

Effects of Marijuana on Mental Health: Psychotic Disorders

ADAIALCOHOL &
DRUG ABUSE
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Highlights

- Cannabis use and use disorders are more common among those with psychotic disorders compared to the general population, however, the prevailing view is that marijuana use itself is neither necessary nor sufficient to cause psychotic disorders.
- In some individuals, marijuana can induce effects that mimic the symptoms of psychosis, including delusions and/or delirium.
- At-risk users of marijuana who are reluctant to discontinue their use should be counseled regarding the potential risk associated with high THC strains of cannabis, and monitored closely for the development or exacerbation of psychotic symptoms.

Introduction

Marijuana is the most commonly used drug of abuse in the United States.¹ As found in the 2015 National Survey on Drug Use and Health, 22.2 million people aged 12 and older had used marijuana in the past month.¹ Research suggests that marijuana use has increased over the past decade²⁻⁴ as perceptions of risk of harm from using marijuana among adults in the general population have steadily declined.⁴ As of June 2017, 26 states and the District of Columbia have enacted laws that have legalized marijuana use in some form, and 3 additional states have recently passed measures permitting use of medical marijuana.⁵ Mental health conditions figure prominently among the reasons given for medical marijuana use⁶, yet there is a dearth of rigorous, experimentally controlled studies examining the effects of marijuana on mental health conditions.⁷ This research brief will summarize what is known about the effects of marijuana on psychotic disorders, a rather heterogeneous group of disorders including schizophrenia, schizophreniform disorder, brief psychotic disorder delusional disorder, schizoaffective disorder, schizotypal (personality) disorder, catatonia, and substance-/medication-induced psychotic disorder. It is important to distinguish between psychosis as a syndrome and psychosis-like experiences or psychotomimetic effects.⁸ Psychotic disorders generally consist of a mix of positive, negative, and cognitive symptoms that are generally stable over periods of weeks, months, or years. Positive symptoms include delusions, hallucinations, and thought-alienation phenomena. Negative symptoms include alogia, avolition, anhedonia, asociality, and affective flattening. Cognitive symptoms include deficits in attention, working memory, problem-solving, and executive function. Psychosis-like experiences or psychotomimetic effects are transient and self-limited and may include loss of reality-testing, derealization (a feeling that one's surroundings are not real), depersonalization, dissociation, hallucination, paranoia, impairment in concentration, or perceptual alterations.⁸

Overview of Complexities in Specifying Marijuana Effects

Any summarization of the effects of marijuana on mental health would be lacking without a brief overview of complexities in specifying marijuana effects. Unlike, say, methamphetamine, marijuana is not a single chemical compound. As a plant, marijuana is composed of more than 500 chemical substances.⁸ Only a fraction of these have been studied. It is generally understood that the psychotropic substance in marijuana that is primarily responsible for its intoxicating effects is delta-9-tetrahydrocannabinol (THC).⁹ More than 100 other compounds have been identified in marijuana that are chemically related to THC, called cannabinoids.⁸ Cannabinoids exert their effects through the relatively recently discovered endocannabinoid system; only since the late 1980s has it been recognized that humans and other mammals have cannabinoid receptors throughout the body and endogenous cannabinoids that modulate the effects of neurotransmitters and other cellular mechanisms in ways that are not yet fully understood but that have generated intense interest as potential targets for therapeutic drug development, including drugs for mental health.⁹

Table 1. CNS and cardiovascular effects of THC and CBD.

	THC	CBD
Anticonvulsant	+	++
Muscle relaxant	++	+
Analgesic	++	+
Anxiolytic	±	++
Antipsychotic	-	++
Neuroprotective	+	++
Antiemetic	++	+
Sedation	+	-
Bradycardia	-	+
Tachycardia	+	-
Hypertension	+	-
Hypotension	-	+

