

Synthetic cannabinoids 2015: An update for pediatricians in clinical practice

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Abstract

Synthetic cannabinoids are a group of substances in the world of designer drugs that have become increasingly popular over the past few years. Synthetic cannabinoids

are a chemically diverse group of compounds functionally similar to THC. Since first appearing on the world market a few years ago these compounds have evolved rapidly. Newer more potent analogues have been developed. Identifying youth who abuse these substances can be difficult. Newer forms of consumption have also evolved. These products are now manufactured in products that look like natural cannabis resin and in liquid cartridges used in electronic cigarettes. Synthetic cannabinoids appear to be associated with potentially dangerous health effects that are more severe than that of marijuana. Some synthetic cannabinoid compounds have been associated with serious physical consequences, such as, seizures, myocardial infarction and renal damage. In addition, psychoactive effects, such as aggression, confusion, anxiety and psychosis have also been reported. The diagnosis remains primarily clinical with toxicological confirmation difficult due to manufacturers constantly developing new analogues to avoid detection. Pediatricians are urged to familiarize themselves with these drugs and the typical presentations of patients who use them.

Key words: Synthetic; Cannabinoids; Youth; Children; Adolescents

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Core tip: Synthetic cannabinoids are a group of substances that are typically much more potent than natural cannabis. These substances have been increasingly abused by youth over the past few years. A number of published reports have emerged documenting the serious health consequences associated with use of these products. Seizures, myocardial infarction and renal damage are some of the significant physical consequences associated with their use. With current limitations of toxicological analyses pediatricians are urged to familiarize themselves with these drugs and the typical presentations of patients who use them.

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INTRODUCTION

Synthetic cannabinoids (SCs), also known as cannabimimetics, were originally synthesized in the 1960's, but emerged as recreational drugs in Europe in about 2004. They became popular as a recreational drug in Germany in 2008, and have been increasingly available worldwide since then^[1-3]. Over 130 different synthetic cannabinoids have been detected in recent years. Most of these substances appear to be manufactured in China. After being shipped in powder form to Europe, the chemicals are typically added to plant material, packaged for sale as "legal high" products and often misleadingly labelled "not for human consumption".

SCs are usually smoked. Recently several countries have also reported finding the substances in products that look like cannabis resin either in branded "legal high" products or simply misrepresented as cannabis resin on the illicit market. This development is likely to be a response to the popularity of cannabis resin in many countries. Another recent development has been the manufacturing of synthetic cannabinoids in the liquid cartridges used in electronic cigarettes. The use of SCs in electronic cigarettes likely reflects manufacturers' opportunistically taking advantage of the recent popularity of "vaping" among young people. Synthetic cannabinoids have also been detected in mixtures containing other psychoactive substances such as stimulants, hallucinogens and sedatives and in a small number of cases, they have been detected in what are sold as ecstasy tablets^[4].

Users often perceive these preparations as a natural way of getting high that is also legal and undetectable. The preparations are far from natural: They consist of unknown mixtures of plant products that are sprayed with a liquid form of the SCs, containing many unidentified chemical structures^[5]. New preparations are constantly being synthesized, leading to the difficulties developing reliable methods of detection. Several identified forms of synthetic cannabinoids have been banned, and are therefore illegal, but newly synthesized SCs are designed to circumvent any laws or regulations that ban them^[6].

SCs are sold commercially under a variety of names, such as Mr. Nice Guy, Green Buddha, Blonde, Summit, Standard, Blaze, Red Dawn X, Citron, Green Giant, Smacked, Wicked-X, AK-47, Spice, Special K, K2, Kronik, Barely Legal, and Fake Weed^[7]. The cost of synthetic marijuana preparations is comparable to the cost of cannabis. These drugs have become increasingly popular among adolescents and young adults^[8]. SCs are the second-most widely used illicit drug in high school seniors

in the United States. In a 2012 national survey of 8th, 10th and 12th grade students, 4.4% of the 8th graders, 8.8% of the 10th graders and 11.3% of the 12th graders admitted using synthetic marijuana. The rise in use of SCs among younger individuals is particularly alarming. Among 8th graders SCs are the third highest category of illicit drug being used after marijuana and inhalants^[9]. A nationally representative sample of nearly 12000 high school seniors revealed 10% of students reported using SCs in the previous 12 mo, and 3.2% reported "frequent use" (at least 6 times) in the previous 12 mo. Females were significantly less likely than males to use SCs in this study. The odds of using SCs was significantly increased if the teenagers endorsed a history of using alcohol, cannabis, or cigarettes and was directly related to the number of evenings per week the teenagers went out "for fun". The strongest correlation was with a history of cannabis use. Indeed, only 0.5% of non-marijuana users in this study reported the use of SCs^[10]. Correlates from this important study of high school seniors can be used by pediatricians in the evaluation of youth who are suspected of using SCs.

