

This COMMENTARY section of *The Journal of Clinical Psychiatry* presents the highlights of the planning teleconference series "The Effect of Marijuana Use on the Risk for Schizophrenia," which was held on June 4, 2012. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc.

The teleconference was chaired by **A. Eden Evins, MD, MPH**, Center for Addiction Medicine, Department of Psychiatry, Massachusetts General Hospital, and Harvard Medical School, Boston. The faculty were **Alan I. Green, MD**, Department of Psychiatry and the Department of Pharmacology and Toxicology, Geisel School of Medicine at Dartmouth, and the Dartmouth Center for Clinical and Translational Science, Hanover, New Hampshire; **John M. Kane, MD**, Department of Psychiatry, The Hofstra North Shore-Long Island Jewish School of Medicine, Uniondale; the Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks; and Behavioral Health Services, North Shore-Long Island Jewish Health System, New Hyde Park, New York; and **Sir Robin M. Murray, MD, DSc, FRCP, FRCPsych, FMedSci, FRS**, Department of Psychosis, Institute of Psychiatry, King's College London, London, United Kingdom.

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The Effect of Marijuana Use on the Risk for Schizophrenia

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Cannabis, or marijuana, is one of the most commonly used illicit drugs, but the debate rages in several countries regarding whether or not it should be legalized. With marijuana's legalization come serious considerations for the medical community, such as What are the consequences of long-term use? What are the medical and psychological risks? and Who are the people most vulnerable to its negative effects? For example, are those with a predisposition for developing schizophrenia likely to have an earlier age at onset if they use marijuana?

Recent research¹ has revealed a connection between cannabis use and schizophrenia outcomes later in life, especially in adolescent cannabis users. Schizophrenia, which affects about 2.4 million Americans, is a chronic brain disorder that causes substantial disability² and has a high worldwide cost and burden of care.³ Although no cure is available, tools can help clinicians accurately diagnose and treat the condition, and possible genetic markers may outline future treatment targets. Because the typical age at onset for schizophrenia is between 18 and 25 years, pediatricians as well as family practitioners and psychiatrists who see young patients should screen them for marijuana use and educate patients and parents on the associated risks.

A. Eden Evins, MD, MPH, assembled an international group of experts to discuss the effect of marijuana on the risk for schizophrenia. The group addressed risk factors of schizophrenia, consequences of cannabis use, the potency of different types of cannabis and its effects, the effects of concurrent alcohol and tobacco use with cannabis, and the implications of legalizing marijuana.

WHO NEEDS TO KNOW ABOUT THE RISKS ASSOCIATED WITH MARIJUANA USE?

Dr Kane: Pinpointing the audience for our concerns about cannabis is a challenge. Pediatricians and child psychiatrists especially need to know about the risks for developing schizophrenia that are associated with cannabis use, but education also should be shared with the public, families with preadolescent children, school counselors, and others who interact with youths. The intention here is not to scare people, but rather, to give them some realistic guidance. The key is to share a balanced message by saying that some people have a substantial increase in risk for psychosis following marijuana use.

Dr Green: The data^{4,5} suggest that cannabis use in early adolescence (ie, early cannabis use) is associated with an earlier onset of schizophrenia in a vulnerable population. Studies^{6–8} attest to gene-environment interactions, and a large Swedish conscript study⁹ showed that heavy marijuana use is associated with a higher rate of developing schizophrenia. The question that clinicians need answered is, Who is likely to be at risk? Marijuana use may be more of a problem for some people than it would be for others.

WHAT IS THE RISK OF SCHIZOPHRENIA FOR MARIJUANA USERS?

Dr Kane: Determining the risk of schizophrenia is complicated because, as Dr Green mentioned, it involves potential gene-environment interactions.

- Recognize patients who may be vulnerable to psychotic disorders through their family history, social problems, and environmental factors.
- Discuss the risks of marijuana use with child and adolescent patients and their parents.
- Warn patients with psychotic disorders to avoid marijuana use.

Because of that complexity, I want to add a word of caution. When a young person who develops schizophrenia has a history of marijuana use, that can sometimes lead to self-blame or blame from family members in thinking that, if he or she had not used marijuana, the illness would not have developed. I have seen this feeling occur in patients and families, and we have to be careful about discussing the risk of developing schizophrenia because we do not know enough about cause to be so specific. When we are talking about risk, we are dealing with complex interactions between multiple factors. The message to young people is that marijuana is not a drug without risk and that there may be some people for whom the risks are particularly concerning.

