Synthetic Cannabinoids

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Abstract: Synthetic cannabinoids (SCBs), also known under the brand names of "Spice," "K2," "herbal incense," "Cloud 9," "Mojo" and many others, are becoming a large public health concern due not only to their increasing use but also to their unpredictable toxicity and abuse potential. There are many types of SCBs, each having a unique binding affinity for cannabinoid receptors. Although both Δ^9-tetrahydrocannabinol (THC) and SCBs stimulate the same receptors, cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2), studies have shown that SCBs are associated with higher rates of toxicity and hospital admissions than is natural cannabis. This is likely due to SCBs being direct agonists of the cannabinoid receptors, whereas THC is a partial agonist. Furthermore, the different chemical structures of SCBs found in Spice or K2 may interact in unpredictable ways to elicit previously unknown, and the commercial products may have unknown contaminants. The largest group of users is men in their 20s who participate in polydrug use. The most common reported toxicities with SCB use based on studies using Texas Poison Control records are tachycardia, agitation and irritability, drowsiness, hallucinations, delusions, hypertension, nausea, confusion, dizziness, vertigo and chest pain. Acute kidney injury has also been strongly associated with SCB use. Treatment mostly involves symptom management and supportive care. More research is needed to identify which contaminants are typically found in synthetic marijuana and to understand the interactions between different SBCs to better predict adverse health outcomes.

Key Indexing Terms: Synthetic marijuana; Cannabinoids; Abuse; Toxicity; Acute kidney injury. **[Am J Med Sci 2015;350(1):59–62.]**

Synthetic cannabinoids (SCBs) were initially synthesized in the early 1960s following the discovery of the structure of Δ^9-tetrahydrocannabinol (THC). These compounds were used to investigate possible therapeutic effects and to study cannabinoid receptor pharmacology. However, in the early 2000s, SCB variations started to be produced commercially and abused. These drugs are marketed under brand names, such as "Spice," "K2," "herbal incense," "Cloud 9," "Mojo" and many others. In addition to its psychoactive effects, synthetic marijuana is popular because it is cheap and undetectable on routine drug screens and was thought to be "natural" and legal, until recently.[1–3]

SCBs are sold over the Internet and in head shops. They come in ready-to-use drug formulations that contain around 3 g of psychoactive plant material, such as "wild dagga" (*Leonotis leonurus*) and "Indian warrior" (*Pedicularis densiflora*), which is laced with SCBs (Figure 1). The presence of these herbal or natural plants gives some of its users the misconception that the drugs are "natural."[4,5] K2 or Spice is made by 1st dissolving the SCB in a solvent, such as acetone or ethanol. The plants are then saturated and dried, allowing the solvent to evaporate; SCBs remain on the plant material (Figure 2). The amount of SCBs left on the plants is highly variable, and this leads to variable potencies of different K2 and Spice formulations.[5,6]

CHEMICAL PHYSIOLOGY AND DETECTION

Similar to natural cannabinoids (THC), SCBs can be smoked, insufflated or ingested and have the psychoactive effects.[7] Both SCBs and THC bind cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2) and stimulate CB_1 more than CB_2. These receptors are found mainly in the central nervous system but are also found in various peripheral tissues, the lungs, liver and kidneys. Within the brain, CB_1 receptors are located in the cerebral cortex, hippocampus, basal ganglia and cerebellum.[8] CB_1 receptors are G-coupled, and stimulation decreases cyclic adenosine monophosphate levels.[9] These receptors are associated with the psychotropic effects of cannabinoids. CB_2 receptors are located in immune and hematopoietic cells; stimulation of this receptor has immunomodulatory effects.[8] The relationship between the 2 receptors is not well understood. SCBs are full CB_1 receptor agonists, whereas THC is a partial CB_1 receptor agonist. Therefore, SCBs bind to the cannabinoid receptors with a higher affinity than THC.[9] When tested on laboratory animals, CB_1 receptor stimulation elicits what is known as the cannabinoid tetrad of hypothermia, analgesia, catalepsy and locomotor suppression.[10] Cannabinoids also bind nonspecifically to cellular membranes and act on opioid and benzodiazepine receptors, prostaglandin synthetic pathways and protein metabolism. These interactions have the potential for complex effects and likely contribute to toxicity.[11] The metabolism of these compounds involves oxidation by cytochrome P450 then conjugation by UDP-glucuronosyltransferase (UGT).[10,12] The metabolites of JWH-018, JWH-073 and AM2201, 3 different SCB structures, retain a high affinity for CB_1 receptors, whereas metabolites of THC have reduced affinity for CB_1 receptors.[10] Patton et al[13] have demonstrated that metabolism of SCBs depends on the drug and the individual user. These differences could help explain differences in clinical toxicity and may reflect the induction or inhibition of cytochrome P450 and UGTs.