In a study of college students, eight to 14% of participants in the study reported the use of SCs, starting at an average age of 18 years^[11]. The attractiveness of these SCs for young people include the lack of readily available methods of detection, the perception that these drugs are legal or "harmless," and availability in shops that sell paraphernalia for marijuana and tobacco users (head shops), in gas stations or convenience stores, or sometimes over the internet. Studies have demonstrated that the motivation for use of these products were not only to "get high" but also to avoid detection^[12,13]. Those individuals who have used both marijuana and SCs describe a "better high" from the natural cannabinoids (fewer negative subjective mood experiences), but may gravitate toward SCs for the reasons described above, especially the difficulties in detection with routine urine toxicology screenings. In a study of patients admitted to outpatient treatment for SC use, those who were on probation reported the main reason for using SC instead of marijuana was to avoid detection^[14].

In a recent study of 5947 athletes in the United States, 4.5% tested positive for SCs (using specialized detection methods unavailable in routine urine toxicology screening). This rate is much higher than the rate found in earlier studies of athletes, making it imperative for physicians to be aware of the possibility of synthetic cannabinoid use in this population. While the ages of the athletes in this study were not specified, pediatricians should be aware of the possibility of synthetic cannabinoid use in middle school, high school, and college athletes^[15].

Young people may perceive these "natural" preparations of SCs as safe. On the contrary, many instances of dangerous reactions to the SCs have been reported. These include seizures, kidney failure, rhabdomyolysis, aggression and psychosis. Calls to poison control centers regarding human exposures to synthetic marijuana have increased.

Poison control centers have already registered 4377 calls in the first 6 mo of 2015 compared with 3680 for the entire year of 2014^[16]. In 2010, more than 11000 emergency department (ED) visits in the United States involved a synthetic cannabinoid: Three-fourths of these visits involved young patients aged 12 to 29^[17]. The following year the number of ED visits involving SCs increased significantly, totaling 28531. Pediatricians should be aware that the number of ED visits involving SCs for patients aged 12 to 17 years doubled from 3780 visits in 2010 to 8212 visits in 2011. Males accounted for nearly 80% of ED visits, but a threefold increase in synthetic cannabinoid-related ED visits for females has been observed^[18]. While it is true that youth who use SCs also frequently use other substances^[10,13,14,19,20], only one third of the synthetic cannabinoid-related emergency department visits revealed use of other substances at the time of the encounter^[18]. These statistics should serve to highlight the frequency and severity of ED presentations of synthetic cannabinoid-related visits in the pediatric population.

Many clinicians are unaware of the prevalence and severity of physical and psychoactive symptoms, and the potentially serious consequences related to the use of SCs. A study of clinically active emergency physicians at a large, urban emergency department revealed that knowledge of SCs came mostly from nonmedical sources, and that most emergency physicians have only a general familiarity with SCs^[21]. Because of the prevalence of the use of SCs in adolescents, and the potential serious consequences of their use, it is imperative that pediatricians and other physicians become educated in the identification, evaluation, and treatment of youth who are using these substances. We will present information below on the identification and evaluation of young patients in the emergency department setting and outpatient office setting who may be using SCs.

PHARMACOLOGY

Cannabinoids may be classified as phytocannabinoids, endocannabinoids, or SCs, based on their origin. THC is the phytocannabinoid found in cannabis plants, and is responsible for the "high" associated with smoking natural cannabis or marijuana. Endocannabinoids are endogenous molecules involved in nervous system and immune system function. SCs are a chemically diverse group of molecules functionally similar to THC. Cannabinoids exert their effects on the nervous system *via* the CB1 receptor, found in the brain and peripheral nervous system. Within the brain, CB1 receptors are located in the cerebral cortex, basal ganglia, and hippocampus. The desired effect, or "high" associated with smoking marijuana or SCs occurs when THC or SCs bind to the CB1 receptor in the brain. SCs are a full agonist at this receptor; THC is a partial agonist. Accordingly, SCs can bind to the CB1 receptor with an affinity up to one hundred times as great as THC^[22,23].

