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OPINION

There's nothing funny about today's highly potent marijuana. It killed my son.

Sally Schindel, Opinion contributor Published 6:00 a.m. ET April 28, 2019 | **Updated 1:35 p.m. ET April 28, 2019**

Modern medical marijuana is much more potent than your father's pot brownies of the 1970s, and that potency is taking a toll on mental health.

As attorneys argued over a section of an Arizona law that differentiates between marijuana and cannabis (https://www.phoenixnewtimes.com/news/arizona-supreme-court-justices-appear-to-favor-medical-pot-extracts-11247789), the state's Supreme Court justices joked about baking pot brownies in their kitchens.

They clearly do not understand how the marijuana industry has irresponsibly manipulated pot into dangerously high levels of potency.

My son could explain it to them. Or he could if he were still with us.

"I want to die," he wrote before hanging himself at the age of 31. "My soul is already dead. Marijuana killed my soul + ruined my brain."

Andy wanted to quit. He couldn't

Andy had been the class clown. He made parties come alive. He helped friends through tough times and served with the Army's 82nd Airborne Division in Iraq.

Then he became addicted to pot, using a medical marijuana card that enabled him to buy enough pot for up to 10 joints a day. That would keep anyone baked all day. He was hospitalized in five mental health hospitals and did two stints of court-ordered mental health treatment.

Andy Zorn served with the Army's 82nd Airborne Division in Iraq. *(Photo: courtesy of Sally Schindel)*

He told me that to live, he needed to quit marijuana. He just couldn't do it.

The marijuana industry doesn't like to acknowledge people like my son, dismissing his case as an aberration. But he is not alone, and new research shows the toll marijuana takes.

A new study shows he's not alone

The peer-reviewed medical journal The Lancet last month published a major study that found people who use high-potency marijuana daily are five times more likely (https://www.apnews.com/4f9b18c6ac0d4cd5a8c5ab85157ce190) to develop psychosis than those who never partake. The researchers compared data for more than 2,100 people in multiple countries.

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They defined "high potency" as at least 10% tetrahydrocannabinol (https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(19)30048-3/fulltext), the psychoactive ingredient in pot. Ten percent isn't all that high. Arizona's medical dispensaries tout cannabis products — the subject of the recent Supreme Court hearings — with THC up to 90%. And modern weed usually contains THC levels of 18% to 30% (https://www.smithsonianmag.com/science-nature/modern-marijuana-more-potent-often-laced-heavy-metals-and-fungus-180954696/) — more than double the levels that were common in buds from the 1980s.

The researchers concluded that up to half of first-episode psychosis cases could be prevented if high-potency marijuana were not available.

This is what Arizona's high court justices missed when they joked about baking marijuana brownies. The low-potency marijuana of their formative years is a relic of history.

Profit-seeking companies have pushed THC levels higher and higher. They have done this primarily by extracting THC from the leafy plant and flowers to create new, high-potency products they call shatter, wax or hash.

This isn't your father's pot brownie

Increased potency means higher highs, necessary to keep customers coming back for more. They are addicted, just like my son was.

And many, like my son, develop psychotic disorders. A happy-go-lucky personality is sucked into a black hole of despair. A life is lost.

Maybe it's easy for the marijuana industry to dismiss my son's suicide. But it can't ignore The Lancet study, which notes that "our findings are consistent with previous epidemiological and experimental evidence suggesting that the use of cannabis with a high concentration of THC (https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(19)30048-3/fulltext) has more harmful effects on mental health than does use of weaker forms."

Today's marijuana has as much similarity to the pot brownies of the 1970s as a smartphone does to a Texas Instruments calculator. Today's marijuana is incredibly potent, powerful enough to destroy lives.

It's not something to laugh about.

Sally Schindel lives in Prescott. She is co-founder of MomsStrong.org (http://momsstrong.org/) and a member of the Marijuana Victims Alliance. This column originally appeared in The Arizona Republic (/story/opinion/op-ed/2019/04/25/medical-marijuana-arizona-supreme-court-andy-zorn/3568234002/).