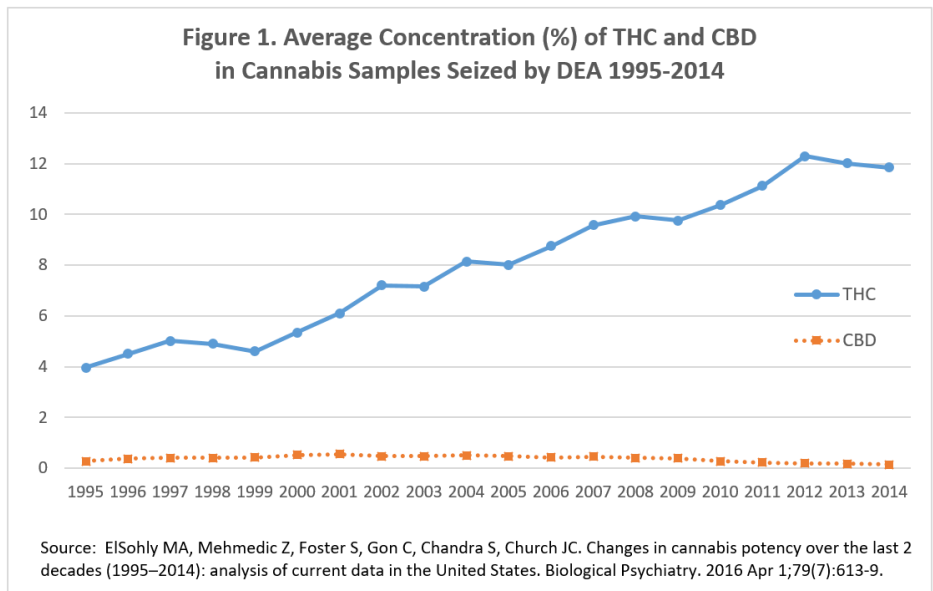
Adapted from Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Medical Hypotheses*. 2006 Dec 31;66(2):234-46.

Of the two known cannabinoid receptors, CB1 and CB2, CB1 is expressed abundantly in the brain and central nervous system (CNS) while CB2 expression is low in the CNS but high in peripheral immune cells and tissues.¹⁰ Psychoactive effects of marijuana are attributed to CB1 receptors whereas CB2 receptors are non-psychoactive.^{9, 10}

Aside from THC, the most studied phytocannabinoid is cannabidiol (CBD).¹¹ CBD has been described as nonpsychotropic due to the fact that it appears to be non-intoxicating and non-reinforcing, but it does appear to be psychotropic insofar as it appears to have pharmacological benefits with regard to anxiety, schizophrenia, addiction, and depression.¹² Table 1 summarizes the major CNS and cardiovascular effects of THC and CBD.¹¹ CBD has been demonstrated to attenuate certain effects of THC, including intoxication, sedation, and tachycardia.¹¹ In modern clinical trials,

this has permitted the administration of higher doses of THC in an effort maximize therapeutic effects while minimizing side effects.¹¹ It is largely unknown how the interaction of THC and CBD plays out in practical use of marijuana by medicinal and recreational marijuana users.

Research on cannabis products seized by the US Drug Enforcement Agency (DEA) shows that the potency of marijuana in common use has increased dramatically in the last 2 decades, at least in terms of THC content.⁸ As shown in Figure 1, from 1995 to 2014, the average THC content of seized cannabis products virtually tripled from approximately 4% to approximately 12%.⁸ On the other hand, average CBD content fell from approximately 0.28% in 2001 to < 0.15% in 2014, resulting in a change in the THC:CBD ratio of 14:1 in 1995 to approximately 80:1 in 2014.⁸ This means that, on average, the cannabis products seized in 2014 were presumably far more intoxicating and than those seized in 1995 – and marijuana and cannabis products that are in common use may bear little resemblance to marijuana supplied by the federal government for marijuana research.¹³ In terms of strength, the National Institute on Drug Abuse considers less than 1% to be low, 1-5% to be medium, 5-10% to be high, and over 10% to be very high.¹⁴ An examination of the online menu of one of Seattle’s most popular recreational marijuana stores in June 2017 listed over 100 varieties of marijuana “flowers” that were labeled as 20% THC or higher, with THC content going as high as 30%. For many of these, CBD content was not listed. By comparison, there were only 20 varieties with listed THC content under 10%. Marijuana concentrates were labeled as having THC content as high as 97%. From a scientific standpoint, the effects of cannabis products with such levels of THC on mental health have largely not been studied.



