Comorbid Cannabis Misuse in Psychotic Disorders: Treatment Strategies

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ABSTRACT
Marijuana abuse can lead to transient psychosis, but can it cause or worsen psychotic disorders like schizophrenia? This article reviews the evidence from key research reports, leading to the conclusion that marijuana use, especially in early adolescence, can lead to psychotic disorders in adulthood, such as schizophrenia. There is a want of treatment approaches for marijuana use in individuals with schizophrenia, or for emerging psychosis in patients dependent on marijuana. Second-generation antipsychotics, especially clozapine, appear to be the best approach to treatment for psychosis co-occurring with—and often secondary to—marijuana abuse. More research is needed to develop appropriate and effective treatments for marijuana dependence, both alone as well as in conjunction with psychosis and psychotic disorders.

INTRODUCTION
Is marijuana dangerous? With an estimated 150 million people worldwide smoking or eating marijuana leaves annually,1 the question is pertinent. Marijuana is perceived as an innocuous drug in many circles due to its association with cultural and religious rituals, and with the fact that unlike alcohol, cocaine, or heroin, it rarely brings individuals to the brink of destitution. However, this perception is changing. In 1997, Tanda and colleagues2 reported that marijuana, like most drugs of abuse, increases dopamine release in the nucleus accumbens. Moreover, the increasing potency of available marijuana has led to the recognition of a withdrawal syndrome, characterized by irritability, restlessness, insomnia, anorexia, and aggressivity, which may last up to several weeks after stopping marijuana.3 Marijuana, like tobacco smoking, also increases the risk of lung cancer in young adults.4 With respect to mental health, marijuana smoking is reported to elicit psychotic disorders in individuals at risk5 as well as worsen psychotic symptoms in patients with psychotic disorders. This last point will be the focus of this article, which will review of the evidence, discuss clinical symptoms that may indicate an enhanced risk of psychosis stemming from marijuana, and present available treatment options.

FOCUS POINTS
• Cannabis use before 15 years of age increases the risk of serious mental illness, especially psychotic illness later in life.
• A family history of psychiatric illness may increase the risk of cannabis-induced psychosis.
• Clinicians need to investigate not only the use of cannabis by patients, but also its effect, in order to determine vulnerability to mental illness from its ongoing use.
REVIEW OF THE EVIDENCE LINKING MARIJUANA TO PSYCHOSIS

Marijuana use appears to be beginning at an increasingly early age. Based on the Substance Abuse and Mental Health Service Administration (SAMHSA) 2002–2003 survey, 90.8 million adults in the United States (42.9%) ≥18 years of age had used marijuana at least once in their lifetime. Among them, 2.1% had reported a first use before 12 years of age, 52.7% between 12–17 years of age, and 45.2% at ≥18 years of age.6 In the same survey, 12.5% of individuals >18 years of age who reported lifetime use of marijuana were classified as having a serious mental illness in the past year. Furthermore, 21% of adults who first used marijuana before 12 years of age were classified as having a serious mental illness in the past year, as opposed to 10.5% of adults who had first used at ≥18 years of age. Strictly with respect to psychosis, results from the US National Epidemiological Catchment Area Study7 highlight that daily marijuana smokers were 2.4 times more likely to report psychotic symptoms than non-daily smokers, even after adjusting for psychiatric conditions and sociodemographic factors.8 Data like these have created the suspicion that marijuana may not be as innocuous as it has been previously thought.

