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.

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. There is, however, evidence that some patients with schizophrenia might benefit from treatment with cannabidiol, another constituent of marijuana, as well as delta-9-tetrahydrocannabinol (Δ-9-THC), the principle psychoactive constituent of cannabis.

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

Experimental conditions. Various cross-sectional epidemiologic studies also have revealed an association between cannabis use and acute or chronic psychosis.

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. These longitudinal studies surveyed for self-reported cannabis use before psychosis onset and controlled for a variety of potential confounding factors (e.g., 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). 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.

There are several ways to explain the link between cannabis use and psychosis, and a causal relationship has not yet been firmly established. One hypothesis is that cannabis use increases the risk of chronic psychosis among vulnerable individuals. Another hypothesis is that cannabis use can cause schizophrenia. Hypotheses linking cannabis and psychosis are presented in Table 1.
established (Table 1). 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. This risk may be greatest for young persons with some psychosis vulnerability (eg, those with attenuated psychotic symptoms).

The overall magnitude of risk appears to be modest, and cannabis use is only 1 of myriad factors that increase the risk of psychosis. 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. 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” (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. Therefore, medical marijuana is not only legal, but generally offers a more potent Δ-9-THC dose than typical street marijuana.

### 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 2**

**Herbal incense brand names**

<table>
<thead>
<tr>
<th>Herbal incense brand names</th>
<th>Cannabinoids they may contain</th>
</tr>
</thead>
</table>

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Continued on page 55
A single case of psychosis emerging in the context of medical marijuana has been reported in the literature. 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, 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. 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-

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**Table 3**

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

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


Disclosure

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

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nabinoi1 and cannabinoid2 (CB1/CB2) receptor agonists, designated by the prefixes JWH-, CP-, and HU-. 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 ∆9-THC.

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.

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. 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. 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. 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. The effects of these newly arising compounds in humans, including their psychotic potential, are largely unknown.

References


**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.
### Case reports of psychosis associated with synthetic cannabinoids

**References**

- f. Van Der Veer N, Friday J. Persistent psychosis following the use of Spice. Schizophr Res. 2011;130(1-3):285-286.