

# Synthetic Cannabis Overdose and Withdrawal in a Young Adult: A Case Report, Commentary on Regulation and Review of Literature

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## Abstract

**Background/Introduction:** Marijuana has been used for its psychotropic effects including enhanced relaxation and perceptual alterations. However, the use of synthetic cannabis (marijuana) leads to more frequent and drastic side effects than the typical use of regular marijuana, owing to the fact that synthetic cannabis has a shorter duration and an earlier peak of action.

Despite all the potential adverse health effects associated with synthetic cannabis use, current health policies on synthetic cannabis are very limited. It is believed that the popularity of synthetic cannabis has increased, due to its easy accessibility in the US and the lack of detection in typical urine drug screens for Tetrahydrocannabinol derivatives (THC).

**Case Report:** One case is presented of a young adult patient, with histories of recurrent synthetic cannabis and recreational cannabis use, who had developed drastic physiological and psychiatric symptoms, including the development of acute-onset psychosis.

**Conclusion/Discussion:** This case, as many others nationwide, exemplifies the impact of synthetic cannabinoid use and abuse in adolescents. Side effects and adverse health consequences of synthetic cannabinoid use warrants stricter regulations and policies in order to decrease psychiatric hospital admissions and associated healthcare costs.

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**Keywords:** Adolescent drug addiction/abuse; Synthetic marijuana abuse/overdose; Addiction to illicit drugs; Psychotropic side-effects from Cannabis and Synthetic Cannabis

**Abbreviation:** SM: Synthetic Marijuana/Cannabis; CB1 and CB2 receptors: Cannabinoid Receptor 1 and Cannabinoid Receptor 2; CNS: Central Nervous System; HC: Tetrahydrocannabinol derivatives; ED: Emergency Department

## Background/Introduction

Marijuana is used for its psychotropic effects including enhanced relaxation and perceptual alterations. The primary psychoactive ingredient found in marijuana is  $\Delta$ -9 tetrahydrocannabinol (THC), which binds to endogenous cannabinoid receptors (CB1, CB2)<sup>[1]</sup>. Specifically, cannabis products including synthetic marijuana (SM) exert all its known psychotropic effects through the CB1 cannabinoid receptors. Such important classes of neurons that express high levels of CB1 receptors are GABAergic neurons in the hippocampus, amygdala, and the cerebral cortex. Additionally, these neurons contain the neuropeptides cholecystokinin. In turn, when these cannabis products activate the CB1 receptors, the inhibition of the release of amino acids and monoamine neurotransmitters occur. Further speaking, lipid derivatives, such as anandamide and 2-arachidonylglycerol, act as endogenous ligands for CB1 receptors (endocannabinoids). They may act as retrograde synaptic mediators of the phenomena of depolarization with



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possible induced suppression of inhibition or excitation in the hippocampus and cerebellum<sup>[2]</sup>. However, some SM products, such as JWH-015 and JWH-133, show affinity not only for the CB1 receptors, but also for the CB2 receptors. These CB2 receptors appear to be much present on the marginal zone of the spleen, tonsils, and immune cells, especially on macrophages, B cells, natural killer cells, monocytes, T-lymphocytes, polymorphonuclear neutrophils and astrocytes<sup>[2]</sup>.

According to<sup>[3]</sup> many of the SM induced psychiatric effects consist of psychotic behavior and anxiety. Evidence suggests that it may trigger / and physical adverse effects, which are strikingly similar to those of marijuana<sup>[3]</sup>. The use of SM leads to more frequent and drastic side effects than the typical use of regular marijuana, owing to the fact that SM has a shorter duration and an earlier peak of action<sup>[4]</sup>. SM use can lead to various adverse side effects including delusions, paranoia, hallucinations, anxiety, panic attacks, agitation, seizures, dizziness, and short term cognitive deficits<sup>[5]</sup>. In addition to the expected CNS effects, such as confusion, psychosis, agitation, loss of consciousness, and seizures, some of these SM based compounds have been associated with tachycardia, kidney damage, rhabdomyolysis, and even death.

Despite all the potential adverse health effects associated with SM use, current health policies on SM are very limited<sup>[6]</sup>. It is believed that the popularity of SM has increased, due to its easy accessibility in the US and lack of detection in typical urine drug screens for THC.