Someday, we may have genetic markers that will help determine a person's risk for schizophrenia, but at the present time, we can watch for early symptoms, such as deterioration in school performance or odd thoughts or behaviors. Those might be people in whom we are particularly concerned about the effect of cannabis.

Dr Murray: I agree. Schizophrenia results from a number of different factors, including genetic predisposition, prenatal problems, insult to the brain during development, childhood adversity, and exposure to addictive drugs (Table 1).¹⁰⁻¹⁴ We cannot point to just one cause and say, "This is why this patient developed schizophrenia." Rather,

we can say each of these factors increases the risk, and they probably act together.

Marijuana use is somewhat analogous to alcohol dependence. The vast majority of people who drink alcohol do it sensibly, moderately, and come to no harm, and the vast majority of people who use cannabis sensibly do not develop psychosis. But, in each case, a minority of drinkers develop alcoholism and a minority of marijuana users develop psychosis. Those of us who see the casualties need to remember that there are far more people who use these substances and do not develop illness than people who do.

Dr Evins: Schizophrenia is highly heritable, and about 80% of the liability is attributable to genetic factors.⁶ Genetic risk may emerge in 2 ways: (1) the interaction of common variants of many genes, each having a small effect, and (2) the rare occurrence of genetic variants such as deletions or duplications.¹⁵ Environmental risk factors interact with genetic factors to contribute to schizophrenia. The consequences of cannabis use can be severe in a person who already has underlying genetic risk factors.

Dr Murray: For example, evidence¹⁶ suggests that having a family history of schizophrenia or a "psychosis-prone" or paranoid personality increases the risk of developing schizophrenia. Adolescents who have these characteristics are also more likely than adolescents without these features to become psychotic if they smoke cannabis.

In terms of genetic markers for schizophrenia, Caspi et al⁸ found in 2005 that carriers of the Met allele of the *COMT* gene were especially likely to develop psychosis if they used cannabis in adolescence. Although this study suggested gene-environment interactions, other studies¹⁷ have had trouble replicating the results. More recently, research¹⁸ has shown that the *AKT1* gene interacts with cannabis in provoking psychosis. However, we are still far from the stage at which we can go to a music festival and genotype everybody,

Table 1. Risk Factors for Schizophrenia^a

Developmental Period	Contextual Risks		
	Individual	Family	Neighborhood
Preconception/prenatal	Genetic predisposition Second-generation immigrant Problems during pregnancy (diabetes and bleeding) Problems with fetal growth and development Maternal stress during pregnancy (such as spousal death) Maternal infection or flu exposure during pregnancy Hypoxia-related delivery complications Male gender	Parental diagnosis of schizophrenia	Urban setting Low socioeconomic status
Infancy	Head injury		Urban setting Social adversity
Early childhood	Head injury Motor, language, and cognitive impairments	Family dysfunction	Urban setting Social adversity
Middle childhood	Head injury Self-reported psychotic symptoms	Family dysfunction	Urban setting Social adversity
Adolescence	Head injury Cannabis use	Family dysfunction	Urban setting Social adversity
Young adulthood	Head injury Family dysfunction		Social adversity

^aReprinted with permission from O'Connell et al.¹⁰

then advise half of the participants to avoid cannabis and tell the other half to go ahead and smoke as they like.

Dr Green: Clinicians can tell patients and their families that marijuana use in the early teenage years seems to increase the risk of psychosis in some people. We currently cannot say which people are more vulnerable.

HOW DOES EARLY OR HEAVY CANNABIS USE AFFECT ADOLESCENTS?

Dr Murray: Sometimes, parents are relieved when their teenager smokes cannabis instead of drinking alcohol because they think it is safer, but they may not realize that their teen is smoking 5 joints per day.

Dr Evins: Early, heavy cannabis use seems to be associated with the greatest risk for developing schizophrenia.

Dr Kane: Can people's reactions to marijuana be used as a guide to their risk for psychosis? For example, some people may experience uncomfortable paranoid ideation after using cannabis. Perhaps paranoia and other unusual effects of marijuana indicate vulnerability to psychosis (Table 2).¹⁹

Dr Green: A study by Caton and colleagues²⁰ differentiated substance-induced psychosis from primary psychosis that co-occurs with alcohol or drug use. Substance-induced psychosis was associated with drug dependence, visual hallucinations, and parental substance abuse. However, it is possible for substance-induced psychosis to convert to a primary psychosis in some people. But, can early and heavy cannabis users develop a primary psychosis later without having an acute substance-induced psychosis first?

