

JUNE 2016

WE NEED A HEALTH APPROACH TO SYNTHETIC CANNABINOID

I. WHAT IS SYNTHETIC MARIJUANA?

"Synthetic marijuana" is a common, but misleading, term that refers to a class of substances more accurately called cannabinoid receptor agonists or synthetic cannabinoids.¹ Whereas marijuana usually refers to the dried flowered buds of the actual plant, which derives its main psychoactive effect through THC², synthetic cannabinoids get their name from their action on various cannabinoid receptors in the brain.

Sacrificing accuracy for simplicity, people in public office, the media, and law enforcement use the term "synthetic marijuana" or the brand names of products sold, such as "Spice" or "K2," that are known to contain various synthetic cannabinoids.³ The first and most well-known synthetic cannabinoids in laboratory research are known as the JWH Series, but soon after those were banned, newer and less researched synthetic cannabinoids, such as XLR-II,⁴ AB- PINACA,⁵ and AB-FUBINACA⁶ were found in products that were still legal.

The substances that were later identified in these products were originally discovered by scientific researchers looking to understand more about the cannabinoid receptor system in the human brain and immune system. Many of these substances have different chemical structures than THC, the main psychoactive ingredient in marijuana, and are full agonists at cannabinoid receptors, which can cause them to produce very different effects than THC,⁷ which is a partial agonist. This is one possible reason for the higher rates of some of the more

extreme side effects that are only occasionally seen in adverse reactions to marijuana.

2. WHY DO PEOPLE USE SYNTHETIC CANNABINOID PRODUCTS LIKE "SPICE" AND "K2?"

The emergence of synthetic cannabinoids has mirrored the same trends seen with other novel psychoactive substances. People may use synthetic cannabinoids when experimenting with other substances, and in some cases use may be accidental.

MOST PEOPLE AREN'T AWARE THAT THE EFFECTS ARE UNLIKE MARIJUANA – THUS REPEATED USE IS RARE. AND, IF GIVEN THE CHOICE, ADULTS WOULD VERY LIKELY CHOOSE TO USE MARIJUANA IF IT WERE LEGALLY AVAILABLE.

Due to the ongoing prohibition of marijuana, emergence of the synthetic cannabinoid market over the last decade has met demand by being a legal or quasi legal alternative. Because standard drug testing only tests for THC found in plant-based marijuana, synthetic cannabinoid products do not trigger a positive result. This appealed to active military personnel, professional athletes, people on parole, and people in treatment for substance misuse who were among the earliest reported users of these products. Another group commonly using synthetic cannabinoids are those suffering from chaotic life situations, often homeless or low income.⁸

Synthetic cannabinoids became an affordable replacement to marijuana or other drugs.

While no specific measures are available, people that continue to use synthetic cannabinoids are perhaps those looking for a cheaper alternative or to pass drug tests, rather than due to preference over marijuana.⁹

3. WHAT'S THE DIFFERENCE BETWEEN SYNTHETIC CANNABINOIDS AND MARIJUANA?

Marijuana is a natural plant that grows both in the wild and is cultivated for its medicinal properties and for recreational use. Though synthetic cannabinoids are considered chemical relatives or analogues to substances in marijuana, they are not actually found in plant-based marijuana and therefore have chemical and pharmacological properties largely unknown outside of the laboratory.¹⁰

Due to the ongoing prohibition of marijuana and advances in technology that allowed for access to drug research and easier chemical production, a market for synthetic cannabinoids developed in the early 2000s.¹¹ Synthetic cannabinoid products began being produced and sold in herbal smoking blends as legal marijuana replacements.¹² The products are packaged and branded to suggest a similarity to the effects of marijuana, but because the material are inert herbal mixtures doused with synthetic cannabinoids, their appearance, taste, and smell are different.

4. WHAT ARE THE EFFECTS OF SYNTHETIC CANNABINOIDS?

Synthetic cannabinoids are mistakenly considered to closely mimic the effects of marijuana, but in fact there are significant differences. As their name suggests, synthetic cannabinoids, like THC and other substances in marijuana, affect the brain by stimulating activity at various cannabinoid receptors.¹³ Although research is limited, preliminary studies suggest that effects include feeling stimulated and energetic, increased appetite,

and producing a dream-like state, but can also include nausea and vomiting, seizures, aggression and agitation, as well as respiratory failure and loss of consciousness.¹⁴ Whereas THC, the main psychoactive substance in marijuana, is a partial agonist, synthetic cannabinoids are full agonists.