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Impact of Cannabis Use on the Development of Psychotic Disorders

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Stimulants, Cannabis, and Club Drugs (AJ Budney, R Vandrey and D Lee, Section Editors)
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Abstract

The link between cannabis use and psychosis comprises three distinct relationships: acute psychosis associated with cannabis intoxication; acute psychosis that lasts beyond the period of acute intoxication; and persistent psychosis not time-locked to exposure. Experimental studies reveal that cannabis, delta-9-tetrahydrocannabinol (THC) and synthetic cannabinoids reliably produce transient positive, negative, and cognitive symptoms in healthy volunteers. Case studies indicate that cannabinoids can induce acute psychosis that lasts beyond the period of acute intoxication but resolves within a month. Exposure to cannabis in adolescence is associated with a risk for later psychotic disorder in adulthood; this association is consistent, temporally related, shows a dose response, and is biologically plausible. However, cannabis is neither necessary nor sufficient to cause a persistent psychotic disorder. More likely, it is a component cause that interacts with other factors to result in psychosis. The link between cannabis and psychosis is moderated by age at onset of cannabis use, childhood abuse, and genetic vulnerability. While more research is needed to better characterize the relationship between

cannabinoid use and the onset and persistence of psychosis, clinicians should be mindful of the potential risk of psychosis, especially in vulnerable populations, including adolescents and those with a psychosis diathesis.

Keywords

Cannabis Psychotic disorders Psychosis Schizophrenia

Introduction

The etiology of psychotic disorders, exemplified by schizophrenia, remains elusive. While it is unlikely that there is one "cause" for schizophrenia, a number of genetic and environmental factors that may contribute to the risk of psychosis have been identified. One environmental factor that has received some attention as possibly contributing to the risk for psychotic disorders is exposure to cannabis. It should be noted that an overwhelming majority of individuals who are exposed to cannabis do not develop a psychosis outcome and most individuals with a psychotic disorder may never have been exposed to cannabis. Thus, cannabis is neither necessary nor sufficient to "cause" schizophrenia. More likely, as reviewed below, cannabis may contribute to the risk for a psychosis outcome in vulnerable individuals.

Here, we review the evidence investigating the association between cannabis and psychotic disorders—the exogenous cannabinoid hypothesis—with special attention to literature from the past 3 years. We describe three distinct relationships: (1) acute psychosis associated with cannabis intoxication; (2) acute psychosis that lasts beyond the period of acute intoxication; and (3) persistent psychosis not time-locked to exposure. We review the strength, consistency, specificity, biological plausibility, and temporality of the relationship between cannabis and psychosis and discuss recent findings implicating specific genes that might make some individuals more susceptible to psychosis-inducing effects of cannabis. Besides the exogenous hypothesis, we also discuss evidence supporting an *endo*genous cannabinoid hypothesis, suggesting that alterations in the endocannabinoid system may contribute to the pathophysiology of schizophrenia.

Schizophrenia, the prototypical psychotic disorder, is characterized by positive symptoms (e.g., hallucinations, delusions, thought disorganization), negative symptoms (e.g., amotivation, blunted affect, and social withdrawal), and cognitive deficits (e.g., deficits in memory, executive function, and attention). While most of the literature has focused on the link between cannabis exposure and positive symptoms of psychosis, here we also review the evidence linking cannabis exposure with both negative symptoms and cognitive deficits.

Overview of Cannabis, Cannabinoids, and the Endocannabinoid System

There are at least two identified cannabinoid receptors (CB1 and CB2), both of which are metabotropic G protein-coupled receptors. CB1 and CB2 are localized primarily in the brain and periphery, respectively [1, 2]. CB1 are G protein-coupled receptors that are distributed in the central nervous system, where they are primarily located presynaptically. Their activation inhibits the release of other neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate [3, 4]. Both receptors are believed to regulate the timing and release of GABA [5]. Relevant to psychosis, in the cerebral cortex and hippocampus, where they are abundant, CB1 modulates the release of GABA within networks of cholecystokinin-containing GABAergic interneurons [6, 7, 8, 9, 10••, 11, 12, 13].

