mhc
MENTAL HEALTH CLINICIAN

LITERATURE REVIEW Open Access

Review of the many faces of synthetic cannabinoid toxicities

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How to cite: Alipour A, Patel PB, Shabbir Z, Gabrielson S. Review of the many faces of synthetic cannabinoid toxicities. Ment Health Clin [Internet]. 2019;9(2):93-9. DOI: 10.9740/mhc.2019.03.093.

Abstract

Introduction: Synthetic cannabinoids (SCs) are psychoactive substances that are gaining popularity for their availability and lack of detection by standardized drug tests. Although some users may perceive SCs as safer alternatives to marijuana, some SCs are more potent and result in more severe toxicities.

Methods: A search of the literature was conducted in the PubMed and SciFinder databases. Results in PubMed were limited to human studies, and only articles in English were included.

Results: Review of the literature illustrates the hazards associated with SC use. A range of severe toxicities affecting numerous systems has been identified, such as arrhythmias, myocardial infarction, sudden cardiac death, psychosis, suicidal ideation, seizures, acute tubular necrosis, and intracranial hemorrhage. Additionally, a recent outbreak of coagulopathies and at least 4 associated deaths due to SCs tainted with brodifacoum have been reported.

Discussion: Synthetic cannabinoids may be perceived as a safer alternative to marijuana; however, SCs can be more potent at the cannabinoid receptors and in turn have greater toxicities. Limited information is available on the metabolism of SCs; however, cytochrome P450 pathways may be involved, which could result in drug interactions and unpredicted adverse effects. Toxicity with SC use is not just related to its effects, but also to additives that may taint these products and enhance their effects. Health care providers should be aware of the range of toxicities related to SC use, and tainted products such as these agents are not detected on routine drug screens.

Keywords: synthetic marijuana, synthetic cannabis, synthetic cannabinoids, cannabinoids, designer drugs, street drugs, toxicity, hemorrhage, bleeding, K2, spice

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Disclosures: The authors of this article have no conflicts of interest to disclose.

Introduction

Synthetic cannabinoids (SCs) available commercially by names such as spice and K2 are man-made compounds that bind to the G protein–coupled cannabinoid receptors (CB_1 and CB_2).[1,2] The CB_1 and CB_2 receptors have been found to affect multiple systems in the human body, including but not limited to the central nervous, respiratory, cardiovascular, and immune systems.[2]

The structural features of many SCs have demonstrated higher binding affinities to the CB_1 and CB_2 receptors when compared to tetrahydrocannabinol (THC), the active ingredient in cannabis.[3-6] Tetrahydrocannabinol displays partial agonism at the CB_1 and CB_2 receptors, whereas SCs may be full agonists at these receptors.[7,8] Additionally, SC metabolites have stronger affinities for the CB_1 and CB_2 receptors compared to THC, which may result in distinct effects.[8] Continued binding of metabo-

lites to the CB_1 receptor may be responsible for the greater potency and longer duration of pharmacologic effects as well as toxicity.[7]

Many SC compounds and cannabinoid structural classes have been placed into Schedule I of the Controlled Substances Act, following signed legislation of the Food and Drug Administration Safety and Innovation Act of 2012 by President Obama.[9,10] Schedule I substances, according to the US Drug Enforcement Administration,[11] are defined as "drugs with no currently accepted medical use and a high potential for abuse." However, new SCs are continuously being created, and therefore, some of these products may not be classified as Schedule I substances currently.[10,12]

Synthetic cannabinoids constitute 1 of the largest groups of psychoactive substances and were originally manufactured for experimentation purposes in 1965.[2,3,13] These compounds, specifically spice, gained popularity for their psychoactive properties in the mid-2000s.[13] Synthetic cannabinoid products were available via the Internet as well as in specialty smoking shops and convenience stores.[6] Synthetic cannabinoids are usually incorporated into fragrances, potpourri, and incense with a warning label "not for human consumption."[6(p526)] It is important to note SCs are not a part of standard drug tests.[14] However, data from US poison control centers indicate calls regarding SC exposures more than doubled from 2906 calls in 2010 to 6959 in 2011.[15]