Before inquiring about psychotic disorders, this article evaluates how prone marijuana users are to experience some form of psychosis. As early as 1972, marijuana use was stated to possibly cause acute psychosis.9 Usually, the effects of marijuana are dose related. Mild intoxication causes drowsiness, euphoria, and heightened sensory perception, while severe intoxication leads to motor incoordination, lethargy, and postural hypotension.10 Psychosis is not considered a usual manifestation of marijuana use. Cross-sectional studies have attempted to look at the types of symptoms that might be elicited by marijuana: positive (perceptual anomalies, magical or paranoid ideation), and negative (asociality, anhedonia) in non-clinical samples. While methodologic differences abound in these studies, these studies11–14 imply that marijuana users are more prone to transient positive symptoms of psychosis; one study15 found an association with negative symptoms as well. It is unclear whether these negative symptoms represent true negative symptoms or the so-called “amotivational syndrome” (loss of interests, motivation, impaired occupational performance, and achievement), which is described as a subacute, reversible encephalopathy caused by chronic marijuana use.16 A review17 of randomized trials unrelated to mental health assessing the antiemetic effects of cannabis found that 6% of patients receiving cannabis experienced hallucinations and 5% paranoia, effects not seen with the other antiemetic drugs tested. Using a method called Experience Sampling Method, which is a structured daily diary method to investigate subjective experience during daily life in which subjects a prompted every three hours to complete the diary, Verdoux and colleagues18 found that in a given 3-hour period the likelihood of reporting unusual perceptions was increased if marijuana was used in the same 3-hour period, and not if used in the previous three hour period. This finding is consistent with the estimated duration of the pharmacologic effects of marijuana.19 With heavy marijuana use, symptoms of hypomania, agitation, auditory hallucinations, and thought disorder have been reported, which have tended to improve substantially after 5–7 days.20 However, one may ask if the association between marijuana use and psychotic experiences extends to psychotic disorders. National surveys support this association, such as the data from the US National Epidemiological Catchment Area study7 presented earlier. Two other national surveys also concur. The Australian National Survey of Mental Health and Well Being revealed that 12% of those diagnosed with schizophrenia also met International Classification of Diseases and Health Related Problems, Tenth Edition21 criteria for cannabis dependence. After adjusting for other disorders and sociodemographic factors, individuals with cannabis dependence were found to be nearly three times as likely to be diagnosed with schizophrenia as those not diagnosed with cannabis dependence.22 In the Netherlands, marijuana use was more prevalent among individuals with psychosis (15.3%) than those without (7.7%).23 Taken together, these findings support the association of marijuana use not only with transient psychosis, but also with the development of psychotic disorder. However, they cannot answer the question: do we need to worry that marijuana use can cause a psychotic illness?

The issue of causality is a difficult one to answer when it comes to conditions such as psychosis which can have multiple etiologies. To establish causality, three factors must be established: association (presented above), a temporal priority, and a direction of effect.24 The latter two factors can only be scrutinized in prospective studies, where a group is selected for assessment of a risk (marijuana use) and followed over time to evaluate how potent the risk is in causing a particular condition (psychotic disorders).

Two landmark prospective studies will be reviewed: the Swedish Conscript Cohort25,26 and the Dunedin study from New Zealand.27 The Swedish study examined a cohort of 50,087 conscripts and found a dose-response relationship between marijuana use at 18 years of age and a schizophrenia diagnosis. Self-described “heavy marijuana users” (>50 lifetime use) were 2.3 times more likely than non-users to have a schizophrenia diagnosis 15 year later (after controlling for pre-existing psychosis).28 When the analysis was extended to 27 years, heavy users were 6.7 times more likely than non-users to carry a schizophrenia diagnosis, after controlling for drug use other than marijuana, low intelligence quotient, and antisocial personality, among other factors.26 Restricting the
analyses to a 5-year window past 18 years of age to examine whether cannabis use might be a result of prodromal psychoses did not change those risks, leading the authors to state that their results were “consistent with a causal relationship between cannabis use and schizophrenia.”