The principal psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (THC). However, cannabis contains over 70 cannabinoids besides THC, including cannabidiol (CBD), cannabigerol, cannabichromene, cannabidivarin, tetrahydrocannabivarin, and terpenoids. Many of these compounds have pharmacologic effects that are distinct from those of THC [14, 15]. Furthermore, while these minor cannabinoids and terpenoids may not have effects individually, they may have effects in combination with others—referred to as "entourage effects."[16]. THC produces its psychoactive effects via actions at CB1, where it functions as a partial agonist with modest affinity [inhibition constant (K_i) = 35–80 nmol] and low intrinsic activity [17]. CBD, a major constituent of cannabis that does not produce euphoria, may have anxiolytic and antipsychotic effects in both preclinical and humans studies (reviewed in Schubart et al. [18]). The CBD content of cannabis varies and lower levels of CBD in cannabis have been associated with higher rates of psychosis [19, 20, 21, 22, 23]. For example, a variant of South African cannabis that is nearly devoid of CBD is associated with higher rates of psychosis [21, 23, 24]. Of note, CBD has been shown to inhibit the psychotomimetic effects of THC [25••, 26]. Last, it warrants mention that a number of synthetic cannabinoids that are full CB1 agonists with generally higher affinity for CB1 are currently being used by a substantial number of individuals [27].

Acute Psychosis Associated with Intoxication

A link between cannabis intoxication and altered behavior, including psychosis has long been recognized [27]. In the nineteenth century, Moreau (de Tours) characterized transient hallucinations, paranoia, dissociative symptoms, thought disorganization, and impairments in attention and memory reminiscent of psychotic symptoms seen in schizophrenia in the context of acute cannabis intoxication (reviewed in Warnock [28]). These phenomena have also been documented in numerous case reports (reviewed by Warnock [28]) and are estimated to occur in about 20–50 % of individuals who use cannabis [29••, 30].

Consistent with the acute psychotogenic effects of cannabis, similar psychotic symptoms have been reported with the use of medicinal cannabinoids such as dronabinol, nabilone, and levonantradol (reviewed in Warnock [28] and Reilly et al. [31]). More recently, there is increasing recognition of psychosis related to the recreational use of newer synthetic cannabinoids [32], which are sold as Spice or K2, and which are more potent CB1 agonists than THC [27].

The best evidence for the acute psychotomimetic effects of cannabis comes from experimental studies using cannabis and THC. Cannabis, THC, and synthetic cannabinoids have been shown to produce a full range of positive symptoms (such as suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations), negative symptoms (such as blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity, and reduced rapport), and cognitive impairments (such as deficits in verbal learning, short-term memory, working memory, executive function, abstract ability, decision making, attention, and time perception abnormalities) in healthy volunteers that bear resemblance to the symptoms of schizophrenia [25••, 33, 34, 35, 36]. Further, THC exacerbates psychotic symptoms in patients with chronic schizophrenia, despite being on stable doses of antipsychotics [37].

Cannabinoids have also been shown to induce abnormalities in electrophysiological indices of brain function that are also known to be present in schizophrenia and other neuropsychiatric disorders. THC reduces amplitude of the novelty P300a and target P300b, measures of the automatic orientation of attention (P300a) and context updating (P300b) in healthy participants [38••, 39] in a dose-dependent manner [40] without affecting processing speed. Furthermore, THC does not affect the N100, suggesting that cannabinoids do not have significant effects on early sensory registration [40]. Self monitoring is compromised in schizophrenia and contributes to deficits in insight [41]. Error-related negativity, an event-related potential component, is theorized to be related to error monitoring and has shown to be reduced in healthy volunteers exposed to THC [42]. There is mounting evidence that disruptions in neural oscillations play a key role in the pathophysiology of psychosis (reviewed in Spronk et al. [43]). Neural oscillations in the theta (θ; 4–7 Hz) and gamma (γ; 31–80 Hz) range are involved in sensory registration, the integration and binding of perceptual features, working memory, and conscious awareness [44, 45, 46, 47, 48], processes that are altered in psychosis. Studies in animals and hippocampal slices have provided evidence that cannabinoid agonists can disrupt synchronized neural oscillations at θ and γ frequencies [49, 50, 51, 52, 53, 54, 55, 56]. In humans, smoked cannabis was shown to disrupt θ band power; further, the degree of disruption correlates with working memory performance [57].

Functional neuroimaging studies with THC and CBD have revealed that they have opposing actions in neural networks involving the medial temporal and prefrontal cortices, regions that are rich in CB1 receptors. The networks recruited in these studies also recapitulate the pattern of activity seen in schizophrenia, thus making a case for the endocannabinoid hypothesis of schizophrenia [58, 59, 60•]. Individuals who experience acute psychotic symptoms induced by THC have a different pattern (medial temporal

cortex and cerebellum) of brain activation compared to placebo, suggesting that these brain regions mediate THC-induced psychotic symptoms [61]. THC attenuated activation in the left parahippocampal gyrus/fusiform gyrus, left middle temporal gyrus/superior temporal sulcus and right cerebellum/fusiform gyrus, and accentuated activation in the right middle temporal gyrus in individuals who experienced transient psychotic symptoms [60•].