Serious adverse health events linked to the ingestion of SCs have been reported.[5] Reported SC toxicities include but are not limited to agitation, anxiety, drowsiness, tachycardia, hypertension, nausea, and vomiting as well as other serious adverse clinical effects, such as psychosis, stroke, seizures, and cardiac complications.[4,5] Additionally, between March and April of 2018, there was an outbreak of severe bleeding events in patients who had ingested SC products tainted with brodifacoum (a rodenticide) with a majority of cases occurring in Illinois.[16,17] Synthetic cannabinoid products have an unpredictable nature due to unregulated manufacturing processes and variability of ingredients.[10] Considering the diverse toxicity profile of these compounds, it is important to identify the scope and severity of the public health threat posed by SC use as described in the literature, including recent bleeding events with tainted SC products. To our knowledge, this is the first published review of SC toxicities to include recent coagulopathies associated with tainted SC use.

Methods

A literature search was conducted in the PubMed MEDLINE and SciFinder databases. Results in PubMed were limited to human studies, and only English articles were included. No database filters were used for publication dates; however, articles from 2012 to 2018 were selected for this review. MeSH (medical subject headings) terms used in the search were *cannabinoids*, *designer drugs*, and *street drugs*. Keywords used were *synthetic marijuana*, *synthetic cannabinoids*, and other related terms. *K2* and *spice* were also used as keywords in the search to include well-known synthetic marijuana brands. Keywords and MeSH terms for *bleeding* in relation to adverse effects of SCs were also used.

A second search of the literature was completed in the SciFinder database. Due to SciFinder's recommended method of searching, the phrase *toxicity of synthetic cannabinoids* was used as the main search query to help the database identify the major concepts of *toxicity* and *synthetic cannabinoids*. Because SciFinder also searches MEDLINE, results were limited to the CAplus index in SciFinder, which is a comprehensive database of the chemistry literature that includes resources not covered in MEDLINE.

Results

Cardiac Effects

Acute cardiac toxicities are relatively common among SC users presenting to medical centers for emergency care.[5,18,19] The presence of tachycardia is 1 of the most commonly reported findings after ingesting SCs.[5,20] Supraventricular tachycardia with heart rates as high as 172 beats per minutes were reported in a 24-year-old after ingestion of e-cigarette fluid mixed with SCs.[21]

In addition, acute myocardial infarction (MI) has been associated with SC use in adolescents and adults.[22] A 15-year-old with a 30-month history of SC abuse presented with ST segment elevation MI and stroke.[23] Myocardial infarction was also reported in the case of a 39-year-old who presented with left-side chest pain and who subsequently collapsed with ventricular fibrillation.[12] The individual was noted to have ST segment elevation and elevated troponin.[12]

Cardiovascular fatalities associated with SC use have also been described in the literature. Cases include sudden cardiac death in a 22-year-old after smoking SC (MDMB-CHMICA) and fatal coronary artery thrombosis in a 41-year-old after using the SC ADB-FUBINACA.[1,24]

Hematological Effects

In March of 2018, the Illinois Poison Center informed the Illinois Department of Public Health of cases of high

