



Top 10 Facts You Need to Know About Synthetic Cannabinoids: Not So Nice Spice

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ABSTRACT

In April and May 2015, the state of Mississippi experienced an unprecedented outbreak of severe reactions to the drug commonly referred to as “Spice.” After numerous calls to the Poison Control Center, it became clear that health care providers were largely unfamiliar with the category of synthetic cannabinoids. This review article briefly highlights cannabinoid effects, chemical characteristics, and treatment for this often-dangerous category of drugs of abuse.

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Recent outbreaks of synthetic cannabinoid-related emergency department visits across the country have been in the news lately. Between April 1 and May 31, 2015, Mississippi reported 1243 emergency department visits due to adverse events from synthetic cannabinoids,¹ with 10% requiring intensive care unit (ICU) admission, 11% non-ICU admission, and 17 potentially related deaths.¹ The US experienced a 229% increase in poisonings attributable to synthetic cannabinoids from January to May 2015 when compared with the same time period in 2014²; Mississippi accounted for a remarkable 35% of all reports.¹ The large number of cases reported in Mississippi is attributable in part to an enhanced surveillance process instituted by the Mississippi State Department of Health and the Mississippi Poison Control Center. Because of the growing prevalence of this problem, providers nationwide should be aware of the facts.

SYNTHETIC CANNABINOIDS ARE NOT MARIJUANA/CANNABIS

Although these illegal substances are commonly referred to as synthetic cannabinoids, cannabinoid receptor agonists, cannabimimetic agents, Spice, synthetic marijuana, or even legal marijuana, they should not be confused with marijuana/cannabis or the legal synthetic cannabinoids/cannabinoid receptor agonists such as Cesamet (nabilone; Meda Pharmaceuticals Inc, Somerset, NJ) or Marinol (dronabinol; Δ^9 -tetrahydrocannabinol; AbbVie Inc, North Chicago, IL).^{1,3-5} Illegal synthetic cannabinoids/Spice are not marijuana/cannabis, but rather a collection of numerous laboratory chemicals that interact with the cannabinoid receptor in the brain to mimic marijuana to induce a marijuana-like high.⁵ The synthetic chemicals designed to mimic marijuana bind to the same cannabinoid receptors in the brain as delta 9-tetrahydrocannabinol (Δ^9 -THC), the primary psychoactive component of marijuana.³

SYNTHETIC CANNABINOIDS ARE OFTEN MORE POTENT THAN MARIJUANA/CANNABIS⁴

One reason Spice may be more potent than marijuana is because the chemical components bind more strongly to the cannabinoid receptor in the brain; they also may interact with other receptors in the brain that marijuana does not.³

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Symptoms may resolve spontaneously without intervention and vary, including mild to moderate intoxication-like symptoms, nausea, emesis, weakness, tachycardia, hypertension, and agitation.^{1,4} Several news reports have described users in states of “excited delirium,” significantly agitated, tearing off their clothes, and sweating profusely. Severe symptoms include significant cardiac arrhythmias, myocardial infarction, psychosis, respiratory depression, flaccid paralysis, hyperthermia, rhabdomyolysis, seizures, coma, and even death.^{1,4,6} Intoxication management usually centers on airway, breathing, circulation, and life-threatening issues first, followed by supportive care.^{4,6} Fluid resuscitation may be needed, as well as electrolyte correction.³ Benzodiazepines are usually first-line treatment for anxiety/agitation; physical restraint may be necessary.^{4,6,7} Significant psychosis with behavioral disturbances can occur, which may not be calmed with typical methods; in these instances, antipsychotics may be helpful.^{6,7} Anecdotally, in our state, some of the patients presented with significant psychotic behaviors; the atypical antipsychotics seemed to assist more than the benzodiazepines in those cases. However, caution should be used with antipsychotics and other medications that can decrease seizure threshold as there have been reports of synthetic cannabinoids causing seizures.^{4,6} Because Spice intoxication presentations are varied, the treatment is individualized by scenario; the specific treatments used, observation time, and whether or not to admit (non-ICU or ICU) should be decided on a case-by-case basis and depend on the severity of the symptoms and comorbid conditions. Consulting a toxicologist may be helpful; Poison Control (800-222-1222) can also assist with management questions.