Interestingly, synthetic cannabinoid preparations do not contain cannabidiol, a substance found in marijuana

that has anxiolytic and antipsychotic properties. In addition to their higher affinity for the CB1 receptor, SCs also have a longer half-life than naturally-occurring cannabinoids^[24]. The potentially longer duration impacts both the desired effects and the adverse psychoactive and physical effects of SCs. The absence of cannabidiol, together with a higher affinity for CB1 receptors and longer half-life compared to marijuana, may account for the increased potential of SCs to produce adverse psychiatric and physical symptoms^[25].

SCs are metabolized in the liver *via* conjugation and oxidation pathways. The complex pharmacokinetics are poorly understood, but it is clear that active metabolites exist, and that cytochrome P450 pathways can be involved in adverse drug-drug interactions in patients who mix SCs with prescription medications^[26].

CLINICAL EFFECTS

Acute effects of synthetic cannabinoid use typically last from 30 to 120 min but symptoms may last until the next day ("Hangover" feelings). Users report effects can be similar to cannabis use with the "rush" being similar to the one from cannabis, but shorter and more intense^[13,27]. Frequently, users report other effects not typical of cannabis use that are more serious in nature^[13,27-29]. Reactions are generally reported to be experienced on a sliding scale of intensity. Users mention inexperience with SC use leading to excessive dosing and type/generation or potency of SCs as influencing factors^[30]. A systematic review was conducted of literature regarding synthetic cannabinoid use in Medline, PubMed, review of abstracts from professional meetings and conferences and government reports and alerts. Our knowledge base of the clinical effects regarding SCs has grown over the past few years but many of the publications reviewed lacked toxicological confirmation. To date there are no randomized controlled studies on the clinical effects of SCs. Most of our current knowledge is based on case series and reports, admissions to emergency services, reports to poison control centers and internet forums.

The adverse effects associated with SCs appear related to both the intrinsic properties of the substances and to the way the products are produced. There have been numerous reports of non-fatal intoxications and a smaller number of deaths associated with their use. Some of these compounds are very potent; the potential for toxic effects is high, even for the experienced user. The process by which synthetic cannabinoid products are manufactured has been associated with uneven distribution of the substances within the herbal material, which may result in some products containing doses that are higher than intended^[4].

Synthetic cannabinoid use has been associated with both physical and psychoactive effects.

Physical effects

Cardiovascular: The most common cardiovascular

side effects are tachycardia and elevated blood pressure. Individuals can also present with palpitations, chest discomfort or tightness, or dysrhythmias^[14,27-29,31-42]. Zimmermann *et al.*^[43] reported on two persons who presented with ischemic stroke after the use of synthetic cannabinoids. More serious cardiovascular consequences of SC use have also been noted. Several studies have documented chest pain, and cardiac ischemia after SC use^[28,29,35,40,44-54]. Evidence that SC use is associated with myocardial infarction also exists^[55,56]. Anecdotal reports describe two adolescents who died in the United States after ingestion of a SC product called "K2", one due to a coronary ischemic event^[57]. At least four case reports now exist of pediatric patients who have been diagnosed with myocardial infarction (MI) associated with smoking SCs^[58,59].

Gastrointestinal: Gastrointestinal effects, such as nausea, vomiting, and gagging, are also common after consumption of SC products^[14,25,28,29,35,42,44,46,47,51,60,61]. SC use can also induce "cotton" mouth or xerostomia typical of marijuana use^[13,31,35,36,46,60,62].

Neurological: A number of motor neurological effects of SCs have been reported including tremors, ataxia, fasciculations, hypertonicity, hyperflexion, and hyperextension^[24,37-39,45-48,62]. Musshoff *et al.*^[63] and the study^[64] describe several case examples of youngsters who displayed impairment of fine motor skills associated with difficulty operating a motor vehicle. Sensory changes, such as numbness, have been reported^[14,47]. Other neurological symptoms associated with SC use include headaches^[37,44,52] and dizziness^[37,51].

There are several instances of SC use being associated with more serious neurological effects such as seizures^[28,29,34,35,40,47,59,64-67], loss of consciousness^[51] and coma^[47,59].

Renal: Over the past two years acute kidney injury has been added to the list of toxicities associated with use of SCs. Recently, over 20 cases of acute renal failure with associated acute tubular necrosis after SC use have been reported^[68-72]. While the precise cause of renal damage in these patients is unclear, one specific synthetic cannabinoid may be implicated^[68,69].