SCBs are more potent, unpredictable and toxic than THC and pose a significant public health concern. The lack of quality control leads to batch-to-batch differences in SCB concentrations in different K2 or Spice products.[5] Furthermore, K2 or Spice products usually contain more than 1 structure or form of SCBs that can interact in unpredictable ways.[14] Brents et al demonstrated that coadministration of JWH-018 and JWH-073, 2 different SCB structures, in mice can produce additive, synergistic or antagonistic interactions depending on study design. The authors cautioned against the use of both SCBs together. Similar synergistic effects occurring among the multiple SCBs present in K2 products may increase their relative potency and contribute to negative side effects commonly associated with these drugs.[15] There are many types of SCBs, and each has a unique binding affinity for cannabinoid receptors (Figure 3). More than 20 different SCB structures have been identified, and new ones continue to be synthesized. These different structures elicit highly variable responses and have unknown contaminants. The structures are different from THC and, therefore, are not detected in routine drug screens.[16]

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FIGURE 1. Plant material (Indian warrior) used as a carrier for synthetic cannabinoids.

SCBs in blood and urine can be identified with gas chromatography-mass spectrophotometry, liquid chromatography-tandem mass spectrometry[17] and time-of-flight mass spectrometry. SCBs can be identified by specialized clinical laboratories but at increased cost and time.

USE PATTERNS

In comparison with traditional marijuana, SCB products are relatively low priced, are widely available and are extremely tempting for young people who may want to try marijuana or other drugs but are afraid of legal or social consequences.[5] These factors, combined with the fact that SCBs are often not detected in standard drug screens, have spurred an epidemic of K2 use on college and high school campuses. One in 9 high school seniors admitted using K2 in 2011, making K2 the 2nd most prevalent illicit drug after marijuana.[7]

A survey by Barratt, including 316 SCB users in Australia, showed that most users were men in their late 20s who were employed or were students. Ninety-six percent of those surveyed self-identified as natural cannabis users as well.[18] Another online survey included 168 SCB users and showed that SCB users were primarily single, Caucasian men with at least a high school education.[7] Although the use of SCBs has become more prevalent, studies have shown that people who have tried both SCBs and natural marijuana prefer

FIGURE 2. Commercial product with synthetic marijuana.

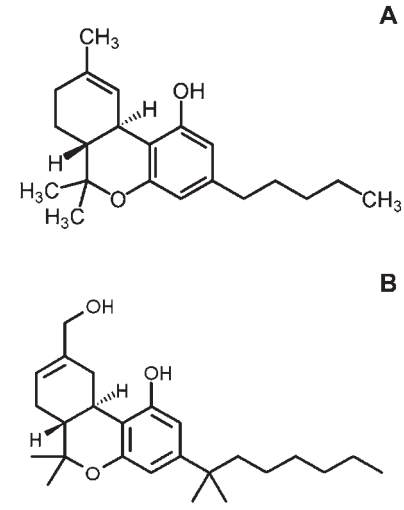

FIGURE 3. (A) Chemical structure for Δ^9-tetrahydrocannabinol (THC). (B) Chemical structure for HU-210, a synthetic analog of THC.

