



## Letter to the Editor

### Synthetic Cannabinoids: A Disturbing Trend

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#### Letter to the Editor

Seemingly “safe” alternatives to marijuana, Synthetic Cannabinoids (SCs) are showing some dangerous trends. Emergency departments are seeing an increase in Intensive Care Unit (ICU) admissions for organ dysfunction and multiple organ failure [1]. Changes to SCs to avoid legal restrictions have led to more potent and potentially deadly new chemicals.

Sold under names such as “K2,” “Spice,” and appropriately, “Insane,” SCs are often legally sold in the United States, advertised as herbal incense or potpourri. While these products are often marketed as “all natural,” the active ingredients are anything but SCs are molecules created in the lab, many of which are not structurally related to  $\Delta^9$ -Tetrahydrocannabinol (THC), but show strong affinity for the CB1 cannabinoid receptor. These chemical compounds are then put into solution and sprayed onto plant material [2], with a final product that resembles an herbal one. This plant material is inert and only functions as medium to smoke the SC chemicals. SCs are also purchased and used in power form and may be snorted or smoked [3].

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Because many of these molecules differ so much from THC, the effects and the toxicity of the chemicals may be vastly different than what is expected from smoked marijuana, such as seizures, hyperthermia, and rhabdomyolysis [4]. Tachycardia and hypertension have been reported [5], but emergency departments have also seen surges of individuals with bradycardia, a symptom not seen with cannabis use [6]. Acute kidney injury, abdominal pain, and hyperthermia are additional complications that have been described with SCs but seen with cannabis [7]. SCs have been involved in the death of some individuals, usually in combination with another substance [8]. The psychoactive properties of SCs have similarities to THC, but most cases are more severe. Paranoia is not uncommon with cannabis use, including more severe symptoms in those predisposed [9], but users of SCs have shown psychotic agitation, auditory and visual hallucinations, and suicidal ideation at a higher rate than users of cannabis [10,11]. First responders may also be at risk for exposure to these compounds. During a 2014 raid on a Nevada illegal laboratory, six of the nine involved agents had detectable levels of either the SC AB-PINACA or mitragynine (commonly known as “kratom”) [12]. Five of agents reported cough, five had throat and eye irritation, and four of the agents reported feeling “high.”

SCs became popular in the 2000’s as “legal highs” and alternatives to cannabis that were not readily detectable by during drug screening, one of the first and most popular being JWH-018. As occurs with designer drugs, the USA Drug Enforcement Agency (DEA) scrambled to list these new compounds under Schedule. Chemistry tends to stay one step ahead of legislation, so new cannabinoid compounds were created, making new legal substances available. Similar legal challenges exist in China, where JWH-018 was created and where much of the current SC manufacturing occurs. The Controlled Substances Analogue Enforcement Act of 1986 sought to plug the designer drug loophole. An exclusion in the act permits analogues to be created for research use. Unsurprisingly, retailers of new SCs now market these rugs for “research or investigational purposes” in order to avoid regulation. There are currently hundreds of SCs, the newest drugs avoiding legal restrictions. To date, the most recent SC sold to the public is 4-Fluoro ADB (4F-ADB), created with the addition of just one methyl group to the illegal 5F-ADB [13]. This is an example of a common change to designer drugs—the addition or substitution of a hydrophobic moiety making the drug even more apt to cross the blood-brain barrier. This concerning trend is producing potentially more dangerous substances as the law catches up to each molecule created.

Initiatives such as the Psychonaut Web Mapping Project are the types of weapons needed to combat the emergence of these new and potentially dangerous designer drugs. This project was a 2-year investigation (2008-2009) funded by the European Union [14]. Internet discussion forums, social media, and online retail sites were crawled in search of new psychoactive compounds. In this project, over 400 substances were found, including Novel Psychoactive Substances (NPS) that had not yet become available to the public. From October 2015-October 2016, the CASSANDRA (Computer Assisted Solutions for Studying the Availability and Distribution of novel

psychoactive substances) Project examined cryptocurrency markets on the deep web, the part of the internet not indexed by search engines. The project found 808 vendors selling 256 unique NPS [15]. During that two-year period, the authors noted a 94% increase in the number of NPS being sold. After a brief web search, it is clear that the trend has continued into 2018. More projects aimed at assessing the vast cavern of the deep web, as well as legal retail sales on the surface web, are needed to assess and curtail the ongoing SC trade.

While deceptively marketed as “natural,” there are more severe medical and psychiatric complications of SCs being reported. For limited periods, new SCs are sold legally, classified as new research compounds. Making progress on controlling this trade requires plugging the hole in the Controlled Substances Analogue Act of 1986. New molecules certainly need to be created and obtained for research, but reform is needed to make new drug discovery safe, yet accessible. Also, because the SC problem is an international one, cooperation is required with countries such as China to curb the flow of these drugs to the USA finally, with the advent of more sophisticated computing power, additional projects are needed for surveillance the deep and surface web. This surveillance may include assessing which drugs of abuse are being popularized by crawling forums and social media, while also tracking retail and cryptocurrency exchanges. There is no doubt that these SCs will become more potent while becoming more accessible-to minimize the harm from these drugs, urgent intervention is needed to curb the availability and use of SC compounds.

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