Dr Murray: Young people who become paranoid or temporarily deluded tend to think they had a bad trip and do not use cannabis again. In this way, they lessen their vulnerability of developing psychosis. Other people who enjoy cannabis at first and do not develop psychotic reactions until months or years later may find themselves dependent and have difficulty stopping cannabis use even if they feel paranoid when using it.

Dr Green: About 9% of people who use cannabis become addicted.²¹ Addiction rates are higher in those who start at a young age or use marijuana daily.²¹

Dr Evins: Some people think that, during the prodromal period of schizophrenia when adolescents are less socially adjusted and less likely to be doing well in school, they are simply more likely to be vulnerable to peer pressure to use marijuana. Do we agree that marijuana use in someone who is already developing schizophrenia is more than a coincidence and could be a risk factor?

Dr Murray: Yes. A 25-year longitudinal study by Fergusson and colleagues²² reported on cannabis use and psychotic symptoms in 1,055 participants at 18, 21, and 25 years of age. The researchers found that cannabis users at age 18 had higher rates of psychotic symptoms than nonusers at 21 and 25 years, but the reverse wasn't true, suggesting that the direction of causality is from cannabis use to psychotic

Table 2. Usual Effects of Marijuana Use and Unusual Effects of Marijuana That May Indicate Risk of Psychosis^a

Usual Effects of Marijuana	Unusual Effects of Marijuana
Mild effects	Anxiety
Altered time perception	Fear
Drowsiness	Hallucinations
Euphoria	Auditory
Heightened sensory awareness	Visual
Moderate effects	Panic attacks
Depersonalization	Paranoia
Memory impairments	Restlessness
Mood alteration	Suspiciousness
Severe effects	
Decreased motor coordination	
Lethargy	
Postural hypotension	
Slurred speech	

^aBased on Raby.¹⁹

symptoms. But, this does not mean that cannabis use is a necessary or single cause of schizophrenia.²³

Dr Green: Disentangling the effects of chronicity of use versus the age of first use is difficult, but it does appear that early cannabis use predisposes people to a greater risk for developing psychosis than does later use.

Dr Murray: In the immature brain, the use of cannabis at a certain point in development may affect brain functions and behavior.²³ Chronically smoking marijuana in early adolescence may also be associated with a greater risk for psychosis. Research²⁴ suggests that white matter connectivity is affected depending on the age at which regular cannabis use begins. Schizophrenia is also a young person's illness. So, if the peak risk for developing the disorder is during early adulthood, using cannabis before then is probably riskier than using it after age 35 or 40 years. Although evidence is not available to support that, it is a logical claim.

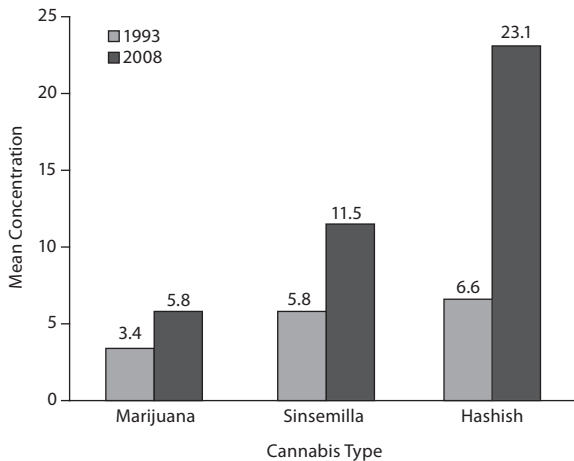
Dr Kane: Is anything known about what happens to the risk of schizophrenia after people stop smoking cannabis? For example, if young people used cannabis for X number of years, stopped, and then remained drug-free for X number of years, are they still at increased risk of developing psychosis?

Dr Murray: I do not think anybody has done a long-term follow-up study on the risk of psychosis in people who smoke, say, until age 20 years and then stop.

Dr Green: Regardless of whether chronicity of use is a factor, early use of marijuana is associated with an earlier age at onset of psychosis.^{5,25}

WHAT ARE THE EFFECTS OF CANNABIS IN PEOPLE WITH PSYCHOTIC DISORDERS?

Dr Kane: For older adolescents or young adults who have already developed schizophrenia, what are the risks if they use cannabis? I have had many patients with schizophrenia who have improved with treatment and want to return to their regular relationships—they want to smoke cannabis because that is what their friends are doing and they want to fit in. People who have serious psychiatric illnesses should be warned about marijuana use.

Figure 1. Mean Δ^9 -THC^b Potency by Cannabis Type^a

^aData from Mehmedic et al.³¹

^bAbbreviation: Δ^9 -THC = delta-9-tetrahydrocannabinol.