Metabolic: Similar to marijuana, SC products have been reported to stimulate appetite^[13,14,27-29,46,59]. However, Buser *et al.*^[73] discovered in a large global sample that users of SCs reported having less appetite-stimulating properties than marijuana. SCs can also induce other metabolic effects, such as hypokalemia, hyperglycemia, acidosis^[25,28,29,36] and diaphoresis^[37,44,48].

Ophthalmologic: Conjunctival injection or redness of the eyes, typical of marijuana use has also been frequently observed after SC use. Other ocular effects include pupillary changes, such as miosis and mydriasis, blurry vision and light sensitivity^[25,31,35-37,40,44,51].

Pulmonary: A handful of case reports have emerged describing respiratory symptoms and complications after SC use. Hyperventilation^[37,40,52], apnea^[51], alveolar infiltrates^[74,75] and pneumonia have been reported^[76].

Other physical effects: Other physical symptoms reported with SC use include hyperthermia, rhabdomyolysis, symptoms suggestive of anticholinergic effects, and tinnitus^[27-29,44,61]. Insomnia^[14,77], hair loss and unspecified "skin problems"^[14] have also been reported.

Psychoactive effects

Cognitive: The most common cognitive effects of SC use are impairments in attention, concentration and memory^[13,27,51,52,63]. Difficulty thinking clearly (not associated with psychosis)^[43] and confusion have also been reported^[4,36,37,40,41,43,44,50,78].

Affective: Although synthetic cannabinoid users frequently experience euphoria with use of these products, negative emotions are also commonly reported. Anxiety and panic are frequently associated with SC use^[13,37,40,48,77,79,80]. Since panic symptoms frequently accompany palpitations, it can be difficult to differentiate to what extent these symptoms are due to anxiety. To a lesser extent, irritability is less frequently reported by users^[13,44,81].

Speech: Dysarthric^[37], pressured^[37], slowed^[37,48] and disorganized speech^[51] as well as inappropriate laughter^[27,40], have been observed with and reported by SC users.

Behavioral: Restlessness^[13,37] and agitation during acute intoxication has been described in several scientific reports^[32,37,40,41,44,46,47,52,79]. Reports of users of SCs exhibiting violent and aggressive behavior have dominated the lay and scientific literature. Many of the subjects displayed symptoms consistent with psychosis and altered mental status^[8,37,77,79,82,83].

Psychosis and perceptual distortions: Researchers have increasingly described the mental status changes associated with SC use and intoxication. Perceptual changes such as, "alteration of perception"^[31] and seeing "things not actually there"^[13,37] have been described. Psychotic symptoms, such as hallucinations, disorganization of thoughts and delusions in subjects with and without a previous history of psychosis have been reported^[14,27-29,32,35,39,40,46-48,80,84-86].

Suicide: Non-fatal, self-mutilatory behaviors secondary to SC use appear rare, with just two cases described in the literature^[52,87]. Multiple reports connecting SC use and suicidal behaviors can be found in the media and throughout the internet^[88,89]. Our review of the scientific literature discovered ten subjects in six different studies describing suicidal ideation^[40,52,77,80,90].

Tolerance, dependence and withdrawal: Case series

and reports have indicated that use of SCs can produce effects beyond acute intoxication, with tolerance and withdrawal symptoms described following prolonged use. These preliminary reports suggest dependency may be associated with chronic SC use. A few reports indicating dependence are noted throughout the literature. Banerji *et al.*^[44], Nacca *et al.*^[91] and Rominger *et al.*^[92] each described one to two person case reports of persons exhibiting significant craving and acute withdrawal, presumably due to prolonged synthetic cannabinoid use. Bozkurt *et al.*^[14] examined one hundred fifty-eight patients enrolled in an outpatient substance abuse clinic. Seventy percent of these individuals had unsuccessful attempts to stop SC usage and/or symptoms of dependence. At the present state of knowledge it appears that the withdrawal syndrome from synthetic cannabinimimetics is similar to but more severe than that from marijuana^[14,92].