Adverse reactions to synthetic cannabinoids saw calls to poison control centers peak at just under 10,000 in 2015,¹⁵ and the number of emergency room visits in the tens of thousands¹⁶ (these figures have since gone down). One explanation for the high number of hospital visits is that other substances in marijuana known to protect against anxiety and psychotic symptoms¹⁷ likely balance out the direct effects of THC on the brain but are absent in synthetic cannabinoids.

Until more research is done on individual synthetic cannabinoids specific causes for these effects will remain only partially understood.

5. WHAT'S THE DIFFERENCE BETWEEN "SPICE", "K2," AND OTHER SYNTHETIC CANNABINOID PRODUCTS?

A synthetic cannabinoid product is a branded package containing herbal matter sprayed or doused with liquid synthetic cannabinoids. "Spice" and "K2" are examples of very early brands of synthetic cannabinoid products. The first synthetic cannabinoids found in these products are known as the JWH series, which were the most extensively studied in laboratory research. As laws banning the JWH compounds took effect, newer and less researched synthetic cannabinoids such as XR-II, AB-PINACA, and AB-FUBINACA were used in products since they had not been banned.

There are hundreds of different name brands, but synthetic cannabinoids are not always sold that way. They may also simply be sold as marijuana might be, as a joint or in a plastic bag without any information as to the actual contents.

Just because synthetic cannabinoids can be sold in a branded package does not mean the synthetic cannabinoids used are always the same.¹⁸

Due to lack of regulation there is no incentive for manufacturers, mostly consisting of clandestine labs in Asia, to ensure a consistent, high-quality product. These labs are constantly changing formulations in an effort to work around laws¹⁹ attempting to prohibit them, and brands often contain an inconsistent and unreliable combination of synthetic cannabinoids.²⁰ Therefore, the difference between synthetic cannabinoid products can be as variable as the difference from packet to packet of the same brand name. Furthermore, material within the packet itself may even have varying levels of potency, which could result in very high levels of chemicals unintentionally ingested.²¹

6. HOW RISKY ARE SYNTHETIC CANNABINOID PRODUCTS COMPARED TO MARIJUANA OR OTHER DRUGS?

These substances are generally more harmful than plant-based marijuana. Many of the adverse reactions to synthetic cannabinoids have been reported to involve dangerous physical symptoms, whereas adverse reactions to natural marijuana typically involve symptoms resembling anxiety and panic, which though worrisome, are not lethal. In 2012, state public health department officials, poison control centers and CDC researchers identified 16 cases of acute kidney injury related to use of synthetic cannabinoids in six states (Kansas, Oklahoma, Oregon, New York, Rhode Island & Wyoming).²²

The sudden rise of synthetic cannabinoid related calls to poison centers, hospitalizations and even instances of fatal reactions has never been seen with marijuana, which has only ever been indirectly associated with drug-related deaths, and never shown to result in a fatal overdose. Deaths linked to synthetic cannabinoids do not compare to numbers from drugs like heroin and cocaine,²³ and while the brief rise in ER visits and poison center calls did signal a temporary cause for concern (these figures have since gone down),²⁴ alarmist responses and harsh law enforcement crackdowns often overshadow the need for public education and harm

reduction measures and ultimately cause more harm than good.

7. IS "SYNTHETIC MARIJUANA" ADDICTIVE?

Given the lack of scientific evidence, the addictive potential of synthetic cannabinoids is inconclusive. The most credible information available are limited to case reports²⁵ and anecdotal accounts. These sources suggest that compulsive use exists, though these alone cannot qualify the argument on addiction.

8. HOW MANY PEOPLE ARE USING "SYNTHETIC MARIJUANA" PRODUCTS?

Despite widespread media attention throughout the country over the past few years, relatively few people are using synthetic cannabinoid products compared to other drugs. While there are a few ways to measure for usage rates of synthetic cannabinoid products, they come with a few caveats. Data from emergency room visits rose sharply in the early 2010s,²⁶ with the most recent national numbers reaching almost 30,000 (from 2011, compared to 2.5 million ER visits in 2011 from all drugs).²⁷ Calls to poison control centers started climbing around the same time frame, going from a couple thousand in 2013 to almost 8,000 in 2015.²⁸ But the Monitoring the Future survey of 8th-12th graders showed less than 5% of 8th graders had tried synthetic cannabinoid products in the past year for 2012-2015, less than 10% for 10th graders, and aside from 2012, less than 10% of 12th graders.²⁹ Based on overall trends from the MFS synthetic cannabinoids actually do not appear to be of much interest to youth in the United States.³⁰

Even when synthetic cannabinoid use peaked in survey data around 2012, overall prevalence has remained relatively low compared to other drugs.³¹ While no specific measures are available, people that continue to use synthetic cannabinoids are likely those looking for a cheaper alternative or to pass drug tests.