Therefore, it is imperative to evaluate the impact of SM on mental health and more importantly the social and legal implications surrounding its use. Accordingly, this case illustrates how easy accessibility and limited regulation on SM adversely impacts mental health thus posing a challenging problem for psychiatrists nationwide. The present case report leads to consideration of the critical need for regulations and effective toxicology screens for SM.

## Case Report

An 18 year old Hispanic male was brought to our emergency department by his parents after five days of acute onset auditory hallucinations, paranoid delusions, and, per the mother, symptoms of panic attacks, including palpitations, shortness of breath, diaphoresis, chest tightness, and hand numbness. The patient presented with impulsivity, agitation, and stated he had suicidal thoughts. Additionally, the patient reported a history of cannabis abuse, and more recently, synthetic marijuana/cannabis (SM) use (3 - 4 days prior to presentation), which were purchased from internet blog sites and convenience stores<sup>[7]</sup>.

It was apparent that the onset of psychosis coincided with the patient's most recent SM use. Of note, the patient did not have any previous psychiatric history, nor a psychotic episode, prior to his synthetic marijuana use. Nevertheless, an antipsychotic regimen was provided to the patient during his hospitalization which was beneficial in controlling his transient acute psychosis. Moreover, a urine drug screen in the ED was negative for THC, which fortified the patient's history of not using regular marijuana since a month prior to hospitalization.

Thereafter, a three month follow up phone call made to the patient, revealed that his mental health had been progressively improving after discharge and, at that moment, he was doing very well. The patient mentioned that the symptoms subsided several weeks (2 - 3 weeks) after his discharge from the hospital. During that time, the patient refrained from any illicit drug use, including SM use. The patient remained under the care of a licensed- psychiatrist throughout the period after inpatient treatment. According to the patient, compliance was maintained regarding attendance of sessions with his outpatient psychiatrist.

## Discussion

It is of utmost importance to note that there may be some differences between a psychotic episode secondary to synthetic cannabis/marijuana use, and an exacerbation of a psychotic episode due to a defined psychiatric illness. For instance, synthetic cannabis/marijuana products can induce a brief acute psychotic state that can subside within several days to weeks, after cessation of the drug, in individuals with no previous diagnosis of a psychiatric disorder. Still, synthetic cannabis/ marijuana products can trigger psychosis in individuals who have a current diagnosis of psychosis. In fact, further use of these products can worsen psychotic symptoms in those individuals with a current diagnosis of psychosis or specific type of a psychotic disorder. It is therefore very ideal to obtain a thorough psychiatric history, a complete mental status assessment, and an appropriate follow up, regarding a patient before determining the etiology of an acute psychotic episode. This would help define if an acute psychotic episode may be secondary to a substance (in this case SM) or secondary to a chronic psychiatric illness (e.g. Schizophrenia, Bipolar Disorder, and Depression). That being said, certain lab findings alone, more specifically a negative urine drug screen for THC, will not make the determination on whether the psychosis is secondary to SM or if it's secondary to a chronic mental illness<sup>[2]</sup>.

Ultimately, in a transient acute psychotic episode caused by SM use, the cessation of use will bring on resolution of the psychosis. The short-term use of an anti-psychotic or a benzodiazepine regimen may be warranted depending on the level of distress. Additionally, it has been shown that psychoeducation and Cognitive Behavioral Therapy (CBT) has been successful in reducing SM use in patients experiencing their first episode of psychosis<sup>[8]</sup>. Moreover, further research has specifically shown Clozapine rather than Risperidone as being more effective in managing acute psychotic like symptoms secondary to SM use<sup>[2]</sup>.

Users of SM products appear to have a variety of physical effects ranging from nausea to more serious sympathomimetic-like symptoms, such as psychomotor agitations, abnormal vital signs, including hypertension and tachycardia, diaphoresis and palpitations. Also, even though infrequently associated with smoking SM, clinical case reports have described generalized convulsions secondary to the usage of 4 different synthetic cannabis derivatives, JWH-018, JWH-081, JWH-250, and AM-2201<sup>[1]</sup>.