TABLE 1: Bleeding with use of synthetic cannabinoids tainted with brodifacoum

	Panigrahi et al[26]	Hussain et al[27]
State, country	Maryland, United States	Illinois, United States
Patient demographics	Case 1: 51-year-old male Case 2: 39-year-old female	38-year-old male
Clinical presentation	Case 1: Bruising of thigh and elbow accompanied by leg swelling and severe back pain. Return visit to ED 2 d later showed worsening hematuria, bruising, leg pain, and swelling. Case 2: Stomach and extremities had spontaneous bruising, hematuria, hemoptysis, epitaxis, and abdominal pain that radiated to the back.	Hemoptysis and dark urine for 2 d prior to presenting to the ED
Radiologic findings	Case 1: Contrast-enhanced CT image: bilateral hemorrhagic, pyelitis, and ureteritis Case 2: CT of abdomen and pelvis: hemorrhagic pyelitis/ureteritis	None listed
International normalized ratio	Case 1: >12.2 (greater than measurable threshold) Case 2: Greater than measurable threshold	>10
Toxicology screen	Case 1: Negative for cannabinoid; positive for opiates (on opiate for back pain) Case 2: Negative for cannabinoid, positive for brodifacoum	Positive for brodifacoum in the serum
Synthetic cannabinoid compound	Case 1: K2 Case 2: Per study authors, likely the same source as her fiancé in case 1	K2
Treatments received	Both patients received intravenous vitamin K × 1 dose, then oral vitamin K while inpatient and subsequently discharged on oral vitamin K. Patient in case 1 received 1 unit of fresh-frozen plasma while in the hospital due to severe coagulopathy	Received intravenous vitamin K followed by oral vitamin K, which was recommended by poison control to be continued on discharge for at least 1 mo

CT = computed tomography; ED = emergency department.

international normalized ratios and unexplained bleeding in emergency departments over the past 2 weeks in individuals who had used SC in the past 3 days.[25] This prompted an investigation by health and law enforcement agencies. Following this investigation, 155 cases were identified: 4 fatalities occurred from major bleeding, 147 individuals required hospitalization, and 8 required only emergency department care.[25] All individuals had high international normalized ratios and reported at least 1 bleeding site.[25] Hematuria was the most commonly occurring sign.[25] Clinical specimens from 81 subjects with probable or confirmed cases tested positive for brodifacoum, which is used in rodenticides as a long-acting vitamin K antagonist.[25] Three case reports were published after the outbreak describing coagulopathy related to K2 tainted with brodifacoum; additional information on these cases[26,27] can be found in Table 1.

Aside from the recent outbreak of severe bleeding occurring mostly in Illinois and also in other states, reports on coagulopathies as adverse effects have been limited. Other reports of bleeding have included the development of a right frontal intracerebral hematoma in a habitual user of spice.[28] In addition, published reports[28,29] have demonstrated instances of intracranial hemorrhage following use of spice.

Neurologic Effects

The possibility that SC abuse may cause neurotoxicity is well documented in the literature.[30] In a recent case report,[31] a 25-year-old presented with symptoms of stroke the morning after smoking an SC-containing product called freeze. An extensive diagnostic workup was conducted, including magnetic resonance imaging, which revealed acute ischemic infarction.[31] Further examination via magnetic resonance angiography and ultrasound showed occlusion of the proximal right middle cerebral artery.[31] Additionally, 2 cases of ischemic stroke within hours of first SC use were reported, suggesting a possible association.[32]

Seizures are another severe adverse effect occurring with SCs, but they are rarely reported with cannabis use given THC's weak affinity for the cannabinoid receptors.[33] The exact mechanism of SC-induced seizures is currently

unknown.[33] However, it is postulated strong binding of the CB_1 receptors may be involved.[33] In a prospective observation study, Hermanns-Clausen et al[18] conducted a toxicological analysis of individuals (n = 44) presenting to emergency departments after the ingestion of SCs. A high frequency of generalized seizures (n = 12, 27%) was seen in patients after using MDMB-CHMICA and/or AB-CHMINACA.[18] In addition, Schep et al[4] described a case in which a 23-year-old experienced seizure activity 6 hours after smoking K2.

