Current PSYCHIATRY

Cannabis, synthetic cannabinoids, and psychosis risk: What the evidence says

Research suggests marijuana may be a 'component cause' of psychosis

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Over the past 50 years, anecdotal reports linking *cannabis sativa* (marijuana) and psychosis have been steadily accumulating, giving rise to the notion of "cannabis psychosis." Despite this historic connection, marijuana often is regarded as a "soft drug" with few harmful effects. However, this benign view is now being revised, along with mounting research demonstrating a clear association between cannabis and psychosis.

In this article, I review evidence on marijuana's impact on the risk of developing psychotic disorders, as well as the potential contributions of "medical" marijuana and other legally available products containing synthetic cannabinoids to psychosis risk.

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Cannabis use and psychosis

Cannabis use has a largely deleterious effect on patients with psychotic disorders, and typically is associated with relapse, poor treatment adherence, and worsening psychotic symptoms.[1,2] There is, however, evidence that some patients with schizophrenia might benefit from treatment with cannabidiol,[3-5] another constituent of marijuana, as well as delta-9-tetrahydrocannabinol (Δ-9-THC), the principle psychoactive constituent of cannabis.[6,7]

The acute psychotic potential of cannabis has been demonstrated by studies that documented psychotic symptoms (eg, hallucinations, paranoid delusions, derealization) in a dose-dependent manner among healthy volunteers administered Δ-9-THC under ex-

Cannabis and psychosis

Clinical Point

Three meta-analyses have concluded cannabis use is associated with an increased risk of psychosis

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Table 1

Hypotheses linking cannabis and psychosis

Hypothesis	Strength of evidence	Evidence for	Evidence against
Cannabis does not cause chronic psychosis	Weak	• No randomized controlled trials • Other possible explanations (demographic/socioeconomic, trauma, other drug use) • Possible reverse causality (psychosis leads to cannabis use) • Possible publication bias (negative evidence not published)	• Controlled (cross-sectional and longitudinal cohort) studies consistently show an association[11-19] • Longitudinal studies include risk calculations adjusted for confounding variables[13-19] • Publication bias not found in meta-analyses[11,21]
Cannabis can cause schizophrenia	Equivocal	Cannabis use precedes the onset of schizophrenia in longitudinal studies[13-19]	The incidence of schizophrenia has not been clearly increasing as expected with increasing cannabis use[11,21]
Cannabis worsens existing psychotic disorders	Strong	• Cannabis is associated with increased symptoms, relapse, and treatment nonadherence among those with schizophrenia[1,2] • Patients with schizophrenia are more vulnerable to cannabis-induced psychosis under experimental conditions[22]	Cannabidiol and Δ-9-THC improve symptoms in some patients with schizophrenia[3-7]
Cannabis increases the risk of chronic psychosis among vulnerable individuals	Strong	• For patients with schizophrenia, a history of cannabis use is associated with illness onset 2 to 3 years earlier compared with non-users[23] • Cannabis use is a risk factor for conversion to psychosis in some studies of prodromal schizophrenia[24]	Cannabis use is not always a risk factor for conversion to psychosis in studies of prodromal schizophrenia[25]

Δ-9-THC: delta-9-tetrahydrocannabinol

perimental conditions.[8-10] Various cross-sectional epidemiologic studies also have revealed an association between cannabis use and acute or chronic psychosis.[11,12]

In the absence of definitive evidence from randomized, long-term, placebo-controlled trials, the strongest evidence of a connection between cannabis use and development of a psychotic disorder comes from prospective, longitudinal cohort studies. In the past 15 years, new evidence has emerged from 7 such studies that cumulatively provide strong support for an association between cannabis use as an adolescent or young adult and a greater risk for developing a psychotic disorder such as schizophrenia.[13-19] These longitudinal studies surveyed for self-reported cannabis use before psychosis onset and controlled for a variety of potential confounding factors (eg, other drug use and demographic, social, and psychological variables). Three meta-analyses of these and other studies concluded an increased risk of psychosis is associated with cannabis use, with an odds ratio of 1.4 to 2.9 (meaning the risk of developing psychosis with any history of cannabis use is up to 3-fold higher compared with those who did not use cannabis).[11,20,21] In addition, this association appears to be dose-related, with increasing amounts of cannabis use linked to greater risk—1 study found an odds ratio of 7 for psychosis among daily cannabis users.[16]

There are several ways to explain the link between cannabis use and psychosis, and a causal relationship has not yet been firmly