## Further Conclusions

Synthetic marijuana use is insidiously becoming a mental illness concern given its appreciable contributions to acute onset of, and exacerbation of existing psychiatric conditions. While there has been a recent increment in the level of awareness for marijuana use for medical purposes in the United States and internationally, there is necessity for strict regulations and control measures in defining limits for recreational use due to potential psychiatric conditions<sup>[9,10]</sup>. More importantly, there is further need for production regulations, including standardization and monitoring designed structural compounds of SM, in order to create the pathway to the formulation of effective toxicology screening techniques.

## Declarations

**Ethical Standards and Informed Consent:** All procedures and interviews conducted were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all individuals for whom identifying information is included in this manuscript.

**Consent for Publication:** Consent and acknowledgement was received from the individual(s) in this case-study in order for this manuscript to be published accordingly.

**Availability of data and materials:** The dataset(s) supporting the conclusion of this article is included within the article and its additional file(s) are located in the Microsoft Word File entitled “Journal of Addiction and Dependence, Synth. Marijuana Case Study (Table 1) JSamaan.”

**Table 1:** Clinical Pearls & Key Points: Synthetic Marijuana Abuse and Its Similarities and Differences to Cannabis.

Topic of Concern	Similarities	Differences
<b>Adverse Side Effects</b>	<p>According to the National Institute of Drug Abuse, Synthetic Cannabinoid users and Cannabis users share have reported the following similar effects <sup>[11-13]</sup></p> <p>Elevated Mood Relaxation Altered Perception-Awareness of Surrounding conditions</p> <p>Symptoms of Psychosis (Delusional or disordered thinking—detached from reality) (Of note, the symptoms of psychosis with synthetic cannabinoid use appears to be more drastic than cannabis use (refer to differences section)</p>	<ol style="list-style-type: none"> <li>1. In contrast to cannabis users, Synthetic Cannabinoid users have reported the following additional adverse effects <sup>:[13]</sup> Extreme Psychosis – with symptoms of extreme anxiety, confusion, paranoia (unreasonable distrust of others) Hallucinations (visual and auditory)</li> <li>2. Unlike with use of cannabis, synthetic cannabinoid users have been shown to exhibit the following severe effects : Tachycardia ( Rapid Heart Rate)</li> <li>3. Severe abdominal pain, nausea, vomiting that occurs over several months and resolves when SM use has been discontinued (known as synthetic Cannabinoid hyper emesis syndrome).</li> <li>4. Unusual violent behavior and suicidal thoughts.</li> </ol> <p>Additionally, current studies do not show current treatment or therapies (including pharmacological) that manage the symptoms associated with synthetic cannabinoid use</p>
<b>Mechanism of Action</b>	<p>Similarities:<sup>[14]</sup></p> <ul style="list-style-type: none"> <li>- Synthetic cannabinoids and cannabis (THC) bind to the same cannabinoid receptors in the brains and other organs as the endogenous ligand –anadamide.</li> <li>-Synthetic Cannabinoids and other identical products seem to have a similar mode of action as marijuana, in which these substances have affinity to various cannabinoid receptors (e.g. CB 1, CB2).<sup>[15]</sup></li> </ul>	<p>Differences:<sup>[14]</sup></p> <ul style="list-style-type: none"> <li>- Many of the substances that contain synthetic cannabinoids are not structurally related to ‘classical’ cannabis</li> <li>-Unlike cannabis, most of synthetic cannabinoid products are lipid soluble and non-polar, consisted of 22 to 26 carbon atoms</li> <li>- Synthetic cannabinoids (‘Spice’) fall into seven major structural groups: Naphthoylindoles (e.g. JWH-018, JWH-073 and JWH-398). <ol style="list-style-type: none"> <li>1). Naphthylmethylindoles.</li> <li>2). Naphthoylpyrroles.</li> <li>3). Naphthylmethylindenes.</li> <li>4). Phenylacetylindoles (i.e. benzoylindoles, e.g. JWH-250).</li> <li>5). Cyclohexylphenols (e.g. CP 47,497 and homologues of CP 47,497).</li> <li>6). Classical Cannabinoids (e.g. HU-210).</li> </ol> </li> <li>-Most of the synthetic cannabinoid products have a great highest affinity for cannabinoid receptors (CB1) and it binds over 100 times more tightly to CB1 receptor than ‘classical cannabis’( Please refer to previous information for additional information)</li> </ul>