Psychiatric Effects

Synthetic cannabinoids have been associated in case reports with numerous psychiatric adverse effects, such as anxiety, agitation, suicidal ideation, depersonalization, dissociation, and psychosis.[6,34,35] Synthetic cannabinoids often result in more amplified neuropsychiatric effects than THC due to their considerably greater potency.[36] Acute intoxication with SCs may result in psychotic-like symptoms, including disorganized behavior, hallucinations, and paranoia, which often last longer than anxiety or motor symptoms.[10] In a multicenter cohort analysis, Monte et al[37] identified 353 cases of SC toxicity from the ToxIC registry, which contains clinical information relating to cases requiring care by medical toxicologists within the United States. In this analysis,[37] toxic psychosis, delirium, and agitation were the most frequently presenting signs. In a systematic review by Tait et al,[5] agitation was identified as the most common presenting psychiatric effect. Overall, although there is a lack of controlled studies of SCs, reports indicate SCs may trigger psychotic symptoms in subjects with no previous history of psychosis and reemergence of psychosis in vulnerable patients.[10]

Jaenicke et al[35] reviewed cases of SC use as detected from blood samples in criminal and traffic offenses. The authors[35] identified 12 cases of SC use with 10 of the cases involving multidrug consumption. Alcohol and cannabis were often co-occurring drugs with SCs.[35] One person experiencing paranoia before cannabinoid agonist use was noted to have worsened paranoia following consumption.[35] The subject had blood samples positive for SC (JWH-122) and cannabis (THC) as well as a cannabis metabolite (11-nor-9-carboxy-Δ9-tetrahydrocannabinol).[35] Dopaminergic pathways interacting with the endocannabinoid system can result in psychosis.[33] This may explain episodes of psychosis and early schizophrenia symptom onset that may develop after cannabis use.[33]

Renal Effects

Case reports and case series suggest an association between the use of SCs and the development of acute kidney injury (AKI).[36,38] A 22-year-old with no previous medical conditions presented 3 days after smoking SC with flank pain, nausea, vomiting, and AKI.[36] Renal ultrasound demonstrated no acute abnormalities; however, acute tubular necrosis was detected on renal biopsy.[36] After receiving supportive management, renal function improved and serum creatinine decreased from 7.05 mg/dL to 2.5 mg/dL before discharge.[36] The authors then summarized 20 other cases of AKI associated with SC abuse.[36] Of the 20 cases identified, 19 of the 20 were men, and their ages ranged from 15 to 33 years old.[36] They presented with nausea, vomiting, abdominal pain, diarrhea, flank pain, back pain, and/or anuria, of which nausea, vomiting, and abdominal pain were the most common.[36] Of the 20, 9 developed acute tubular necrosis, acute interstitial nephritis was identified in 3, and dialysis was required in 5.[36]

Buser et al[38] published a case series on individuals who developed AKI (defined as a creatinine >1.3 mg/dL) after using SCs. Included individuals had to be between the ages of 13 and 40 years of age "without known preexisting renal disease."[38(p665)] Based on this criteria, 9 men were identified with ages ranging between 15 and 27 years of age and presented with nausea, vomiting, abdominal pain, or back pain. All individuals required hospitalization, of which 1 needed dialysis. The authors[38] reviewed laboratory data and patient history and did not find any other causes for the development of AKI.

Discussion

Synthetic cannabinoids have been advertised as legal or harmless alternatives to marijuana, leading to the misconception of the safety of these substances, when, in fact, severe adverse effects and need for emergency medical treatment are more likely to occur with SCs than cannabis.[5,7,10,37] According to Martinotti et al,[7] the risk of an emergency room visit is approximately 30-fold higher with SC than with cannabis. The difference in severe adverse effects highlights the increased safety risk as agitation and cardiotoxicity are, respectively, 3.8 and 9.2 times more likely to occur with SCs than traditional cannabis.[7] Synthetic cannabinoids are full agonists with higher potency when compared to the partial agonist THC at the CB_1 and CB_2 receptors, which may account for their greater toxicities.[39]