Individual differences in objective and subjective effects of marijuana vary by individual, variety/strain, dosage, route of administration, personality, degree of tolerance, and other factors.⁹ Many of the psychological effects of cannabis and THC are biphasic and bidirectional.⁹ Acute marijuana intoxication is generally associated with euphoria, subjective quickening of associations, relaxation, decreased motor activity, a sense of calm, increased awareness of sensory experience and internal sensations of the body, transient sensory experiences, synesthesia, craving sweet and salty foods, enhanced perception of current activities, increased salience of stimuli, simultaneous focus on multiple things,

impaired shifting of focus, fantasies of power, and belief of having arrived at a transcendent insight.¹⁵ With regard to neurocognition, marijuana intoxication is associated with deficits in processing speed, attention, working memory, decision-making, motivation, time-perception, and reality testing.¹⁵ Considering the broad range of effects, one can begin to imagine how marijuana could have beneficial or harmful effects with regard to mental health.

Tolerance to certain effects of marijuana develops with regular use, within several days in some cases,⁹ as a function of CB1 receptor expression downregulation.¹⁰ Research suggests that after tolerance develops it can take several weeks of THC-free recovery for CB1 receptor expression to return to baseline levels.¹⁰ Because of tolerance, the eventual downregulation of CB1 receptors with chronic use means that any benefit derived from THC with regard to mental health could result in symptom exacerbation when users are not under the influence of THC.¹⁰

Association between Marijuana and Psychotic Disorder

An association between marijuana and psychosis has been described in the medical literature since at least the 1930s, when Bromberg¹⁷ characterized the “insanity-producing effect of cannabis” as three types of syndromes: “a) intoxication, b) toxic psychosis with or without an admixture of other types of mental reactions (schizophrenic, manic-depressive), and...c) chronic dementia and deterioration following prolonged use...[which] has not been observed in American clinics.”

A large body of evidence has established an association between marijuana and psychotic disorder. The question that remains is the precise nature of the relationship. At this time, the prevailing view that is supported by the evidence is that marijuana use is a component cause of schizophrenia spectrum disorder, i.e., that it is neither necessary nor sufficient to cause these disorders on its own.¹⁸ Support for this conclusion comes from findings that marijuana use often precedes psychosis independent of alcohol consumption and even after removing or controlling for other drug use and that persistent marijuana use after a first episode is associated with poorer prognosis even after controlling for other substance use.¹⁹ Marijuana-related factors that appear to strengthen the relationship between marijuana and psychosis include younger age of onset of marijuana use, higher level of marijuana use during adolescence, and higher potency of marijuana that has been used.¹⁹ Individual differences that appear to strengthen the relationship between marijuana and psychosis include having a familial history of psychotic disorder, early trauma, growing up in an urban environment, and carrying certain genetic variants.^{18, 19} Alternative explanations for the observed relationship between marijuana use and psychotic disorders, such as the explanation that psychosis causes marijuana use as a form of self-medication, remain viable until underlying causal mechanisms are conclusively demonstrated.¹⁸

Psychotomimetic Effects of Marijuana

There is extensive anecdotal, case report, and survey evidence that marijuana intoxication can produce psychotomimetic effects, including depersonalization, derealization, paranoia, ideas of reference, flight of ideas, pressured thought, disorganized thinking, persecutory delusions, grandiose delusions, auditory/visual hallucinations, and impairments in attention and memory in up to 50% of individuals.⁸ In lab-based studies, administration of THC has also been shown to induce psychotomimetic effects in a dose-dependent manner in healthy, non-psychotic individuals.²⁰ CBD has been shown to have anxiolytic properties and even inhibit the psychotomimetic effects of THC.²¹⁻²³

Research suggests that there may be a positive relationship between susceptibility to psychosis and susceptibility to psychotomimetic effects of marijuana. Two groups of patients, those with recent-onset first episode psychosis (ROFEP) and those at ultra-high risk of psychosis (UHROP), retrospectively assessed subjective effects of marijuana (ROFEP patients were asked to rate effects before their recent episode). Compared to cannabis-using controls from the general population, the patient groups were more likely to endorse psychotomimetic symptoms. Of the ROFEP patients, 37% reported that their first psychotic symptoms occurred during cannabis intoxication.²⁴