The prodromal phase of schizophrenia is marked by gradual but profound changes in behavior, perception, and cognition, raising the question as to whether marijuana use may be a consequence of emerging psychosis rather than a cause of it. Although small in contrast to the Swedish study, the Dunedin study27 provided unique insights in this regard, studying a birth cohort of 1,037 individuals born in Dunedin, New Zealand between 1972–1973, with a 96% follow-up rate at 26 years of age. It gathered information on self-reported psychotic experiences at 11 years of age, before the onset of marijuana use, and on self-reported use of marijuana at 15 and 18 years of age. All individuals were assessed to yield Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnoses if present at 26 years of age, allowing the investigators to note the presence of psychotic symptoms along a continuum or the presence of a formally diagnosed psychotic disorder. Psychotic symptoms stemming from alcohol or other drugs were ruled out. Cannabis use by 15 and 18 years of age, respectively, led to higher rates of psychosis at age 26 compared to non-users, even after controlling for psychotic experiences preceding marijuana use. Age of first marijuana use was a significant factor: 10.3% of individuals who had used marijuana by 15 years of age were diagnosed with schizophreniform disorder at 26 years of age, compared to 3% of controls. The risk for adult schizophreniform disorder remained elevated after controlling for psychotic experiences at 11 years of age, with an odds ratio of 3.1. Marijuana use by 15 years of age did not predict depression at 26 years of age, and other drug use did not pose a risk for schizophreniform disorder above the one posed by marijuana. Marijuana use begun between ages 15 and 18 was associated with a heightened risk for schizophreniform disorder, but only if preceded by psychotic experiences at 11 years of age. This study corroborated the notion that marijuana use in adolescence is a risk factor for schizophrenia in later life, especially if used at an early age, suggesting both a temporal priority and direction between early marijuana use and schizophrenia. The issue of age may be especially important because at ≤15 years of age, the developing brain may be especially susceptible to suspected trophic and neurobiologic effects of marijuana exposure, for which there is accumulating evidence.29-31

Since the Dunedin study, other studies and reviews have lent support to its findings. Semple and colleagues32 conducted a meta-analysis in which odds ratio from 2–9 were found between early exposure to marijuana and psychosis, leading them to conclude that early marijuana is an independent risk factor for psychosis and psychotic disorders. Arendt and colleagues33 reported on a cohort of 535 patients who had been diagnosed with marijuana-induced psychotic disorder and found that 47% of the patients received a diagnosis of schizophrenia 1 year later. Ferdinand and colleagues34 concluded, after a 14-year follow-up study of 1,580 individuals 4–16 years of age at study entry, that there was a specific link between marijuana use and psychosis, independent of other forms of psychopathology. In a nationwide population-based sample of 2 million individuals, the authors concluded that marijuana-induced psychosis could be an early sign of schizophrenia rather than a distinct form of psychosis.35 In individuals with prodromal symptoms of schizophrenia, marijuana increased the intensity and frequency of psychotic symptoms, especially hallucinations, and did so during and shortly after marijuana use.36 This lead the authors to ponder whether marijuana could worsen prodromal symptoms and increase the likelihood of developing schizophrenia in young adolescents at risk. Genetic predisposition may further enhance this risk. In a study of the Dunedin cohort, Caspi and colleagues37 reported that individuals with a functional polymorphism in the catechol-O-methyltransferase (COMT) gene were at increased risk of schizophreniform disorder after use of marijuana during adolescence as compared with those who did not carry this polymorphism. Similar evidence is being found for polymorphisms at the cannabinoid receptor (CB1).38 These genetic factors may influence future risk of schizophrenia by interacting with other potential risk factors. For example, accumulating evidence points to dysregulation of the endogenous cannabinoid anandamide in patients with schizophrenia, with elevation of anandamide levels in blood and cerebrospinal fluid during acute exacerbations of psychosis and resolution after treatment (Figure).10,39-41 Hence, exogenous cannabinoids may worsen preexisting states that could make some individuals more at risk to develop schizophrenia from consuming marijuana.

Faced with this mounting evidence that marijuana use, particularly at an early age, can increase the risk of schizophrenia in adults, what is a clinician to do? The next section will describe an approach that may help in advising patients on the risk inherent to marijuana use and on the risk of developing a psychotic disorder.