The literature[5,6,15,37,40] indicates a range of adverse effects associated with SC use (see Table 2) from tachycardia to more severe cases, such as MI, stroke, psychosis, seizures, and associated deaths. A 2016 systematic review by Tait et al[5] identified adverse events due to SC use. Nausea, agitation, and tachycardia presented most often in young men and generally resolved with supportive care.[5] Serious adverse events and related deaths were less common.[5]

TABLE 2: Reported effects with synthetic cannabinoid intoxication[5,6,15,37,41,45]

System	Synthetic Cannabinoid Intoxication Effects
Cardiac	Tachycardia, supraventricular tachycardia, ventricular fibrillation, myocardial infarction, sudden cardiac death, coronary arterial thrombosis
Hematological	Immune thrombocytopenia, intracranial hemorrhage, coagulopathy
Neurological	Dizziness, drowsiness, tremor, altered mental status, seizure, acute ischemic infarction
Psychiatric	Agitation, anxiety, paranoia, psychosis, suicidal ideation, delirium, dissociation, depersonalization, hallucinations, disorganized behavior
Renal	Acute kidney injury, acute tubular necrosis
Other	Nausea, vomiting, rhabdomyolysis, hyperthermia

Monte et al[37] reported agitation, toxic psychosis, and delirium as the most commonly occurring symptoms in their multicenter analysis. Although treatment is not the focus of this review, caution should be exercised when treating psychosis related to SC use as antipsychotic treatment may decrease the seizure threshold, and SC use has been associated with seizures.[41] Although there is limited data on the pharmacology of SCs, literature[10,36,42,43] suggests possible involvement of the cytochrome P450 system and possible unforeseen drug-drug interactions and toxicity. Cytochrome P450 (CYP) metabolism of the SCs JWH-018 and AM2201 was found to be primarily by CYP2C9 and CYP1A2.[43]

Manufacturing of SCs is not regulated, leading to variation in components and amounts in the variety of products available.[41] Therefore, in addition to concern for possible toxicities directly associated with SCs, additional toxicity concerns exist due to dangerous substances that may have been incorporated into these products.[41] Synthetic cannabinoids may be mixed with other psychoactive substances, such as bath salts or ecstasy/Molly by dealers to increase sales.[41] The recent outbreak in the United States of severe bleeding events leading to at least 4 deaths due to SCs tainted with the rodenticide, brodifacoum, underscores these dangers.[16,25,27,41] As a super warfarin, brodifacoum has been used by humans for intentional harm.[27] Compared to warfarin, brodifacoum is up to 100 times as potent and has a half-life that is at least 9.6 times longer (16 days vs 40 hours).[27] Because of the very long half-life, bleeding may last up to months after poisoning.[27] Brodifacoum may be stored in and released from lipids over a long time period.[27] It is suggested that the storage of brodifacoum prolongs and enhances the high of these products, which may explain its presence in SCs.[27]

Phytonadione (vitamin K1) has been used to treat these individuals, but the optimal dosage is yet to be determined.[16] Phytonadione doses of up to 200 mg/d have been required during the hospitalization of some individuals.[16] Difficulty arose when outpatient doses were required at discharge due to the high cost of this medication and pharmacies not stocking adequate supplies.[16] Although prescription phytonadione is costly, individuals should be warned not to use phytonadione dietary supplements as they do not provide enough phytonadione to adequately treat coagulopathy.[16] More severe bleeding may necessitate the use of fresh-frozen plasma or prothrombin complex concentrate.[16]

The outbreak of severe bleeding events also highlights the need for better detection and awareness of SCs as they may not be identified on standard drug screenings.[5] Davies et al[44] describe the challenges of identifying SCs but mention that tandem mass spectrometry, accurate mass technique, and simple method modification may be useful. The lack of readily available methods to detect these compounds coupled with the variability of their composition may limit our ability to further quantify the prevalence of toxicities.[5] When patients present to emergency departments after ingesting SCs with behavioral adverse effects or severe illness, SC use is not immediately discovered.[5] Therefore, health care professionals should be aware of life-threatening toxicities of SCs.[5]

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