SYNTHETIC CANNABINOIDS ARE EVER-CHANGING

The 2012 Synthetic Drug Abuse Prevention Act made 15 synthetic cannabinoids Schedule I⁸; the Drug Enforcement Administration continues to designate active Spice chemicals and their analogs Schedule I, making these products illegal to sell, buy, or possess.⁸ In January 2015, 3 more were made Schedule I, including AB-CHMINACA⁸ (Figure 1). However, the clandestine manufacturers change the chemical formulations frequently to evade law enforcement.³ MAB-CHMINACA is an example of the tweaked difference from AB-CHMINACA (Figure 1). Like all of these emerging synthetic cannabinoids, the full extent of their physiological and toxicological effects is unknown at this time. Some states have enacted broad/generic language describing synthetic cannabinoids and analogs; for example, per Mississippi Code 41-29-113, all synthetic

cannabinoids are currently illegal. However, because synthetic cannabinoids are not marijuana, they will not show up as marijuana on a typical urine drug screen.³ Confirmation testing such as gas chromatography/mass spectrometry will detect some specific synthetic cannabinoid compounds; but with rapidly changing components, even confirmation detection is unlikely because “their identification and quantitative analysis is limited by the availability of pure reference samples.”⁵

CLINICAL SIGNIFICANCE

- The drug commonly referred to as “Spice” is actually a category of several hundred chemicals in the group known as synthetic cannabinoids.
- Reference to the term synthetic marijuana is misleading and suggests these drugs are well tolerated. In actuality they are dangerous and unpredictable.

SYNTHETIC CANNABINOID RESEARCH WAS “HIGH JACKED”^{9,10}

Synthetic cannabinoids research began over 40 years ago to evaluate their use as pharmaceutical agents.¹¹ These synthetic cannabinoids were never designed to be abused as they are today but were legitimate scientific and medical research. Unfortunately, clandestine manufacturers began illegally synthesizing some of the compounds and distributing for illicit use.⁹ Early examples of legitimate research compounds that started showing up in illegal products include JWH-018 and HU-210, as well as other analogs (Figure 2).⁹⁻¹¹ The products were seen in Europe as early as 2004, and the first Drug Enforcement Administration forensic lab detection of these products was in 2008.¹¹ Thus emerged the abuse of the original research.^{9,11}

SYNTHETIC CANNABINOIDS ARE DANGEROUS CHEMICALS WITH UNPREDICTABLE COMPOSITION AND HUMAN TOXICITY

The user does not really know what he/she is consuming because the chemicals are rapidly changing; amount of drug is unknown; and the herbal components are typically unknown.¹¹ The vast majority of these chemicals have never been evaluated in a controlled setting with laboratory animals or humans. Many of these products are laced with substances ranging from simple flavors to more dangerous substances such as other drugs, rat poison, and embalming fluids.^{11,12}

SYNTHETIC CANNABINOIDS HAVE MANY STREET NAMES

Common street names for Spice are listed in the Table.^{4,13} The “trade names,” along with catchy packaging, are used to “market” the products; dealers may also try to increase sales by adding flavors or mixing other drugs such as methamphetamine, ecstasy, bath salts, or phencyclidine, making the products even more dangerous.¹² “Trade names” are not necessarily indicative of a specific synthetic cannabinoid; any available type could be present in any labeled

