Organic and Synthetic Cannabinoid Use in Adolescents

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According to current statistics from the US Centers for Disease Control and Prevention, 39.9% of adolescents surveyed have used organic cannabinoids at least once and 23.1% have used it regularly within the last month.1 These statistics show a 3.1% increase from the survey results in 2009. Similar data show that 11.4% of US 12th graders have used “Spice” or “K2” (brand names of synthetic cannabinoids) in the past year, making synthetic cannabinoids the second most commonly used illicit drug among high school seniors.2

In the Monitoring the Future Survey 2011, data tabulated on drug use in 8th, 10th, and 12th graders, found that organic cannabinoid use among teens rose (ie, 0.6%) in 2011, showing an increase for the fourth straight year. This is in contrast to the decline that had occurred in the preceding decade. It also found that daily organic marijuana use is now at a 30-year peak level among high school seniors.3

Recent trends indicate a decrease in perception of harm from cannabinoids in addition to a decrease in disapproval of use by older peers may be leading to the upswing of cannabinoid use over the past few years.3 Other risk factors, including pre-existing conditions or comorbidities such as mood and anxi-
nety disorders, may also play a role.\textsuperscript{4}

With the increased potency of cannabinoids in both organic marijuana and newer classes of synthetic cannabinoid compounds, the issue of cannabinoid abuse likely will become a greater challenge. The purpose of this article is to help the primary care pediatrician understand the nuances, changes, and current complexities of cannabinoid abuse, and how to treat its abuse and possible dependence.

\textbf{DEFINITIONS/Legal Status}

Organic cannabinoids (ie, marijuana) are dried flower remnants of *Cannabis sativa*. Although *Cannabis* species can contain more than 60 cannabinoids (which are aryl-substituted meroterpenes), the most potent and psychoactive cannabinoid is delta-9-tetrahydrocannabinol, known as THC. Marijuana can be smoked in a “joint” or self-made cigarette, in pipes, or in “bongs” (ie, by inhaling smoke from an air- and watertight vessel). It can be eaten or baked into foods via extracting THC into butter or oil, as it is quite fat-soluble.

Advances in cultivation (such as hydroponic farming and plant-breeding) have also increased the potency of marijuana. In the 1960s and 1970s, the average marijuana joint contained about 10 mg of THC. Now, a joint may contain as much as 150 mg of THC. Thus, marijuana in current circulation puts users at risk of exposure to greater quantities of THC, greater intoxication, and potentially longer-term risks than in prior generations.\textsuperscript{5}

Synthetic cannabinoids are nonorganic cannabinoids that are synthesized and sprayed onto dried herbs or concentrated into powder forms. These are then advertised and sold as incense products. Common brand names include “Spice,” “K2,” “Genie,” and “Aroma,” and they are sold in “head shops” (ie, stores that sell paraphernalia for tobacco and cannabis users), convenience stores, or over the Internet. They are labeled as “not for human consumption,” but are used in ways similar to marijuana or through infusion for psychoactive effects similar to THC. Although they do not contain THC, they include other cannabinoids and other unknown substances.

Synthetic cannabinoids have been banned throughout the developed world, including the US. The first synthetic cannabinoid was made in 1995 by a Clemson University professor. Following the publication of a paper detailing the experiment, including the description of the method and ingredients required, the cannabinoids first appeared in the European “party scene” before becoming more commonly known and used.\textsuperscript{6} Unfortunately, as cannabinoids are often altered to avoid federal regulations and bans, new cannabinoids are frequently being created. Currently, there are more than 100 compounds with cannabinoid-like activities waiting for identification.\textsuperscript{7}

Organic cannabinoids are Schedule I substances in the US and are illegal if found in possession.\textsuperscript{8} Eighteen states and the District of Columbia have also legalized medical cannabis or essentially decriminalized it.\textsuperscript{9} In 2011, the Drug Enforcement Administration (DEA) temporarily banned five synthetic cannabinoids: JWH-018; JWH-073; JWH-200; CP-47,497; and CP-47,497-C8. This ban, effective for at least 2 years, makes this class of drugs Schedule I. However, as mentioned earlier, new cannabinoids can be made by altering the original molecules, and thus can effectively bypass the ban.

\textbf{USE, ABUSE, AND DEPENDENCE}

Organic cannabinoid intoxication is described as euphoria, anxiety, the sensation of slowed time, impaired motor coordination, and/or social withdrawal that develops during or shortly after use. Physiologic symptoms such as conjunctival injection, increased appetite, dry mouth, and tachycardia, can occur within 2 hours of use.\textsuperscript{10} According to the *Diagnostic and Statistical Manual-IV-Text Revision* (*DSM-IV-TR*), marijuana abuse is defined as a maladaptive pattern of use leading to clinically significant impairment or distress during a 12-month period, manifested either by recurrent use that interferes with major role obligations at work, school, or home; occurs in situations in which it is physically hazardous; results in legal problems related to use; or persistently occurs despite continued social or interpersonal problems caused or exacerbated by the effects of the use.\textsuperscript{10}

In addition, the above criteria require that the symptoms mentioned must have never met criteria for marijuana dependence.