9. ARE SYNTHETIC CANNABINOIDS LEGAL?

For the most part, no.

When synthetic cannabinoid products began to appear in convenience stores in the mid-2000s they contained substances that were not specifically banned by state or federal drug laws. But by the end of the decade, a few states passed laws to ban their sale, and in 2011 the DEA used emergency protocols to temporarily schedule some of the substances found in synthetic cannabinoid products. The next year, President Obama signed the Synthetic Drug Abuse Prevention Act, permanently placing several different classes of psychoactive substances,³² including many synthetic cannabinoids, into Schedule I of the Controlled Substances Act (CSA) – the most restrictive classification.

Each state is currently using various administration actions, prosecution strategies, and regulations for product labeling and branding to either quickly ban individual substances or criminalize sales. Most states have also enacted (and many others have pending legislation) criminal and civil penalties for sale of products that attempt to avoid being advertised as “synthetic drugs” by claiming products are, “not for human consumption.” Recently, states like New York, Virginia and several others have pushed for new laws that broaden the chemical definitions meant to be outlined in Schedule I, as well as call for harsher penalties for sale of synthetic cannabinoid products.

However, these laws essentially “mark the battle lines” as manufacturers of synthetic cannabinoids can make small changes to the chemical formulas in order to skirt these laws, producing newer synthetic cannabinoids that have not yet

been scheduled. Regulation that would permit commercial sale but hold retailers accountable for products they sell is an alternative that would keep the public safer than prohibition.

10. WHAT'S A HARM REDUCTION APPROACH TO SYNTHETIC CANNABINOIDS?

As demand persists despite attempts to prohibit supply, a regulated framework is needed to control the market. Without requiring labelling and product consistency, people determined to use these products have no idea what they're getting.

Instead of further criminalization, alternative approaches to reduce accidental deaths and hospitalizations related to drug use, improve public health outcomes, care for vulnerable populations, and protect young people include:

- Provide outreach and resources for vulnerable populations.
- Provide comprehensive drug education about emerging substances.
- Revisit plans to tax and regulate marijuana as a means of reducing demand for synthetic cannabinoids.