Negative Symptoms and Marijuana

Marijuana use can produce effects that are similar to negative symptoms of schizophrenia spectrum disorders, including blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity, and reduced rapport.⁸ Chronic and heavy marijuana use has been associated with apathy, lack of motivation, social withdrawal, restricted

range of interests, lethargy, impairment in memory and concentration, impaired judgment and decision-making, and poor socio-occupational functioning, termed amotivational syndrome, which shares similarities with the negative symptoms of schizophrenia.⁸ However, a few studies have shown that patients with schizophrenia who use marijuana have less negative symptoms compared to non-users.^{25, 26}

Reasons for Marijuana Use in Psychotic Disorders

A number of studies have explored self-reported reasons for substance use in patients with psychotic disorders. Regardless of the substance used, motives for use include to relieve dysphoria, to enhance positive mood, to be social, to relieve psychotic symptoms, and to decrease side-effects of medication. Symptoms that motivate cannabis use include social isolation, lack of emotion or feeling for others, lack of energy, difficulty sleeping, depression, anxiety, agitation and tremor or shaking. These symptoms may occur as part of the psychotic illness, be due to anxiety/depressive illnesses, and occasionally may be side-effects of medication.²⁷

Effects of Marijuana Use on Outcomes in Psychotic Disorders

Zammit et al.²⁸ noted one reason people with psychosis may use marijuana is that the perceived benefits such as a reduction in anxiety and increased sociability are judged to outweigh any perceived harmful consequences. Clinicians generally believe that marijuana use produces worse outcomes in psychotic disorders; however, it is possible that this opinion is mistaken if it is confounded by other factors. The researchers conducted a systematic review to examine the evidence regarding whether marijuana use predicts worse outcomes in psychotic disorders, paying particular attention to potentially confounding factors, such as baseline illness severity. Cannabis use was consistently associated with increased relapse and non-adherence. Associations with other outcome measures, such as positive and negative symptoms, were more inconsistent and attenuated, sometimes substantially, when confounding variables were taken into consideration.

Rates of Cannabis Use and Use Disorders in Individuals with Psychotic Disorders

Cannabis use and use disorders (CUD) are prevalent among people with psychotic disorders. Estimates of prevalence rates among those with schizophrenia spectrum disorders range from 27 to 42%.^{29, 30} A meta-analysis of 35 studies found the median rate of current CUD among those with schizophrenia was 16.0%, and the median rate of lifetime CUD was 27.1%.³¹ By comparison, the 12-month and lifetime prevalence of CUD in the general population were recently estimated to be 2.5% and 6.3%, respectively.³² A systematic review of treatment of CUDs among those with schizophrenia spectrum disorders indicated that that knowledge about interventions for CUDs in this population is scarce.³³ Most interventions included combinations of motivational interviewing (MI), cognitive-behavioral therapy (CBT), and case management (CM). When marijuana use was treated as a separate outcome these were generally found to be ineffective; however, when marijuana use was treated as a grouped outcome they were generally found to be effective. Two studies of contingency management found a positive effect of offering money or vouchers for clean urine samples; however, abstinence rates dropped to baseline-levels when the researchers withdrew positive reinforcement, indicating that such an intervention would have to be ongoing to be effective. Two studies found positive effects for currently FDA-approved medications quetiapine (Seroquel) and clozapine (Clozaril) on cannabis use, but neither study had a control condition. Results on 12-step approaches were mixed, and no studies tested these with marijuana as a separate outcome. The researchers concluded that insufficient evidence exists on treating these dually diagnosed patients, studies grouping several types of substances may overlook differential effects, and future randomized controlled trials should investigate combinations of different types of treatments.³⁰

Conclusions

In summary, effects of marijuana on psychotic disorders are complex. Marijuana can induce psychotomimetic effects in some individuals and is also associated with effects that resemble negative symptoms observed in psychotic disorders. Cannabis use and use disorders have elevated prevalence among those with psychotic disorders compared to the general population. With regard to whether marijuana use causes psychotic disorders, the prevailing view is that marijuana use is neither necessary nor sufficient to cause these disorders on its own. However, the available evidence suggests that marijuana users with psychotic disorders and those at increased genetic risk of developing such disorders should be cautioned regarding the use of marijuana. At-risk users of marijuana who are reluctant to

discontinue their use should be counseled regarding the potential risk associated with high THC strains of cannabis and monitored closely for the development or exacerbation of psychotic symptoms.⁷

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