Dr Green: Marijuana use, both in my clinical experience and in the literature,^{21,26–28} can worsen the symptoms of psychotic disorders.

Dr Murray: I agree. I have had patients who recover and go home for the weekend, and after smoking a joint, they are psychotic again. In a 4-year follow-up study²⁷ of patients with recent onset of psychosis, those who stopped using cannabis had fewer positive symptoms and a less continuous illness course; negative symptoms were not different. However, another follow-up study²⁹ found a reduction in negative symptoms and a better functional outcome over 8 years for those with first-episode psychosis who stopped using cannabis versus those who continued to use.

Dr Evins: Like cigarette smoking, people have to stick with abstinence for a while to see an effect.

Patients often think that cannabis makes them feel better or more relaxed, but they come back clinically worse. Clinicians should alert patients to this.

Dr Green: I agree. Although people with schizophrenia may say that marijuana makes them feel better, studies do not provide support for a “self-medication” basis for substance use in these patients.³⁰

HOW DOES THE POTENCY OF CANNABIS AFFECT THE RISK FOR SCHIZOPHRENIA?

Dr Green: The potency of cannabis has increased over time (Figure 1).³¹

Dr Murray: Potency depends on the type of cannabis and its percentages of THC (tetrahydrocannabinol) and cannabidiol (CBD). The marijuana plant’s growing conditions and preparation affect these properties.^{31,32} The concentration of THC has increased in most forms of cannabis over time, and accordingly, usage has shifted from the forms with less THC to those with higher concentrations.^{31,33} In the UK in the 1990s, old-fashioned resin (or hashish), which was most

commonly used, would have had about 3% each of THC and CBD, whereas the engineered plants like sinsemilla or ‘skunk,’ which became the most often used form of cannabis by 2008, have up to 18% THC and almost no CBD.³³

Researchers are interested in whether or not CBD has antipsychotic effects. Leweke and colleagues³⁴ reported that CBD was as effective as amisulpride for psychotic symptoms in patients with acute schizophrenia, which may be attributable to increased anandamide levels. And, a small study³⁵ found that pretreating healthy people with CBD prevented acute psychotic reactions to intravenous THC. Because CBD concentrations have decreased in cannabis over time, it could be that old-fashioned cannabis had a slightly protective component against psychosis that is absent from the newer, high-potency types.

Dr Green: The percentage of CBD that happens to be in the plant may change the way people react to it. The problem is that we do not know exactly what type of marijuana people are using.

Dr Evins: This may mean that recent epidemiologic studies are more relevant than older ones because people are likely smoking marijuana with a higher potency, higher THC, and lower CBD.

Dr Kane: Marijuana is also different in different parts of the world.

Dr Green: So, making generalizations from some of the data may be difficult because people in the past or in other places are using different varieties of marijuana.

Dr Murray: One study³³ found that 78% of first-episode psychosis patients, versus 37% of control group participants, used high-potency cannabis (sinsemilla/skunk). Those with first-episode psychosis were also 2 times more likely to have smoked cannabis for more than 5 years and 6 times more likely to be daily users. It will be a while before proper longitudinal studies on high potency are conducted. Of course, sometimes people who use cannabis have no idea what kind it is. Also, those who smoke high-THC cannabis may not inhale as deeply as those using less potent forms. Tracking the titration of cannabis is complicated because it would require testing blood levels, and nobody has done that.

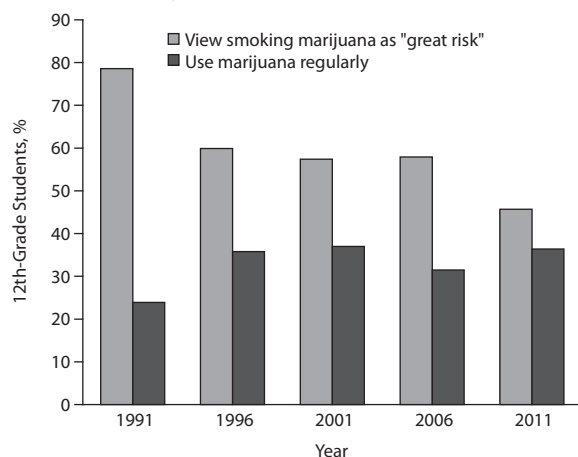
WHAT ARE THE COGNITIVE EFFECTS OF CANNABIS USE?

