology screens aren't designed to detect synthetic cannabinoids.[20] Although drug tests do exist for some synthetic cannabinoid compounds, the frequency at which new compounds are made available to users, and the extended time needed for results to materialize compared with traditional DAU screens, limit the testing resources available to clinicians.

Clinical manifestations of synthetic cannabinoid use[31-34]

The most common adverse reactions associated with synthetic cannabinoid use are tachycardia, agitation, and vomiting. These and other mild-to-moderate signs and symptoms, which may include slurred speech and nystagmus, usually resolve in about 8 hours. Signs and symptoms of more serious, potentially life-threatening toxicity from synthetic cannabinoids have also been reported, including:

- central nervous system disorders, such as coma, stroke, toxic psychosis, seizures, delirium, and hallucinations
- cardiovascular disorders, such as myocardial ischemia or infarction
- hyperemesis
- rhabdomyolysis
- AKI.

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Research is ongoing

Published synthetic cannabinoid research has greatly increased since 2010. Most publications and research on THC poisoning are coming out of ED and poison center surveillance reports. EDs focus on illnesses requiring emergent treatment. Therefore, as long as EDs are the epicenter of research, effects of chronic synthetic cannabinoid use are unlikely to be addressed and remain an area of future research.[2]

Marijuana-related morbidity and mortality surveillance can be useful in tracking yet unknown long-term consequences of synthetic cannabinoid consumption.[30] The development of highly sensitive and specific blood or urine testing for the many derivatives of synthetic cannabinoids will enhance early diagnosis and targeted treatments.[3]

A sociological, epidemiologic, and economic analysis should be made of the relationship between synthetic cannabinoid use and natural marijuana use.[2] Nearly all users of synthetic cannabinoids report previously using natural marijuana and often use the synthetic form concurrently with other drugs.[5] But as natural marijuana legalization becomes more common, a closer evaluation of their relationship may provide useful information in understanding the dynamics of substance abuse. Another important area of research is to assess knowledge and practice gaps among nurses and other direct care providers of patients experiencing synthetic cannabinoid poisoning.

If a synthetic cannabinoid is the only agent a patient has ingested, then urine will test negative for all other drugs, including natural THC. Those who've used a synthetic cannabinoid won't test positive on a blood or urine test for natural THC. This crucial difference has made synthetic cannabinoids a popular drug of abuse among substance users who wish to avoid a positive drug test.[21]

Although Mr. G had reported using only synthetic cannabinoids, coingestion of other psychoactive substances remained a possibility. Urine testing was performed for common drugs of abuse, such as cocaine, methadone and other opioids, phencyclidine, and benzodiazepines, but results were negative.

Unlike cocaine, a molecule of an active ingredient in synthetic cannabinoids is capable of existing in many different structural forms. Specific compounds found in synthetic cannabinoids have been placed under Schedule I by the FDA, making these products illegal to sell, buy, or possess throughout the United States.[7] However, new compounds created by clandestine manufacturers pose an ongoing challenge for law enforcement.[2] The FDA action covers only a small number of chemicals, leaving manufacturers legal room to sell similar chemicals in their place, often disguising the product as "incense" or "plant food," or stating that the product isn't for human consumption.[4]

As of 2012, the FDA had identified 158 synthetic cannabinoid substances.[22] As fast as common synthetic cannabinoids are banned, however, producers create different versions and stay a step ahead of legislators who seek to protect the unsuspecting public.

Nursing care and collaborative management

No antidote is available for synthetic cannabinoid poisoning and specific practice guidelines have yet to be developed for patients experiencing synthetic cannabinoid poisoning.[1] (See *Research is ongoing*.) Acute management is extrapolated from emergency medicine. Although patient care is focused on emergency care and symptom management, nurses must remember the benefits of a holistic care approach.

As in most emergencies, follow the ABCs (airway, breathing, and circulation) in assessment and intervention. General guidelines for patient management include:

- maintaining and supporting the airway
- providing supplemental oxygen as needed
- frequently monitoring vital signs and cardiac rhythm
- maintaining venous access
- monitoring blood urea nitrogen and serum creatinine levels
- providing supplemental fluids or electrolytes as needed
- monitoring intake and output
- maintaining safety for the patient, visitors, and staff.

Given the absence of an antidote for synthetic cannabinoid poisoning, care priorities include maintaining patient safety and hemodynamic stability, establishing venous access, and developing prompt differential diagnoses. Because some substance users also have medical, surgical, and psychiatric comorbidities, the presenting complaint will guide clinicians as they set priorities of care. For example, chest pain or hemiparesis will trigger activation of established clinical protocols for acute coronary syndromes or stroke. If the patient sustained a fall before arrival in the ED, head CT and relevant cardiology or neurology evaluation may be warranted. If

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the patient is at risk for seizures, initiate seizure precautions. Intoxication-like signs and symptoms such as nausea, vomiting, weakness, tachycardia, hypertension, and agitation may resolve without treatment.[4,23] Clinicians need to be aware of whether synthetic cannabinoid testing is available on site and send specimens to the lab along with a standard toxicology panel.

In a busy unit such as the ED, the nurse should also take into consideration the safety of the staff, visitors, and other patients. As was the case with Mr. G, a progressively agitated or potentially violent patient may require chemical and/or physical restraints. If physical or chemical restraints or seclusion is initiated, follow evidence-based monitoring protocols according to facility policy and procedure.