Organic marijuana has increased in potency and is more likely to build tolerance in its users, possibly resulting in increased withdrawal symptoms. Thus, marijuana dependence is likely to be a bigger issue now than it has been in the past. According to the *DSM-IV-TR*, marijuana dependence is defined as a maladaptive pattern of use resulting in clinically significant impairment or distress in a 12-month period with three symptoms that signify tolerance, including the use of markedly increased amounts of marijuana to achieve the desired effect or intoxication; markedly diminished effect with continued use of the same amount of marijuana; and marijuana being used in larger amounts or over a longer period than was intended.

Symptoms also include a persistent desire and unsuccessful efforts to cut down or control use, and spending a

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great deal of time in obtaining marijuana, using it, or recovering from its effects. The last two symptoms are the neglect of important social, occupational, or recreational activities due to use; and the persistent use despite knowledge of having a recurrent or ongoing physical or psychological problem that is probably caused or exacerbated by use.\textsuperscript{10}

The DSM-IV-TR criteria for marijuana dependence only includes physiologic tolerance and does not specify a withdrawal period.\textsuperscript{11} However, current data suggests a withdrawal period does exist. A US epidemiologic survey found that among frequent marijuana users who did not use other substances, 44\% reported two or more withdrawal symptoms and 34\% reported three or more symptoms when discontinuation of use.\textsuperscript{12} The most prevalent withdrawal symptoms included fatigue, hypersomnia, psychomotor retardation, anxiety, depression, and yawning.\textsuperscript{12}

Although withdrawal can be distressing, it is not life-threatening. The withdrawal syndrome begins the day or so after cessation, peaks between days 2 and 6, and resolves within 1 to 2 weeks. Other symptoms such as sleep disturbances and irritability might continue to persist for weeks.\textsuperscript{13} This may be due to THC being highly lipophilic and redistributing quickly into body fat. The high lipid storage of THC increases its elimination half-life and may immediately diminish the severity of withdrawal symptoms, while possibly extending their duration.\textsuperscript{11}

There is a lack of DSM-IV-TR criteria for synthetic marijuana intoxication, abuse, or dependence. Synthetic marijuana intoxication has been reported to lead to symptoms of conjunctival injection, tachycardia, anxiety, aggressive behavior, paranoia, hallucinations, inability to speak, dystonia, and short-term memory deficits.\textsuperscript{14} There are also case reports that demonstrate a withdrawal syndrome and thus a level of tolerance from synthetic marijuana use.\textsuperscript{7}

The recently approved and yet to be published Diagnostic and Statistical Manual 5 (DSM-5) will make significant overhauls to the category of substance use disorders. Per the American Psychiatric Association, the DSM-5 will combine the DSM-IV-TR categories of substance abuse and substance dependence. The belief is that by combining criteria, the diagnoses will be strengthened and more accurate. For example, previous substance abuse criteria required only one symptom while the DSM-5’s mild substance use disorder will require two to three symptoms.\textsuperscript{15} In addition, it is postulated that the DSM-5 will acknowledge cannabis withdrawal.\textsuperscript{16} Currently, it is unknown if synthetic marijuana will be discussed in the DSM-5.

**RISKS OF USE**

Individual risks of cannabinoid use fall into both physical and psychological domains. As organic marijuana has been available and used for much longer than synthetic cannabinoids, considerably more is known about the effects of its use.

In the physical domain, certain disease processes have been looked at in greater detail. In terms of pulmonary medical risks, there was found to be no association between long-term marijuana smoking and airflow obstruction measures.\textsuperscript{17} However, it has been noted that long-term marijuana smoking was associated with increased respiratory symptoms, including cough, phlegm, and wheezing.\textsuperscript{17} In terms of cancer risk, a 2005 review of epidemiologic studies concluded that there were not sufficient studies available to adequately evaluate the effect of marijuana use on cancer.\textsuperscript{18}

Multiple studies have demonstrated that cannabinoids affect the immune system, and there is evidence that organic marijuana use appears to suppress aspects of immunological function. However, it is unclear whether this suppression results in any increased rates of disease.\textsuperscript{19} Lastly, marijuana smoking is implicated in having an increased risk of periodontal disease in chronic users.\textsuperscript{2}

In the psychological domain, a recently published study found that a pattern of persistent organic marijuana use was associated with a neuropsychological decline that occurred broadly across all domains of functioning, even after controlling for years of education. Impairment was concentrated among adolescent-onset organic marijuana users, with more persistent use associated with greater decline. Further, cessation of use did not fully restore neuropsychological functioning among adolescent-onset organic marijuana users.\textsuperscript{21} This negated previously held notions, which stated that there was no evidence of significant long-term effects of persistent organic marijuana use on neurocognitive processes.\textsuperscript{22}