<p><b>Availability</b></p>	<p>Similarities: <sup>[13,16]</sup></p> <ul style="list-style-type: none"> <li>-The availability of cannabis and synthetic cannabinoids seem to be more accessible to the young adults and adolescents</li> <li>-In most countries around the world, including the United States, synthetic cannabis is illegal. Spice use is also banned for U.S. Military personnel.<sup>[9]</sup></li> <li>-However, synthetic cannabinoid use appears to be more of a legal alternative</li> </ul>	<p>Differences: <sup>[13]</sup></p> <p>Unlike Cannabis, Synthetic Cannabinoids appear to be more accessible by users</p> <ul style="list-style-type: none"> <li>-For several years, synthetic cannabinoid substances have been easy to buy :             <ul style="list-style-type: none"> <li>- At drug paraphernalia shops</li> <li>- At novelty stores</li> <li>- At gas stations</li> <li>- And through the Internet</li> </ul> </li> <li>- Still, the chemicals used in them have a high potential for abuse and no medical benefit, authorities have made it illegal to sell, buy, or possess some of these chemicals.</li> <li>-However, manufacturers try to bypass these laws by changing the chemical formulas in their mixtures.</li> </ul>
<p><b>Screening &amp; Detection</b></p>	<p>Similarities :<sup>[17,18,19]</sup></p> <ul style="list-style-type: none"> <li>-For Cannabis users, the THC ingredients can be detected by a simple blood &amp; urine drug test, along with an oral swab test</li> <li>-Similarly, newly developed labs have successfully detected and reported the following 20 synthetic cannabinoid chemicals, in which these metabolites can be detected in the urine, blood and oral fluid (salvia) of users -</li> </ul> <p>A-796260 ; AM-1248 ; AM-2201 ; AM-223 ; AM-694 ;</p> <p>JWH-018 5- chloropentyl,; JWH-018; JWH-019; JWH-022; JWH-073; JWH-081; JWH-122; JWH-200; JWH-203; JWH-210 ;JWH-250</p> <p>RCS-4, RCS-8 UR-144 and XLR-11)</p>	<p>Differences : <sup>[18,19]</sup></p> <p>Unlike cannabis, synthetic cannabinoid cannot be tested on a general urine drug screen, in which it appears to test negative for THC.</p> <p>However, new advances have shown that liquid chromatography/tandem mass spectrometry (LC-MS/MS) and gas chromatography/mass spectrometry (GC/MS) can detect several metabolites of synthetic cannabinoid substances in the urine: JWH-018 and JWH-073, along with other various metabolites (as listed previously). These metabolites can last up to 72 hours in the urine.</p>

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**Authors' Contributions:** The authors of this case report have contributed to this manuscript / case study in the following ways:

[1] Patricia Jonquiere (Attending Psychiatrist at Jackson Memorial Hospital, Miami, FL, USA), Juan Oms MD (Program Director of Larkin Community Hospital's Psychiatry Residency Program, South Miami, FL, USA), and Gerardo F. Ferrer MD (Chief Resident/Attending Psychiatrist at Larkin Community Hospital's Psychiatry Residency Program, South Miami, FL, USA) had provided substantial contributions to the conception and analysis of the data provided in the manuscript, primarily in regards to their expertise and knowledge on the effects of synthetic marijuana overdose and use.

[2] Boye Akinyemi MD (PGY-1 (First Year Psychiatry Resident at Larkin Community Hospital's Psychiatry Residency Program, South Miami, FL, USA) had been involved in drafting the manuscript. Dr. Akinyemi was also responsible for revising the manuscript critically for important intellectual content, as well as being responsible for composing the "Further Conclusions" section of this manuscript.

[3] Rhaisa Dumengio MD (Director of In-Patient Services at Larkin Community Hospital's Psychiatry Residency Program, South Miami, FL, USA) had given final approval of this version to be published after reviewing the manuscript numerous times.

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