Dr Evins: A burgeoning literature³⁶ exists on cognitive effects of cannabis in people who do not have psychosis. Most cognitive deficits from cannabis use appear to be reversible, but some may be enduring.

Dr Murray: I would think that cognitive effects, although milder than psychosis, are much more prevalent. For example, cannabis use is associated with poor school performance and dropping out.³⁷ A very recent study³⁸ has shown that adolescent cannabis use is associated with an 8-point loss of IQ over the subsequent decades.

Dr Green: I have read reviews³⁹ about marijuana users who have psychosis with slightly better functioning than

Figure 2. 12th-Grade Students' Perceived Risk and Regular Use of Marijuana by Year^a



^aData from The University of Michigan.⁵⁰

those with psychosis who do not use cannabis, which seems counterintuitive. But, did these people have somewhat higher functioning to begin with?

Dr Murray: That would be my experience. The psychotic people who are using cannabis may actually be clever, and they could have started with a higher premorbid IQ than the nonusers. To obtain marijuana at age 13, adolescents need a certain level of street smarts and social skills, as well as the ability to obtain money.

Dr Evins: Recent publications^{40,41} are recognizing some cognitive abnormalities in chronic cannabis users, such as hippocampal changes, learning difficulties, and memory problems including encoding, consolidation, and retrieval. Chronic cannabis use seems to cause cognitive impairment in nonpsychotic people that is similar to the cognitive abnormalities that are intrinsic to schizophrenia.⁴² A few cognitive symptoms can last, but most symptoms resolve within 30 days.

Dr Murray: Studies^{43,44} with nonpsychotic and psychotic people who are not chronic cannabis users have proved that people who have had THC do not perform as well cognitively. Other studies^{45,46} have suggested that heavy cannabis users have a decrease in brain volume. I am interested to know if this is true or not.

WHAT IS THE RISK WHEN MARIJUANA IS COMBINED WITH ALCOHOL, TOBACCO, OR OTHER DRUGS?

Dr Murray: A portion of cannabis users are taking other drugs, such as amphetamines or cocaine. A recent cohort study⁴⁷ in California found that methamphetamine use alone increased the risk of schizophrenia as much as cannabis did. But, a longitudinal study⁴⁸ in New Zealand found that the risk was specific to cannabis use and not the use of other drugs, like cocaine or opiates. I would expect, however, that stimulants interact negatively with cannabis.

Dr Kane: What about the combination of marijuana and alcohol use? Does that influence the risk of developing psychosis?

Dr Green: The data are unclear.

Dr Murray: A study⁴⁹ in Scotland found that both alcohol and cannabis use were associated with brain changes and an increased subsequent risk of psychosis for those who already had a high genetic risk of schizophrenia. Having a family history of schizophrenia may make the brain more sensitive to the risk-modifying effects of alcohol, tobacco, and cannabis.

Dr Green: There is no question that alcohol use causes trouble in people who are already psychotic.

Dr Kane: Yes.

Dr Murray: Even Emil Kraepelin, an early, influential German psychiatrist, thought that alcohol caused psychological problems, but not specifically schizophrenia. He was a member of the Temperance League, and he campaigned against alcohol.

HOW COULD THE ISSUE OF LEGALIZING MARIJUANA AFFECT ADOLESCENTS?

Dr Murray: It appears that different US states are on opposite sides of the issue regarding legalizing marijuana.

Dr Green: You are absolutely right. Debates continue about decriminalizing the possession of small amounts of marijuana.

Dr Murray: The British government has also wavered on this question over the past decade.

Dr Evins: The idea of legalizing marijuana may give the message to young people that it is safe.

Dr Green: The term *medical marijuana* makes it sound like a therapeutic agent, which may encourage more people to use it.

Dr Evins: In US high schools, I talk about tobacco use, which the students perceive as harmful, but that is not the case with marijuana use (Figure 2).⁵⁰

Dr Green: Although legalization is a complex sociopolitical question, when focusing on the medical and psychiatric aspects, we all agree that there are serious risks with cannabis use in at least some adolescents.

CONCLUSION

Although the overall risk for people developing schizophrenia is small, a vulnerable minority must be warned that using marijuana during adolescence increases their risk for developing schizophrenia. Clinicians should screen children and adolescents for marijuana use and watch for signs of declining school performance or odd behavior that could indicate a predisposition for psychosis. With the potency increases in cannabis, patients must be aware that heavy, chronic cannabis use can cause serious effects on cognitive function, and patients with psychosis should avoid using cannabis because it can worsen their symptoms.

Disclosure of off-label usage: Dr Evins has determined that, to the best of her knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this activity.

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