END NOTES

1. Atwood, Brady K, John Huffman, Alex Straiker, and Ken Mackie. "JWH018, a Common Constituent of 'Spice' Herbal Blends, Is a Potent and Efficacious Cannabinoid CB1 Receptor Agonist." *British Journal of Pharmacology* 160, no. 3 (2010): 585-93. <https://doi.org/10.1111/j.1476-5381.2009.00582.x>.
2. Taura, Futoshi, Supaart Sirikantaramas, Yoshinari Shoyama, Yukihiro Shoyama, and Satoshi Morimoto. "Phytocannabinoids in Cannabis Sativa: Recent Studies on Biosynthetic Enzymes." *ChemInform* 38, no. 47 (2007). <https://doi.org/10.1002/chin.200747225>.
3. "Drug Enforcement Administration's National Forensic Laboratory Information System NFLIS Home." Drug Enforcement Administration's National Forensic Laboratory Information System NFLIS Home. Accessed June 09, 2016. <https://www.nflis.deadiversion.usdoj.gov/>.
4. "UR-144 (TCMP-018; KM-XI) and XLRII (5-F-UR-144)." Drug Enforcement Administration, Office of Diversion Control: Drug & Chemical Evaluation Section. May 2013. Accessed June 9, 2016. http://www.deadiversion.usdoj.gov/drug_chem_info/spice/spice_ur144_xlrii.pdf.
5. "N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (AB-CHMINACA), N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA) and [1-(5-fluoropentyl)-1H-indazol-3-yl](naphthalen-1-yl)methanone (THJ-2201): Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5, and 6) for Temporary Scheduling." Drug Enforcement Administration, Office of Diversion Control: Drug & Chemical Evaluation Section. December 2014. Accessed June 9, 2016. <https://www.grassley.senate.gov/sites/default/files/news/upload/3-factor%20analysis%20AB-CHMINACA%20AB-PINACA%20THJ2201%2012172014.pdf>.
6. "AB-FUBINACA" Drug Enforcement Administration, Office of Diversion Control: Drug & Chemical Evaluation Section. April 2014. Accessed June 9, 2016. http://www.deadiversion.usdoj.gov/drug_chem_info/spice/ab_fubinaca.pdf.
7. Fantegrossi, William E, Jeffery H. Moran, Anna Radomska-Pandya, and Paul L. Prather. "Distinct Pharmacology and Metabolism of K2 Synthetic Cannabinoids Compared to 9-THC: Mechanism Underlying Greater Toxicity?" *Life Sciences* 97, no. 1 (2014): 45-54. <https://doi.org/10.1016/j.lfs.2013.09.017>.
8. Winstock, Adam R, and Monica J. Barratt. "Synthetic Cannabis: A Comparison of Patterns of Use and Effect Profile with Natural Cannabis in a Large Global Sample." *Drug and Alcohol Dependence* 131, no. 1-2 (2013): 106-11. <https://doi.org/10.1016/j.drugalcdep.2012.12.011>.
9. *Missing*
10. *Missing*
11. *Missing*
12. *Missing*
13. *Missing*
14. *Missing*
15. *Missing*
16. *Missing*
17. *Missing*
18. *Missing*
19. Walton, Alic G. "Why Synthetic Marijuana Is More Toxic To The Brain Than Pot." *Forbes*. August 28, 2014. Accessed June 09, 2016. <http://www.forbes.com/sites/alicegwalton/2014/08/28/6-reasons-synthetic-marijuana-spice-k2-is-so-toxic-to-the-brain/#1db656f849eb>.
20. Griffiths, Paul, Roumen Sedefov, Ana Gallegos, and Dominique Lopez. "How Globalization and Market Innovation Challenge How We Think about and Respond to Drug Use: 'Spice' a Case Study." *Addiction* 105, no. 6 (2010): 951-53. <https://doi.org/10.1111/j.1360-0443.2009.02874.x>.
21. Vandrey, Ryan, Kelly E. Dunn, Jeannie A. Fry, and Elizabeth R. Girling. "A Survey Study to Characterize Use of Spice Products (synthetic Cannabinoids)." *Drug and Alcohol Dependence* 120, no. 1-3 (2012): 238-41. <https://doi.org/10.1016/j.drugalcdep.2011.07.011>.
22. "Synthetic Cannabinoids." Synthetic Cannabinoids. Accessed June 09, 2016. <http://www.aapcc.org/alerts/synthetic-cannabinoids/>.
23. "Update: Drug-Related Emergency Department Visits Involving ." Accessed June 9, 2016. <http://www.samhsa.gov/data/sites/default/files/SR-1378/SR-1378.pdf>.
24. Campos, A. C., F. A. Moreira, F. V. Gomes, E. A. Del Bel, and F. S. Guimaraes. "Multiple Mechanisms Involved in the Large-spectrum Therapeutic Potential of Cannabidiol in Psychiatric Disorders." *Philosophical Transactions of the Royal Society B: Biological Sciences* 367, no. 1607 (2012): 3364-378. <https://doi.org/10.1098/rstb.2011.0389>.
25. Auwärter, Volker, Sebastian Dresen, Wolfgang Weinmann, Michael Müller, Michael Pütz, and Nerea Ferreirós. "Spice' and Other Herbal Blends: Harmless Incense or Cannabinoid Designer Drugs?" *Journal of Mass Spectrometry J. Mass Spectrom.* 44, no. 5 (2009): 832-37. <https://doi.org/10.1002/jms.1558>.
26. "Synthetic Cannabinoids and 'Spice' Drug Profile." EMCDDA. Accessed June 09, 2016. <http://www.emcdda.europa.eu/publications/drug-profiles/synthetic-cannabinoids>.
27. "Notes from the Field: Increase in Reported Adverse Health Effects Related to Synthetic Cannabinoid Use — United States, January–May 2015." Centers for Disease Control and Prevention. 2015. Accessed June 09, 2016. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6422a5.htm?s_cid=mm6422a5_w.
28. "Overdose Death Rates." National Institute on Drug Abuse (NIDA). 2015. Accessed June 09, 2016. <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>.
29. Zimmermann, Ulrich S, Patricia R. Winkelmann, Max Pilhatsch, Josef A. Nees, Rainer Spanagel, and Katja Schulz. "Withdrawal Phenomena and Dependence Syndrome After the Consumption of 'Spice Gold'." *Deutsches Ärzteblatt International*. 2009. Accessed June 09, 2016. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719097/>.
30. Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.
31. "Monitoring the Future Study: Trends in Prevalence of Various Drugs." National Institute on Drug Abuse (NIDA). Accessed June 09, 2016. <https://www.drugabuse.gov/trends-statistics/monitoring-future/monitoring-future-study-trends-in-prevalence-various-drugs>.
32. "MTF Data Tables and Figures." MTF Data Tables and Figures. Accessed June 09, 2016. <http://monitoringthefuture.org/data/15data.html#2015data-drugs>.