Additionally, a systematic review of longitudinal studies did not find a significantly increased risk of depression for cannabis users.\textsuperscript{23} There is one risk however, which was validated by that review. Marijuana use was found to show an increased risk of psychosis. This was for any type of psychotic outcome in an individual who had ever used marijuana, and the findings were consistent with a dose-response effect. There was greater risk in those who used marijuana most frequently.\textsuperscript{23} Also, according to a more recent meta-analysis, it was found that psychosis or schizophrenia-related illness occurred 2.7 years earlier in those who abused marijuana. This signifies a possible causal role of marijuana in inducing psychosis or schizophrenia-related illness.\textsuperscript{24}

However, there is additional evidence that indicates that a genetic predisposition may influence the risk of developing psychosis in those who used marijuana...
as adolescents. This would help explain why the majority of those who use marijuana do not develop psychosis.25

Less is known about the long-term effects of synthetic marijuana use, given its recent introduction to the public. There have been multiple reports of psychotic symptoms occurring in individuals who used synthetic cannabinoids that have occurred after the acute effects of intoxication.7 There have also been reports of two deaths in the US, one due to suicide and one due to an ischemic cardiac event.7

INTERVENTION AND TREATMENT

The first step is to screen individuals who have admitted to any organic or synthetic marijuana use and determine whether they meet criteria for abuse or dependence. Another option for use that is suspected, but not admitted to, is drug testing. This also is useful for monitoring progress for patients in treatment. Urine drug testing is the most common type of testing, as it is readily available and inexpensive. Of note, a positive urine test only establishes past use. As cannabinoid metabolites are highly lipophilic, they can persist for extended periods of time, and urine tests for cannabinoids can remain positive after discontinuation of cannabis for up to 7 to 10 days in a casual user, 2 to 4 weeks in a heavy user, and months in a chronic heavy user.11

Currently, there is no widespread commercially available drug testing for synthetic cannabinoids. As mentioned earlier, synthetic cannabinoids are often altered to avoid legal bans, and thus, it is difficult to test for all cannabinoids currently available. There are some sophisticated tests for known and banned synthetic cannabinoids, such as JWH-018 and JWH-073; however, these tests are not easily available nor necessarily conclusive of use.26

Treatment for acute ingestion of organic marijuana may require placing the user in a quiet, low-stimulation environment with gentle interactions until acute effects subside. For some individuals, further symptomatic treatment is required with closer observation and low-dose benzodiazepines or antipsychotics for sedating effects to reduce paranoia or psychotic symptoms from acute use.27 Treatment for acute ingestion of synthetic cannabinoids is similar and may require longer-acting benzodiazepines.28 In general, acute ingestion of either does not require medical treatment; however, users may seek treatment for dysphoria, severe paranoia, or psychotic symptoms.27, 28

The standard treatment for organic marijuana abuse and/or dependence is psychotherapy. This is based on controlled studies proving the benefits of psychotherapy and the lack of establishment of effective pharmacological treatments.27 Of note, one recent double-blind, randomized, placebo-controlled study showed some benefit of N-acetyl cysteine in producing cessation in adolescents with marijuana dependence (in conjunction with psychotherapy); however, further studies will need to be conducted to determine its role in treatment.29

Psychotherapies that have been found to have a positive effect in organic marijuana cessation include cognitive-behavioral therapy, family therapy, voucher-based incentives (ie, a behavioral therapy that uses rewards such as monetary vouchers as incentives for therapeutically desired behaviors), and motivational enhancement therapy.27 In addition, self-help groups such as Marijuana Anonymous are available; however, no studies have been conducted to determine their effectiveness in cannabinoid use disorders. There are no long-term studies on the treatment for synthetic marijuana abuse at this time.

The approach to synthetic marijuana could be similar to organic marijuana because the substance effects are also similar. However, due to the variable potencies of synthetic marijuana, as well as its fully not yet known properties, future studies may indicate other treatments necessary to combat its effects.

In the adolescent population, prevention is key. A meta-analysis of four studies involving middle school students compared a school-based social skills program that advocated for substance use prevention against the usual curriculum. Results showed that the program significantly reduced the use of marijuana at follow-up assessments.30 Thus, educating adolescents on the presence and effects of illicit substances, including organic and synthetic cannabinoids, may help reduce their use.

In addition, protective factors, including adequate self-control, parental support and supervision, academic competence and achievement, anti-drug use policies and education, strong community and neighborhood attachments, and access to health services, may also help deter from substance abuse in this vulnerable population.
CONCLUSION

Organic and synthetic cannabinoid use in the adolescent population has become increasingly prominent in the popular media. The recent rise of synthetic use and its lack of regulation make it a new issue and, oftentimes, one that is difficult to detect. In addition, as the concentration of the active cannabinoid ingredient THC increases in organic use, the effects of marijuana abuse and/or dependence are worsened.

Evidence has shown that marijuana’s negative effects are greater on the psychological domain than on the physical domain. In treatment, prevention is key in the population, and this article may aid those able to educate the adolescent population of these illicit substances and their effects.

REFERENCES


FEATURE