EVALUATION

In an emergency department (ED) setting, adolescent or young adult patients often present in a state of acute intoxication with SCs (either alone, or in combination with other substances)^[93]. Physical consequences of SC intoxication can affect any system of the body. The pediatrician should always be aware of the potential serious medical sequelae of SC intoxication, such as myocardial infarction, seizures and acute kidney injury. In light of current limitations of toxicological testing in the emergency department, a diagnosis requires a high index of suspicion and knowledge of the typical history of users and possible symptoms. Evaluation of the patient should therefore include a thorough medical history, physical examination with documentation of vital signs, and laboratory studies to evaluate kidney function, electrolytes, and hepatic function. An EKG is recommended, and other cardiac testing as appropriate depending on the clinical presentation (including serial cardiac enzymes if chest pain is present)^[94].

Acute intoxication with SCs can produce alterations in mental status, behavioral disturbances, changes in mood and affect, and psychotic symptoms. In an acute emergency setting a typical presentation may include confusion, hallucinations, anxiety and panic, agitation and aggression as well as suicidal behaviors. Evaluation of the youngster should include a mental status examination, with particular attention to the suicide risk assessment, and also an assessment of the risk of aggressive behavior toward others^[37]. Given the fact that the patient may present with confusion or agitation, gathering collateral information from other informants such as family members or friends is important. Obtaining information about pre-existing psychiatric conditions will help guide the treatment of the patient. Information from paramedics or others who transport the youngster to the ED about the possible ingestion of substances, a history of substance use or the presence of drug paraphernalia, may be very helpful.

The clinician must suspect intoxication with SCs

in any young person who presents with the sudden onset of otherwise unexplained psychosis. Psychotic symptoms frequently include paranoid thoughts, disorganized thoughts, flat or inappropriate affect, visual misperceptions, and auditory and/or visual hallucinations. Psychotic symptoms may represent the direct effects of the SCs, vs exacerbation of a pre-existing psychotic disorder such as schizophrenia. Patients may sometimes present to the ED in a state of withdrawal from SCs, with symptoms of insomnia, anxiety, nausea, and lack of appetite^[91]. Since SCs are not detectable in routine urine toxicology screening, the pediatrician should be familiar with the characteristic symptoms and signs of intoxication and have a high index of suspicion to help make the diagnosis of SC intoxication. Alcohol and drug use are not rare in teenagers. Seventy percent of 12th graders in the United States are reported to have at least tried alcohol. Marijuana is by far the most widely used illicit drug used by youth in the United States. The most commonly used illicit drugs by 12th graders (lifetime) include marijuana (45%), ecstasy (7.2%) and cocaine (4.9%)^[9]. Synthetic cannabinoid intoxication should be strongly suspected in an adolescent who is known to use other substances such as marijuana and/or alcohol, is in a setting where he or she is undergoing periodic urine toxicology screening, and presents to the ED with the characteristic symptoms and signs of synthetic cannabinoid intoxication described here^[95]. Urine toxicology screening may be helpful in that a positive screening test for marijuana, together with the characteristic presentation, greatly increases the likelihood of synthetic cannabinoid use/intoxication^[14,20,34].

Adolescents rarely present to the pediatrician's office in a state of acute SC intoxication. In the office setting, the diagnosis of SC use is based more on the clinical history than on the mental status examination. Some persistent symptoms and signs resulting from SC use can, however, be identified on examination in the pediatrician's office. These include fatigue, persistent psychotic symptoms, and conjunctival injection^[95]. Routine urine toxicology screening in the office setting may be helpful in identifying other substances the patient may be using, such as marijuana. If the diagnosis of SC use is made in the outpatient setting, laboratory screening for liver function and kidney function, as well as an evaluation of cardiac function, would be appropriate.

Some general principles involved in the evaluation and diagnosis apply in both the ED and office settings. The discovery of paraphernalia used in the consumption of SC products (pipes, rolling papers, electronic cigarettes) increases the likelihood that the patient is using these substances^[4]. There is no characteristic odor of SCs, but the presence of the characteristic odor of marijuana may be present in a youngster who is using both substances. Manufacturers are constantly producing new synthetic cannabinoid compounds. Toxicological exams that screen for routine drugs of abuse may not detect most synthetic cannabinoid compounds. Unfortunately, many clinical laboratories do not routinely test for these recreational drugs because of financial

Table 1 Symptoms and history supportive of synthetic cannabinoid use

Synthetic cannabinoid use should be strongly suspected if a youngster presents with
A history of marijuana or other drug use
Symptoms and signs consistent with cannabis use
Unexplained sudden onset of psychotic symptoms
Unexplained sudden-onset renal, neurological, and/or cardiovascular problems is in a situation in which his or her urine is being routinely monitored for illicit substance use has had negative routine urine toxicology screens

constraints, analytical capabilities, and time limitations. Long turnaround times for the sophisticated laboratory examinations necessary to detect SCs greatly diminish the usefulness of these tests in the acute ED setting. The newest SC compounds on the street are chemically different than the earlier generation compounds. For this reason many SC compounds are invisible to older designer drug screens and traditional drug tests. This diversity of new products make detection by emerging enzyme-linked immunosorbent assay (ELISA) tests difficult. If possible, healthcare professionals are urged to utilize a laboratory experienced in testing for emerging drugs that uses comprehensive mass spectrometry testing^[40,96-98].