natural marijuana. For example, 17% of 14,966 participants in an online survey reported the use of synthetic marijuana. Respondents (41%) who reported recent use in the previous 12 months also reported using natural cannabis on a consistent basis. Ninety-three percent preferred natural cannabis to SCBs due to a more pleasurable effect with natural cannabis when high. They reported more hangover effects and more negative effects when high with SCBs. However, 7.2% preferred synthetic marijuana due to its convenience, low cost, heightened psychoactive effects and difficult detection.[19]

Studies have shown that users of SCBs use other drugs as well. In the online survey reported by Vandrey, many respondents endorsed the use of other drugs, including alcohol (92%), cannabis (84%), tobacco (66%), hallucinogens (37%), opioids (34%), 3,4-methylenedioxymethamphetamine (MDMA, 29%), benzodiazepines (23%), amphetamines (22%), cocaine (17%), salvia divinorum (17%), heroin (7%), inhalants (7%) and methamphetamines (3%).[7] In the study of Winstock, over 95% of the respondents reported use of alcohol and natural cannabis in the past year. Over 50% reported using either MDMA or tobacco in the past year, and 33% reported use of mushrooms, cocaine, lysergic acid diethylamide, benzodiazepines or amphetamines in the past year.[19]

ABUSE POTENTIAL AND TOXICITY

Synthetic marijuana is becoming a large public health concern due not only to its increasing use but also to its unpredictable toxicity and abuse potential. In a study conducted by Forrester comparing SCB and marijuana exposures reported to Texas Poison Control, the number of reported cases of synthetic marijuana toxicity was more than 4 times that of natural marijuana. Of the 418 cases of SCB toxicities reported, the following clinical effects were noted: tachycardia (36.6%), agitation and irritability (19.1%), drowsiness (17.5%), hallucinations or delusions (11.2%), hypertension (9.6%), nausea (9.3%), confusion (8.9%), dizziness and vertigo (8.9%) and chest pain (6.9%).[20] A second study by Forrester in 2012, based on 749 SCB exposures reported to Texas Poison Control Centers from January 2010 to June 2011, compared toxicities seen in the adolescent and adult users. The 10 most common adverse effects in adults and adolescents were, respectively, tachycardia (38% and 41.6%), drowsiness/lethargy (14.6% and 24.3%), agitation/irritability (24.9% and 16.4%), vomiting (16.0% and 13.1%),

hallucinations/delusions (11.3% and 11.5%), nausea (10.1% and 8.5%), confusion (11.3% and 8.2%), hypertension (11.3% and 7.5%), chest pain (5.6% and 6.9%) and dizziness/vertigo (8.2% and 5.2%).[21] These 2 databases did not have any information confirming the use of SCBs using drug assays. Consequently, the information on use depended on reports from involved parties. Gurney et al[22] have published an extensive review of the pharmacology, toxicology and adverse effects associated with SCBs. This study includes summary tables of case series and case reports with either no toxicological data or with confirmed assays using both qualitative and quantitative tests.

SCB use has been associated with various other neurological and psychiatric toxicities. Case reports have identified seizure-like activity,[23] catatonia[24] and self-mutilation behaviors[25] from SCB use. The cases with seizure-like activity and catatonia had confirmed SCB use with toxicological assays. There is speculation based on these case reports that, similar to THC, synthetic marijuana can trigger acute psychosis in genetically predisposed individuals.[26] Furthermore, the use of SCBs in patients with preexisting psychotic disorders can worsen current psychotic symptoms or facilitate the appearance of new psychotic symptoms.[27,28] Glue et al studied 21 admissions to psychiatry wards by 17 different patients who reported using synthetic marijuana. Four of the patients had no previous psychiatry ward admissions. Ten patients had recurrences of previous psychotic symptoms, and 4 had new psychotic symptoms.[28] Patton et al[29] reported a fatal case of self-induced trauma with metabolites of AM2201 in postmortem blood. Saito also reported a fatal case with MAM-2201 poisoning with SCB in the blood (12 ng/g), liver (8.1 ng/g), kidney (12.4 ng/g), brain (4.3 ng/g) and adipose tissue (1,535 ng/g).[30] Based on the autopsy, the cause of death was not clear based on the autopsy.