Given the role of dopaminergic hyperactivity in the pathophysiology of positive symptoms, and prefrontal dopaminergic hypoactivity in the pathophysiology of negative symptoms and cognitive deficits [62, 63], a number of neuroreceptor imaging studies in humans have attempted to demonstrate THC-induced dopamine release. One small study showed reduced regional binding of the radiotracer [11C]raclopride to be suggestive of a very small increase in dopamine release following inhaled THC [64]. However, two other studies using comparable doses but different radiotracers failed to show any changes [65, 66]. Similarly the effects of dopamine D_2 antagonist antipsychotics on THC-induced effects have been mixed. The psychotomimetic effects of THC were not blocked by the dopamine receptor antagonist haloperidol [67] in healthy volunteers and THC was also shown to exacerbate psychotic symptoms in patients with chronic schizophrenia despite being on stable doses of antipsychotics [37]. However, other studies suggest that haloperidol [68] and olanzapine [69] may attenuate THC-induced psychotomimetic effects in healthy volunteers. In a study using [18 F]-fallypride, inhaled THC was associated with significant ligand displacement (dopamine release) in striatal subregions among schizophrenic patients and their relatives but not in controls [62].

In summary, cannabinoids can produce an array of transient positive symptoms, negative symptoms, cognitive deficits, and electrophysiological indices of information processing abnormalities that are relevant to psychosis. These effects appear to be dose related and do not last beyond the period of intoxication. For example, in the laboratory studies, the above-mentioned effects resolved between 2 and 4 h [25••].

Acute Psychosis Outlasting the Period of Intoxication

In some individuals, cannabis use is associated with immediate psychosis that lasts longer than the period of acute intoxication and warrants clinical intervention. Cannabis-induced acute persistent psychosis has been documented in multiple case-series [23, 70••, 71, 72, 73, 74, 75, 76, 77]. The psychosis is characterized by hallucinations, paranoia, delusions, depersonalization, emotional lability, amnesia, confusion and disorientation, which followed the ingestion of large doses of cannabis. These psychotic episodes tend to resolve relatively faster than schizophrenic psychotic episodes, and do not usually recur without re-use of cannabis [23, 74, 77, 78, 79, 80, 81, 82, 83, 84, 86] (reviewed in Hall and Solowij [85]).

The long-term course and outcome of cannabis-induced acute psychosis is also under study. Several large longitudinal studies suggest that up to 50 % of individuals without a pre-existing condition who were initially hospitalized for cannabis-induced psychosis were re-diagnosed with a schizophrenia spectrum disorder during long-term (~8 years) follow-up [70••, 87]. That proportion increased to 75 % when the diagnosis was expanded to *any* psychotic outcome [70••]. However, in one of these studies [87] there were significant limitations to the diagnostic approach, including retrospective assessment, the validity of the diagnosis of schizophrenia, and confounds related to change from using *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-IIIR) to *International Classification of Diseases, 10th Edition* (ICD-10) criteria during the study [88]. Limitations notwithstanding, hospitalization for cannabis-induced persistent psychosis may portend a recurrent psychotic disorder that in our current knowledge base and diagnostic schema is categorized as schizophrenia. It is conceivable that these cases may represent a distinct recurrent psychotic disorder [89].

Cannabis and Persistent Psychotic Disorders

While accumulating evidence suggests a link between cannabis exposure and the development of schizophrenia, whether cannabinoids can "cause" *persistent* psychosis remains controversial (reviewed in Warnock [28]). Common criteria to establish disease causality include strength of association, consistency, biological gradient (dose), specificity, and biological plausibility (reviewed in D'Souza [90•]). Much of these data come from large epidemiological studies (see Table 1). We review the evidence in terms of these criteria, highlighting the most recent findings. It should be noted that most studies have focused on positive symptom outcomes; there is a dearth of studies examining negative symptoms and/or cognitive deficits.

Table 1

Recent epidemiological studies