Synthetic cannabinoid use should be strongly suspected if a youngster presents with: (1) a history of marijuana or other drug use; (2) symptoms and signs consistent with cannabis use; (3) otherwise unexplained sudden onset of psychotic symptoms; (4) otherwise unexplained sudden-onset renal, neurological, and/or cardiovascular problems; (5) is in a situation in which his or her urine is being routinely monitored for illicit substance use; and/or (6) has had negative routine urine toxicology screens (Table 1).

TREATMENT

A thorough clinical history, knowledge of clinical effects of synthetic cannabinoids and high index of suspicion are necessary for the diagnosis. Interventions for acute intoxication with all designer drugs target the presenting symptoms. No medications are currently available to treat synthetic cannabinoid intoxication *per se*. Symptoms of SC intoxication may be self-limited and resolve spontaneously, generally within 4-14 h^[28,29]. In EDs, intravenous hydration, electrolyte replenishment and monitoring may suffice for youngsters who present with mild to moderate signs and symptoms of intoxication. Treatment of any particular renal (*e.g.*, acute tubular necrosis), neurological (*e.g.*, seizures) or cardiovascular (*e.g.*, cardiac ischemia) morbidities should be implemented promptly. Patients who present with symptoms of anxiety, panic, agitation, and arousal after SC exposure may benefit from a benzodiazepine. Lorazepam administered intravenously or intramuscularly, is the benzodiazepine most often utilized by practitioners^[28,29,37,58,99]. An antipsychotic medication may be indicated when a patient presents with symptoms of psychosis, particularly when the psychosis is associated with behavioral disturbances (*e.g.*, agitation, aggression);

the patient has a history of a psychotic disorder; or the psychotic symptoms do not appear to be remitting spontaneously or with supportive measures^[28,29,99].

Our review of the literature did not identify any studies that have addressed formal treatment of SC use. Synthetic cannabinoids can be more psychologically addictive than marijuana. Outpatient services are a viable option for less severe cases, especially if synthetic cannabinoids are the only drugs being used and the youngster is displaying little or no symptoms of withdrawal. Inpatient or residential treatment centers offer intensive care that can help youth get through the early stages of withdrawal in a prompt manner. The length of inpatient or residential synthetic cannabinoids treatment depends on the severity of the use and/or addiction, whether the youngster is also abusing other substances and varies from patient to patient.

Because substance abuse and addiction are multi-dimensional and disrupt so many aspects of a person's life, treatment is complex. Parents and other family members should be engaged to ensure appropriate linkage and follow-up with a qualified substance abuse professional and/or program. Intensive therapy helps the youngster apply new behavioral skills to daily life. Effective substance use treatments are typically comprehensive and incorporate various components, each targeting a particular aspect of the illness.

CONCLUSION

Synthetic cannabinoids are a group of substances in the world of designer drugs that present potentially dangerous health effects. These compounds have evolved rapidly since first appearing on the world market a few years ago. Identifying youth who abuse these drugs can be difficult. Since the safety profile of synthetic cannabinoid compounds is largely unknown, the ability to perform human studies to determine their effects presents an ethical challenge. As more research continue to emerge our understanding of both the extent of use and the associated harms will continue to develop. Our review of the literature suggests that synthetic cannabinoids may have adverse effects that are more severe than that of marijuana. In addition to the psychoactive effects, some SC compounds have been associated with more serious physical consequences, such as, seizures, myocardial infarction and renal damage. Clinicians are urged to familiarize themselves with these drugs and the typical presentations of patients who use them. Synthetic cannabinoid use should be strongly suspected if a youngster presents

with a history of marijuana use, symptoms and signs consistent with cannabis use, unexplained sudden onset of mental status changes and/or renal, neurological, or cardiovascular problems, and is in a situation in which his or her urine is being routinely monitored for illicit substance use.

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