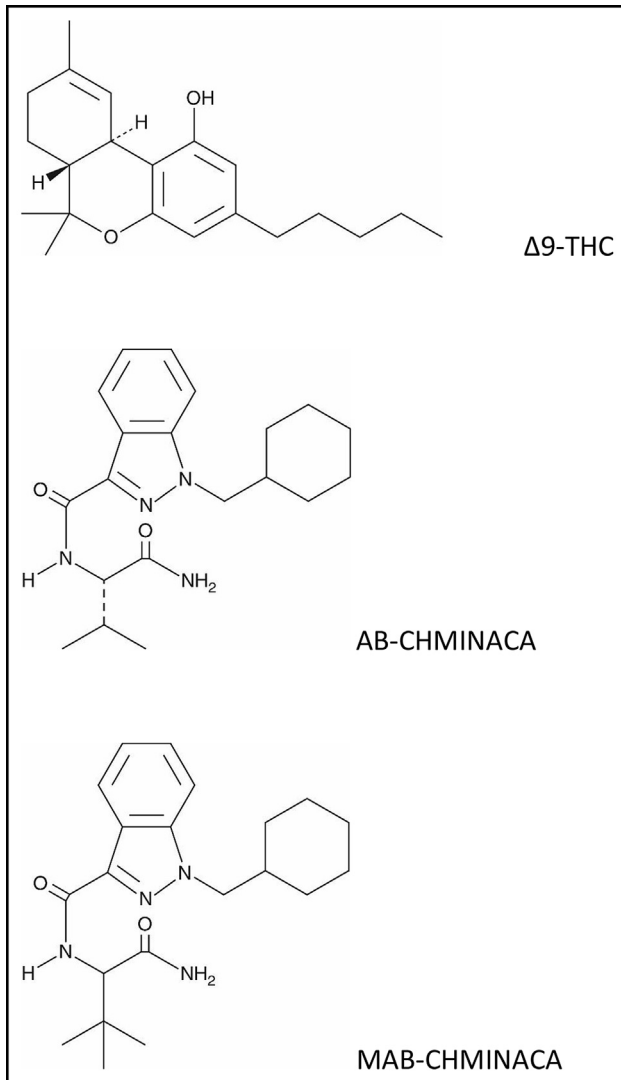


Figure 1 The molecular structures for Δ^9 -THC, AB-CHMINACA, and MAB-CHMINACA. Source: Courtesy of Cayman Chemical Company.

package or an unlabeled bag.¹² Newly introduced Spice, with unknown toxicities, may be sold under previously used names.¹² Providers should try to keep abreast of the current terms. The best way to do this is to ask patients specifically what they are using, and if a patient uses an unfamiliar term, ask for clarification. See [Supplementary Figures \(online\)](#) for some examples of different Spice packaging.

SYNTHETIC CANNABINOIDS USAGE IS NOT LIMITED TO YOUNG PEOPLE

The 2014 Monitoring the Future survey reports Spice usage by 12th graders has fallen steadily since 2012.¹⁴ Its overall decline nationally with young people, according to the National Institute on Drug Abuse likely stems from increased perception of risk.¹³ The recent outbreaks, however, could represent that the perception of risk is reversing, and its use is not limited to young people. In our state, the

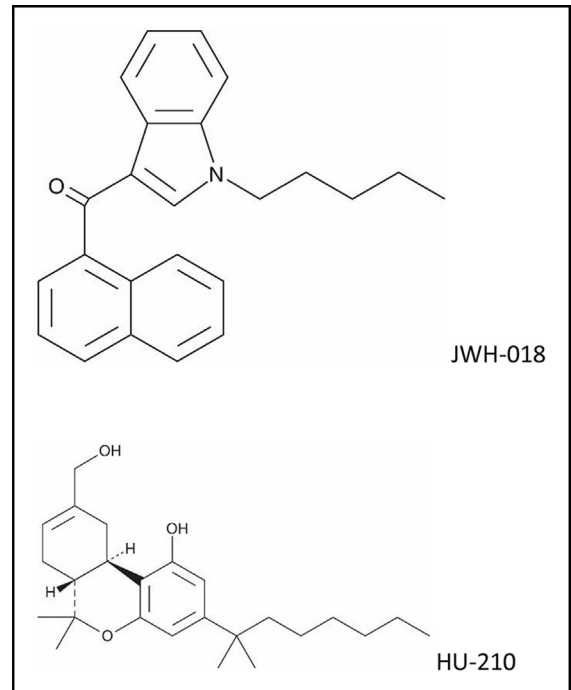


Figure 2 Molecular structures of JWH-018 and HU-210. Source: Courtesy of Cayman Chemical Company.

ages for the recent emergency department visits ranged from 12-69 years.¹⁵ Perceived safety and availability, and the fact that Spice is not picked up on random work drug screens have been cited as reasons patients are choosing these products.⁴ The stereotypes of who may be abusing drugs may change by the year 2020.¹⁶ The need for substance abuse treatment in those 50 years of age and older is estimated to triple due to the impact of baby boomers aging and this age group's experiences of drug use in the past.¹⁶

SYNTHETIC CANNABINOIDS ARE EASILY OBTAINED

Individual drug dealers were involved in the majority of our state cases and likely were selling chemicals being imported

Table Common Street/"Trade Names"