**CLINICAL APPROACHES TO ADVISING PATIENTS**

Given the prevalence of marijuana use, psychiatrists and clinicians will encounter patients who smoke marijuana. As a starting point, not only is it important to know which substances have been and are being used (marijuana in this instance), but it is useful to ask the patient about what they experienced when smoking marijuana. Usually, mild intox-
cation can be followed by drowsiness, euphoria, heightened sensory awareness, and altered time perception. Moderate intoxication may produce memory impairments, depersonalization, and mood alteration. Severe intoxication can lead to decreased motor coordination, lethargy, slurred speech, and postural hypotension. These are the usual symptoms of marijuana use. Individuals who consistently experience these symptoms may have smoked marijuana for many years, with perhaps an ensuing decline in motivation, mental acuity, and a stalling in their personal and professional achievements. These later symptoms are often those that bring these patients to seek treatment. For those other patients who may be unknowingly more at risk of psychosis from marijuana, the experience of consuming marijuana seems to be different.

Clinicians are encouraged to look for any symptoms that might differ from the usual effects of marijuana stated above. After first smoking marijuana, or after some time thereafter, some patients may experience dysphoria, restlessness, generalized anxiety, panic attacks, paranoia, and sometimes hallucinations (Table). In most cases, marijuana-induced psychiatric symptoms, such as panic attacks, agitation, or persecutory delusions, are transient. Although no literature appears to exist looking at how these early effects of marijuana may portend future risk of mental illness, they may represent a first warning. In this author’s experience, marijuana-smoking patients with these symptoms frequently have a family history of psychiatric illness as well, be it depression, bipolar disorder, anxiety disorders, or schizophrenia. How these familial risks enhance the probability of acquiring a psychotic disorder from marijuana is not yet elucidated. Nonetheless, this author has witnessed patients with these anomalous effects of marijuana go on to develop autonomous psychotic disorders from not stopping their marijuana use in time. In the face of current evidence, the most conservative stance would dictate that patients be told that symptoms contrary to the usual effects of marijuana may signal that continued use of marijuana may possibly and seriously jeopardize their future mental health, although no definite proof of this exists for now. Presently, the state of reimbursement for clinical care forbids ancillary testing that might substantiate this risk, such as genetic testing for polymorphisms in the COMT or CB1 receptor genes.

### TREATMENT FOR MARIJUANA-RELATED PSYCHOSIS

Compared to psychosis unrelated to marijuana, marijuana-associated psychosis is emerging as more challenging to treat. In established schizophrenia, marijuana or other drug abuse leads to decreased adherence to treatment as well as increases recurrence of symptoms, episodes of violence, victimization (such as being used as drug “mules” to carry drugs), hospitalizations, and suicide. This underlies the seriousness of the problem, and the importance of developing effective treatments. Before moving on to potential medication treatments, the context of treatment deserves special mention. Programs that integrate counseling for substance abuse, psychosocial support for mental illness, and medication treatment provide the continuity and comprehensiveness

### FIGURE

**ENDOGENOUS CANNABINOID (ANANDAMIDE) SYNTHESIS FROM CELLULAR MEMBRANE PHOSPHOLIPID COMPONENTS**

![Diagram](https://example.com/cannabinoid_diagram.png)

**TABLE**

<table>
<thead>
<tr>
<th>Marijuana Withdrawal</th>
<th>Anomalous Marijuana-related Symptoms</th>
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<tbody>
<tr>
<td>Irritability</td>
<td>Anxiety</td>
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<tr>
<td>Insomnia</td>
<td>Fear</td>
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<tr>
<td>Anorexia</td>
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<tr>
<td>Restlessness</td>
<td>Suspiciousness and paranoia</td>
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<td>Aggressivity</td>
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Anomalous symptoms usually manifest early in the course of marijuana use, either during the first marijuana use or shortly after continued use. These are distinguished from signs and symptoms of marijuana withdrawal that may develop after abruptly ceasing smoking marijuana after dependence has developed.
that is more likely to make such treatment a success with the severely mentally ill. The inclusion of cognitive-behavioral and motivational interviewing approaches enhances treatment success.44,45,51 Features such as contingency management, where abstinence is rewarded with small prizes, can further increase success.52 For the most recalcitrant patients, long-term residential programs must be considered.53 However, many clinics are not equipped to provide such comprehensive services, and much remains to be overcome to disseminate such services throughout the current mental health network and to a wider population.