Table 2

Herbal incense products and synthetic cannabinoids

Herbal incense brand names	Cannabinoids they may contain
Spice, K2, Mojo, Aroma, Dream, Chill, Chaos, Sence, Smoke, Skunk, Space Diamond, Silent Black, Genie, Algerian Blend, Yucatan Fire, Tai Fun, Sensation, SpicyXXX, Spike 99, Bonsai-18, Banana Cream Nuke, Wicked X, Natures Organic, Zen	• JWH-018, JWH-019, JWH-073, JWH-167, JWH-250, JWH-253, JWH-387, JWH-398 • CP-47,497; cannabicyclohexanol • HU-210, HU-211 • AM-694

established (***Table 1***).[1-7,11-19,21-25] Current evidence supports that cannabis is a "component cause" of chronic psychosis, meaning although neither necessary nor sufficient, cannabis use at a young age increases the likelihood of developing schizophrenia or other psychotic disorders.[26] This risk may be greatest for young persons with some psychosis vulnerability (eg, those with attenuated psychotic symptoms).[16,18]

The overall magnitude of risk appears to be modest, and cannabis use is only 1 of myriad factors that increase the risk of psychosis.[27] Furthermore, most cannabis users do not develop psychosis. However, the risk associated with cannabis occurs during a vulnerable time of development and is modifiable. Based on conservative estimates, 8% of emergent schizophrenia cases and 14% of more broadly defined emergent psychosis cases could be prevented if it were possible to eliminate cannabis use among young people.[11,26] Therefore, reducing cannabis use among young people vulnerable to psychosis should be a clinical and public health priority.

Medical marijuana

Although cannabis extracts were marketed by major pharmaceutical companies and widely used by consumers for various ailments during the late 1800s, medicinal cannabis use in the United States declined significantly during the early 20th century. In 1937, the Marihuana Tax Act was passed, effectively putting a stop to physicians prescribing cannabis for medical purposes. The FDA currently classifies cannabis as a Schedule I drug (eg, high abuse potential, no currently accepted medical use, lack of safety data) and the use of cannabis and its prescription by physicians are prohibited under federal law.

However, in recognition of the potential medical benefits of cannabis, 16 states have legalized medicinal use ("medical marijuana") over the past several years. Laws and regulations governing medical marijuana vary from state to state. For example, in California, adults who obtain a recommendation from a physician and register for a Medical Marijuana Identification Card can legally purchase cannabis from a state-recognized dispensary and use it in a non-public setting. The physician's "recommendation" (not a prescription) is based upon the determination that "the person's health would benefit from the use of marijuana in the treatment of cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, or *any other illness for which marijuana provides relief*"[28] (emphasis added). Although no state has yet legalized cannabis use for recreational purposes, with such regulations, an increasing number of jurisdictions have provided a way for consumers to easily obtain marijuana for loosely defined medical purposes.

Medical marijuana dispensaries offer a variety of cannabis strains, each with a different advertised "high" based upon variable proportions of Δ-9-THC and other constituents. The Δ-9-THC content of medical marijuana is about twice that of "street" marijuana, even with the latter's Δ-9-THC content rising to >10% over the past 15 years.[29,30] Therefore, medical marijuana is not only legal, but generally offers a more potent Δ-9-THC dose than typical street marijuana.

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Clinical Point

The magnitude of psychosis risk tied to cannabis use is modest and most users do not develop psychosis

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Table 3

Case reports of psychosis associated with synthetic cannabinoids

Study	N (age)	Herbal product or suspected cannabinoid	Previous psychotic disorder	Symptoms
Müller et al, 2010[a]	1 (25)	JWH-018 "Spice"	Yes	Anxiety, exacerbation of paranoid delusions, delusions of control, auditory hallucinations
Vearrier et al, 2010[b]	1 (17)	JWH-018	No	Tachycardia, hypokalemia, agitation, visual hallucinations
Every-Palmer, 2010[c]	5	JWH-018 CP-47,497	Yes	Agitation, disorganization, paranoid and grandiose delusions
Rodgman et al, 2011[d]	3	JWH-018 ("Mojo")	—	"Mojo psychosis"
Benford et al, 2011[e]	1 (20)	JWH-018 ("Spice")	—	Tachycardia, anxiety, paranoia, auditory and visual hallucinations
Van Der Veer et al, 2011[f]	3 (20 to 30)	"Spice" "Spike 99"	No	Anxiety, disorganization, paranoia, Capgras delusion
Every-Palmer, 2011[g]	9 (20s to 40s)	JWH-018 ("Aroma")	Yes	Anxiety, agitation, paranoia
Hurst et al, 2011[h]	10 (21 to 25)	"Spice"	No	Anxiety, agitation, confusion, disorganization, paranoia, ideas of reference, hallucinations

Source: For reference citations, see this article at CurrentPsychiatry.com

Clinical Point

Medical marijuana generally offers a more potent Δ-9-THC dose than typical illicit marijuana

A single case of psychosis emerging in the context of medical marijuana has been reported in the literature.[31] A 24-year-old man with mild, transient psychotic symptoms switched from street cannabis to medical marijuana for its superior potency and to conform with the law. He obtained a physician's recommendation based on diagnoses of "posttraumatic stress disorder" and "pain." After several months of increasingly frequent medical marijuana use, he developed florid and persistent psychotic symptoms necessitating antipsychotic medication, and was diagnosed with schizophrenia.