Spice	"Moon Rocks"
"K2"	"Ninja"
"Angry Birds"	"Mr. Nice Guy"
"Bhang"	"Outer Space"
"Bliss"	"Scooby Snax"
"Black Mamba"	"Sexy Monkey"
"Bombay Blue"	"Skunk"
"Dr. Feel Good"	"Smacked"
"Fake weed"	"Smoking Santa"
"Gangsta"	"Tomcat"
"Mojo"	"WANTED"
"Killa Gorilla"	"Yucatan"

from overseas (ie, China/India).^{11,12} A recent article in *The Guardian* stated that the majority of these chemicals are being produced in China, which is now being called the “new front in the global drug war.”¹⁷ The chemicals are usually white, mixed with acetone, and typically sprayed onto an herbal concoction, labeled “not for human consumption.”^{3,4,8,11} They usually have no human instructions/doses but are intended to be smoked or mixed as an herbal infusion for drinking; they also can be in liquid form, “dissolved in propellant intended for e-cigarette use”/vaping.^{3,4,8} The “herbal” products resemble potpourri and may be marketed as incense.^{3,11,18} Nationwide, Spice can also be found at head shops, gas stations, or on the Internet.^{3,11} The cost of spice is usually \$10 per gram, but can be cheaper in bulk.¹³ It is big business. An April 2015 report stated that \$8 million of Spice was seized from a Jackson, Mississippi apartment.¹⁹

SYNTHETIC CANNABINOIDS CAN BE ADDICTING, WITH UNKNOWN LONG-TERM CONSEQUENCES

Proposed factors that contribute to their addiction potential include the increased binding affinity, full agonism of the receptor (THC partially agonizes the receptor), and active metabolites; some bind over 100 times more tightly than THC.^{5,20} Cannabinoid-1 (CB₁) and CB₂ receptors are found mainly in the central nervous system and immune tissues, respectively. While both receptor types are affected by synthetic cannabinoids, stimulation of CB₁ causes a greater psychoactive effect through its modulation of glutamate and gamma-aminobutyric acid neurotransmitters.²¹ Due to the unknown chemical content of synthetic cannabinoids and varying activity of related metabolites, addiction potential, and long-term consequences are unclear. Long-term users may be vulnerable to new-onset or relapse of psychosis and cognitive deficits, including reduced attention span and memory. Withdrawal potential can be unpredictable as well. One case report of a daily user of “Spice Gold” in Germany over an 8-month period reported the patient experiencing drug cravings, sweating, hypertension, headache, restlessness, and nightmares.²²

PROVIDER EDUCATION IS KEY

Numerous misconceptions about synthetic cannabinoids exist in the community, including that these products are “natural,” “safe,” or “legal marijuana.”³ Any Spice product is likely to be of different chemical composition and of varying potency at different points of sale, leading to inconsistency in effect.¹¹ Spice can be unsafe in any quantity or frequency of use; using these products is a big risk.¹¹ It may seem to be a daunting task for providers to keep up with all of the changes in substance abuse trends. The National Institute on Drug Abuse (www.drugabuse.gov) outlines specific substances/trends and provides practice resources such as screening tools, patient handouts, and continuing education modules. The Substance Abuse and

Mental Health Services Administration Web site (<http://store.samhsa.gov>) provides free print resources aimed at assisting physicians in detecting substance abuse, brief interventions, screening, and referral resources for substance abuse. Providers may also be able to use resources that are closer to home, such as state health departments and toxicology consultants.

CONCLUSION

Synthetic cannabinoids have emerged as a significant problem resulting in many emergency department visits and even fatalities. To counter this growing problem, it is imperative that providers be aware of these dangerous substances and their effects on patients. Also, given the variability in clinical presentations, providers need to keep the use of synthetic cannabinoids in the differential for any patient who presents with symptoms described above. Educational tools such as the ones mentioned here are available for physicians to be self-informed. It is important for providers to stay abreast of local trends and, when necessary, partner with pharmacists, law enforcement, toxicologists, and mental health providers to discuss trends and treatment options in your area that may be most beneficial, as there are regional variations with substance abuse and available resources.

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APPENDIX

Supplementary figures accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.amjmed.2015.10.008>.



Supplementary Figure 1 An example of a labeled packaged Spice product. Source: Mississippi Bureau of Narcotics



Supplementary Figure 3 An example of a labeled packaged Spice product. Source: Mississippi Bureau of Narcotics



Supplementary Figure 2 An example of a labeled packaged Spice product. Source: Mississippi Bureau of Narcotics.



Supplementary Figure 4 An example of a unlabeled and unmarked Spice product. Source: Mississippi Bureau of Narcotics.