Cardiovascular, renal and gastrointestinal (GI) toxicities have also been associated with the use of SCBs. Case reports have attributed acute cerebral ischemia,[31] myocardial infarctions[32,33] and hyperemesis[34] to SCB use. There is substantial evidence linking SCBs to acute kidney injury and acute tubular necrosis.[35,36] One case series identified 16 patients with histories of recent synthetic marijuana use and studied their renal function.[37] Eight patients had proteinuria, 5 had casts and 8 had red blood cells in their urine. Twelve had renal ultrasounds, and 9 showed increased cortical echogenicity. Eight patients had renal biopsies which demonstrated acute tubular injury (6 patients) and acute interstitial nephritis (3 patients). Six patients had analysis of clinical specimens (blood and/or urine), and 4 had a fluorinated SCB (XLR-11) detected.

The most common pulmonary injuries associated with cannabinoids have not been from SCB use but rather from its production. Inhalation or blast injuries have been reported during the production of "wax," a high potency marijuana made by butane extraction of plants to remove the cannabinoids. When the butane evaporates, the cannabinoids are concentrated leaving a "waxy" material that can have up to an 85% THC concentration. There have been multiple reports of butane exploding while being evaporated, resulting in inhalation injuries, pneumothorax and pneumomediastinum.[38]

Treatment for acute intoxication of SCBs includes observation and supportive care. There is no antidote. The most common intervention is intravenous fluids for volume expansion. Sedation with benzodiazepines can reduce psychomotor agitation and seizures. GI decontamination with forced emesis or gastric lavage can be used if a large amount of the substance is ingested. If necessary, antipsychotics, such as haloperidol, can be used for acute psychosis, and antiemetics can be used for nausea.[39–41] Patients may require hospital admission for observation and rarely require intubation and mechanical ventilation.[41] Patients who present with hypertension and tachycardia might benefit from a mixed alpha-1 adrenergic receptor blocker and nonselective beta blocker, such as labetalol. In cases of acute kidney injury, volume expansion with 0.9% sodium chloride or isotonic sodium bicarbonate is usually the 1st step in care.

Several studies have shown that withdrawal symptoms can occur after discontinuation of both SCBs and THC, contributing to the abuse potential of drugs.[42–45] Zimmermann et al identified a case of withdrawal phenomena and dependence syndrome according to the *DSM-IV* criteria after the discontinuation of large amounts of daily Spice Gold consumption. This syndrome is marked by drug craving, elevated blood pressure, nausea, tremor, diaphoresis and nightmares after the discontinuation of the drug.[45] Hirvonen et al found region-specific downregulation of CB_1 receptors with chronic THC use that likely contributes to dependence of the drug. This downregulation reversed 4 weeks after drug discontinuation.[43] Because SCBs stimulate the same receptors as THC, it can be hypothesized that chronic SCB use could result in a similar downregulation of CB_1 receptors; however, there have been no studies reported to support this hypothesis.

CONCLUSIONS

The use of SCBs has significantly increased throughout the world. These drugs are full agonists of CB_1 receptors, and their metabolic derivatives often have receptor activity. Multiple chemical compounds with this activity have been synthesized, and they are not usually detected in routine assays for cannabinoids. They can have multiple adverse effects, including central nervous system effects, cardiovascular, GI effects, and acute renal failure. Death has been reported with their use. Physicians should suspect possible toxicity with SCBs in patients presenting to emergency departments and hospitals with unexplained symptoms even if drug screens are negative. More research is needed to identify contaminants in synthetic marijuana, to understand metabolic pathways and to develop rapid screening assays. The public needs more information about the hazards associated with these drugs.

KEY POINTS

1. SCBs are popular new drugs of abuse that have many different names, structures and clinical effects.
2. SCBs are more toxic and unpredictable than natural cannabinoids.
3. SCBs are often used with other illicit drugs. Patients who test positive for other drugs of abuse should be asked about recent use of SCBs. However, these drugs are not usually detected with routine assays for cannabinoids.
4. Emergency room physicians or intensivists should closely monitor renal function tests if SCBs toxicity is suspected.

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