Although causality cannot be established based on this report, taken together with evidence that higher-potency cannabis is associated with a greater risk of psychotic emergence,[32] this case raises concerns about the iatrogenic and psychotoxic liability of medical marijuana use among those vulnerable to psychosis. Policy decisions about medical marijuana and its use among patients with psychiatric illness must be informed by evidence of its psychotic potential.

Synthetic cannabinoids

Synthetic cannabinoids were developed in the 1960s for research purposes and potential clinical applications, but have not been FDA-approved for therapeutic use.[33] Over the past 5 years, however, a variety of "herbal incense" products bearing names such as "Spice," "K2," and "Aroma" have emerged in Europe and the United States that contain botanicals laced with synthetic cannabinoids (***Table 2, page 51***).

Although herbal incense products are labeled "not for human consumption," they are sold by "head shops" and on the Internet without age restrictions and typically are purchased for the sole purpose of ingesting them, usually by smoking. Their desired effects resemble cannabis intoxication, including sedation, relaxation, altered consciousness, and euphoria. The products initially had the added appeal of being legal and undetectable in routine drug screening. Although not listed among the product's ingredients, chemical analyses confirmed these products typically contained 1 of 3 families of synthetic can-

Clinical Point

Case reports have linked use of herbal incense products containing synthetic cannabinoids to psychosis

Related Resources

- Murray RM, Morrison PD, Henquet C, et al. Cannabis, the mind and society: the hash realities. Nat Rev Neurosci. 2007;8(11):885-895.
- European Monitoring Centre for Drugs and Drug Addiction: Synthetic cannabinoids and "spice." www.emcdda.europa.eu/publications/drug-profiles/synthetic-cannabinoids.
- U.S. Department of Justice, Drug Enforcement Agency, Office of Diversion Control: Schedules of controlled substances: temporary placement of five synthetic cannabinoids into Schedule I. www.deadiversion.usdoj.gov/fed_regs/rules/2011/fr0301.htm.

Disclosure

The author reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

nabinoid1 and cannabinoid2 (CB1/CB2) receptor agonists, designated by the prefixes JWH-, CP-, and HU-.[34] The compounds most commonly found in these analyses (JWH-018; CP-47,497; HU-210) have significantly greater potency (ie, CB1 receptor affinity) compared with Δ-9-THC.[33,34]

The growing popularity of herbal incense products has prompted health concerns based on reports of emergency presentations for adverse effects, including tachycardia, agitation, excess sedation, and loss of consciousness.[33,35,36] In addition, 8 anecdotal reports of psychosis associated with herbal incense (with a total of 33 patients) have emerged since 2010 (***Table 3, page 55***). Among them, a variety of psychotic symptoms are described in patients ranging in age from adolescence to adulthood, both with and without histories of psychosis. For those without a pre-existing psychotic disorder, symptoms were typically self-limited.

In the most recently presented case series of patients without pre-existing psychosis (N = 10), symptoms resolved in 70% of patients within 8 days, but 30% had psychosis that persisted beyond 5-month follow-up.[37] Collectively, these reports suggest that synthetic cannabinoid intoxication is associated with acute psychosis as well as exacerbations of previously stable psychotic disorders, and also may have a propensity to trigger a chronic psychotic disorder among vulnerable individuals.

Because of health concerns and the abuse potential of herbal incense products, many have been banned in several European countries, 18 U.S. states, and the U.S. military.[33,38] In March 2011, the FDA placed 5 synthetic cannabinoids (JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol) on Schedule I, making them illegal to possess or sell in the United States.[38] However, there are hundreds of synthetic cannabinoid homologues, and herbal incense manufacturers have rapidly adapted by substituting other synthetic cannabinoids not yet banned by existing legislation.[34] The effects of these newly arising compounds in humans, including their psychotic potential, are largely unknown.

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Clinical Point

The FDA has placed 5 synthetic cannabinoids on Schedule I, but there are hundreds of synthetic cannabinoid homologues

Bottom Line

Evidence has consistently demonstrated that cannabis use is a risk factor for psychosis, both for those with existing psychotic disorders and for young people vulnerable to psychosis. Clinicians must be aware of the psychotic potential of cannabis and synthetic cannabinoids, monitor for psychotic emergence among users, and take care not to neglect cannabis use disorders when planning treatment.

Table 3

Case reports of psychosis associated with synthetic cannabinoids

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