In the event of significant behavioral disturbances, such as psychosis, violence, or self-harm, benzodiazepines are generally considered to be safe and effective.[1] However, atypical antipsychotics, such as quetiapine and olanzapine, have been anecdotally shown to be more beneficial than benzodiazepines.[7]

An important consideration in the pharmacologic management of synthetic cannabinoid poisoning is that first-generation antipsychotics, such as haloperidol, can decrease the seizure threshold.[24] Additionally, the use of antipsychotic drugs in the context of synthetic cannabinoid poisoning requires close monitoring for ECG changes such as QTc prolongation and dysrhythmias.[15] Continuous cardiac monitoring should be instituted and a baseline ECG should be obtained before drug administration whenever possible. If QTc prolongation is identified, avoid other drugs that may cause it and closely monitor serial serum electrolyte levels. Electrolyte disturbances (particularly hypokalemia and hypomagnesemia) increase the risk of acquired QTc prolongation and TdP because ratio disturbances disrupt the ion pump channels critical to cardiac function.[16]

If benzodiazepine administration is the treatment of choice for managing psychotic symptoms, the potential for respiratory depression and hypotension calls for close monitoring of the patient's respiratory status and BP.

Because not all chemicals in synthetic cannabinoid products are known, withdrawal potential can be unpredictable.[7] Monitor physiologic changes in the patient's clinical status closely and seek expert consultation as needed. Nurses are encouraged to have an active role in developing interdisciplinary practice guidelines, facilitating quality improvement through practice councils, and presenting case reports in grand rounds.

Public health initiatives: Education and policy

Synthetic cannabinoid use is an emerging public health threat. As of 2011, every state has banned synthetic cannabinoids.[25] The Synthetic Drug Abuse Prevention Act of 2012 bans synthetic cannabinoid analogs.[26] A sweeping law prohibiting the sale, possession, offer to sell, or manufacture of any synthetic cannabinoid substances has been passed in New York as of 2012 and an additional two compounds were added to the banned substances list by Governor Cuomo as recently as 2015.[27,28] New York has been the state with the most synthetic cannabinoid exposures reported to the American Association of Poison Control Centers over the last 2 years.[29] Wherever they practice, nurses are encouraged to stay informed about local, state, and federal laws related to synthetic cannabinoids.

The healthcare community needs to prepare itself for what's already a significant threat to patients' health. Recent outbreaks suggest a need for greater public health surveillance and community awareness, targeted public health messaging, and enhanced efforts to remove these products from the market.[6,27] Those in the community who identify someone who's used synthetic cannabinoids should refer the user for immediate evaluation or call 911 if indicated, particularly if the user manifests violent psychotic behaviors, hyperthermia, chest pain, palpitations, stroke-like signs, seizures, abnormal breathing, or loss of consciousness.[7]

Primary prevention must be the focus of public health education of populations at risk.[6] Dissemination of evidence-based information regarding synthetic cannabinoids can be downloaded from federal and local health agencies. (See *Sources of information about synthetic cannabinoids*.) Educational materials, such as posters and brochures, must be made prominently visible in areas where healthcare recipients congregate; for example, the waiting room of healthcare providers' offices,

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Sources of information about synthetic cannabinoids

- **American Association of Poison Control Centers**
  www.aapcc.org/
- **CDC**
  www.cdc.gov/media/releases/2015/a0611-cannabinoid-use.html/
- **Gateway Foundation**
  http://recovergateway.org/substance-abuse-resources/facts/synthetic-drugs/synthetic-marijuana-k2/
- **National Council on Alcoholism and Drug Dependence**
  https://ncadd.org/
- **National Institute on Drug Abuse**
  www.drugabuse.gov/publications/drugfacts/synthetic-cannabinoids
- **New York City Department of Health and Mental Hygiene**
  www1.nyc.gov/assets/doh/downloads/pdf/ah/synthetic-cannabinoids-7-14-16.pdf/
- **Office of National Drug Control Policy**
  http://abovetheinfluence.com/
- **Substance Abuse and Mental Health Services Administration**
  www.samhsa.gov/

EDs, hospital visitors' lounges, pharmacies, school clinics, and sports venues.

A key topic in public education is making the distinction between synthetic cannabinoids and natural marijuana, emphasizing that the latter is being increasingly recognized for its medical uses. ED nurses, school nurses, and primary care providers should educate themselves about local epidemiologic trends in the communities they serve, as well as best practices in screening and motivational interviewing. An interdisciplinary public health effort that combines expertise from healthcare experts, law enforcement, policy makers, and public advocates is called for.

Concerted efforts needed

Synthetic cannabinoids pose a multitude of potential complications for vulnerable individuals. Leading users include high school and college students, and those who may have psychosocial, mental health, and physical comorbidities. A multidisciplinary effort to combat the growing use of synthetic cannabinoids is warranted. NM

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In New York, N.Y., Jeffrey Phillips is an RN in the ED at NewYork-Presbyterian Hospital/Weill-Cornell Medical Center and the assistant director of the ED nurse residency program, Fidelindo Lim is faculty at New York University College of Nursing, and Richard Hsu is a graduate of New York University's global public health program.

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