There are few guidelines concerning the pharmacologic treatment of co-occurring marijuana abuse or dependence and psychotic disorders. With respect to marijuana dependence itself, the cannabinoid receptor antagonist rimonabant is showing promise in primate trials to alter marijuana-seeking behavior.54 Low dose naltrexone (12 mg) has been reported to reduce the effects of marijuana, an approach that may hold promise in schizophrenia patients.55 Nefazodone, bupirone, and dronabinol show some promise as well in attenuating the manifestations of marijuana withdrawal.56 However, this research is in the preliminary stages, and it is yet to be made clear how these various approaches can be implemented in schizophrenia patients with marijuana dependence. As psychosis must be addressed in any approach to treatment for these patients, antipsychotics have featured prominently in the attempts to treat psychosis and marijuana dependence.

The first-generation antipsychotics appear to have little role in the treatment of other cannabis use disorders, and indeed, there are reports that they may worsen substance abuse.57 Older antipsychotics, especially high-potency dopamine antagonists, may further disrupt an already dysregulated mesocorticolimbic dopamine pathway, a feature common to both schizophrenia,58 and drug dependence.59 Marijuana or other drug use may very well transiently relieve core deficits in schizophrenia patients, even though it may worsen psychotic symptoms.60,61 Buckley and colleagues62 reported on a 6-month study with clozapine, showing equal response in individuals for schizophrenia who did and did not use recreational drugs. Outcomes from dual diagnosis programs are of interest as well; for the 36 out of 151 schizophrenia patients on clozapine, remission rates from marijuana and alcohol were reported at 67% to 79%, compared to 34% for the remaining patients on first-generation antipsychotics.63 A 10-year follow-up study of this group showed that schizophrenia patients on clozapine and in remission had an 8% relapse risk in the following year compared to 40% on typical antipsychotics.64 Results have been more equivocal for the other second-generation antipsychotics.65 These antipsychotics, most prominently clozapine, seem to offer the best approach to the treatment of marijuana-associated psychosis, based on the literature available and in the personal experience of the author who has treated many patients with emerging psychosis due to marijuana use. Few treatments for individuals with emerging psychosis from marijuana use can be sifted from the existing literature. This author has found clozapine, olanzapine, and aripiprazole to be most useful in treating such patients that do not yet meet criteria for schizophrenia or other psychotic disorders.

CONCLUSION

Despite the major public health problems posed by marijuana abuse, the weight of disability imposed by schizophrenia, and the emerging consensus that marijuana use—especially at an early age—can lead to psychotic disorders in adults, treatment approaches to schizophrenia patients with marijuana dependence or for emerging marijuana-related psychosis are still sorely lacking.66 Any medication approach will likely not deliver its promise without the proper supportive and psychotherapeutic environment. Although medications like naltrexone or rimonabant may be applicable to the treatment of marijuana dependence in patients with schizophrenia as these might be less likely to exacerbate psychosis, they remain to be tested. Clozapine offers the best promise thus far among antipsychotics to mitigate both psychosis and marijuana misuse, both in individuals with schizophrenia and in patients with incipient psychosis due to marijuana. The difficulties of using clozapine have reduced its acceptability to patients and still pose a major hurdle to its more widespread use. Alternatives to clozapine that preserve its benefits and shed its severe liabilities are being actively sought after. Much more work is necessary to address the issue of marijuana-related psychosis, especially in light of the risk of serious mental illness posed by marijuana use in adolescents. Intervening early to stop marijuana use, as with overall drug use in the US, must remain a public health priority and may represent a unique and significant preventative measure to preserve good mental health in individuals at risks. PP

REFERENCES
