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SUBSTANCE USE AND RELATED DISORDERS (F LEVIN AND E DAKWAR, SECTION EDITORS)

Cannabis and Psychosis: a Critical Overview of the Relationship

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Abstract Interest in the relationship between cannabis use and psychosis has increased dramatically in recent years, in part because of concerns related to the growing availability of cannabis and potential risks to health and human functioning. There now exists a plethora of scientific articles addressing this issue, but few provide a clear verdict about the causal nature of the cannabis-psychosis association. Here, we review recent research reports on cannabis and psychosis, giving particular attention to how each report provides evidence relating to two hypotheses: (1) cannabis as a contributing cause and (2) shared vulnerability. Two primary kinds of data are brought to bear on this issue: studies done with schizophrenic patients and studies of first-episode psychosis. Evidence reviewed here suggests that cannabis does not in itself cause a psychosis disorder. Rather, the evidence leads us to conclude that both early use and heavy use of cannabis are more likely in individuals with a vulnerability to psychosis. The role of early and heavy cannabis use as a prodromal sign merits further examination, along with a variety of other problem behaviors (e.g., early or heavy use of cigarettes or alcohol and poor school performance). Future research studies that focus exclusively on the cannabis-psychosis association will therefore be of little value in our quest to better understand psychosis and how and why it occurs.

Keywords Marijuana · Schizophrenia · Mental illness · Cognition · THC · Psychotic disorder

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Introduction

There has been a recent explosion of interest in the relationship between cannabis use and psychosis, with over 100 papers addressing this topic each year since 2012, compared to fewer than 10 per year during the 1990s (data from PubMed). This increased interest is likely due, at least in part, to increasing approval within the USA of medicinal marijuana laws at the state level and accompanying concerns that more widespread cannabis use might increase the risk of schizophrenia [1]. Intense interest in this area is expected to continue as cannabis becomes legally available to adults for recreational purposes as has been done in four states and Washington DC. We look to science to provide direction for public policy, but we are confronted with limitations on the ability of research to deliver a clear answer as to whether cannabis exposure is itself a causal factor in the onset and subsequent course of psychotic illness [2].

Before embarking on a more detailed examination of the scientific evidence, it is worth stating what we do know without any real question. First, people diagnosed with first-episode psychosis or with schizophrenia are more likely to report current or prior use of cannabis, compared to the general population. This statistical association between the use of cannabis and the incidence of psychotic disorders has been

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reported so many times based on so many types of data and from so many parts of the world that it cannot be dismissed. Several recent articles contribute further evidence in support of the relationship, with data from Italy [3], the USA [4], Sweden [5], France [6], and South Africa [7].

Another fact that we do know without question, again based on many studies of a variety of populations from many parts of the world, is that cannabis use does not occur in a vacuum, cleanly isolated from other potential confounding variables. In 1976, Jessor [8] reported results from a 4-year longitudinal study of 432 adolescents, finding a statistical cluster of correlated behaviors that included cannabis use, early alcohol use, early sexual activity, poor school performance, less involvement in religion, and a measure of "general deviant behavior" (lying, stealing, fighting, truancy, etc.). During the intervening years, many studies have corroborated this basic finding, most often referring to these other behaviors as "risk factors" for marijuana use [9, 10].

A third fact of which we can be certain is that schizophrenia has been linked to a wide variety of variables, including family history of schizophrenia, exposure to toxins or infections in utero, older age of the father, birth month [11] (possibly related to vitamin D deficiency), and perhaps even growing up in a home with cats [12]. Also, people diagnosed with psychosis have been reported to be more likely to smoke tobacco cigarettes heavily and to use excessive amounts of stimulants and opioids. Thus, if cannabis were a cause for schizophrenia based simply on association studies, it would be one of the many [13•].

Given the insurmountable difficulty of isolating the contribution of cannabis use from the many other behaviors with which it is highly associated in large-scale population studies, unequivocal proof of cannabis exposure causing psychosis would require the experimental manipulation of cannabis use, with other confounding factors controlled for by random assignment of participants to different groups. Either adolescents could be assigned to use/not use or to varying amounts of use or groups of current users could be randomly assigned to continue, quit, or reduce use. Given the low incidence of psychosis in the population, such an experiment would require a very large number of participants, ideally followed over several years. No such experiment has been conducted nor likely ever will be, for both ethical and practical reasons (e.g., participant compliance with assigned cannabis use levels).

In the absence of such experiments, we are left with correlational and longitudinal studies of naturally occurring cannabis use, which implies that naturally occurring confounds can never be completely ruled out. We must then ask, "What is the most likely explanation for the relationship between cannabis use and psychosis, given everything we know about both?" Fifty years ago, Hill [14] published an often-cited list of criteria by which we might impute the likelihood of disease causation based on environmental exposure. That paper was written at a time of much discussion about the consequences of cigarette smoking, and whether or not research could "prove" that smoking causes lung cancer and other diseases. The Hill criteria remain the standard, not for proof, but for acceptance that direct causation is the best explanation. Even within each criterion, whether or not the evidence is sufficient to meet that criterion is often a judgment call rather than a clear yes-or-no decision, as we shall see when we examine each criterion in the context of cannabis exposure.

The diathesis-stress model is relevant to both explanations. We accept that a variety of genetic, gestational, infectious, nutritional, and other factors increase the vulnerability (diathesis) to psychosis. The causal model then gives cannabis a role as a later environmental stressor which, in vulnerable individuals, may help to trigger the appearance of psychotic behavior. We believe that one reason the causal hypothesis has been readily adopted by so many is that it is simple and easily understood (exposure to the chemicals in cannabis, especially in a developing brain, might cause some long-lasting change that increases the chances for the later appearance of psychosis [1, 15]. We believe that there is another viable explanation for the relationship between these two forms of behavior, as suggested in a previous review [16]. Those individuals burdened by the diathesis have an increased susceptibility not only to psychosis [17] but also to other psychiatric disorders, including substance use disorder, and other "problem behaviors." As the individual develops, some subset of these behaviors may appear at different ages, depending upon stresses, opportunities, and other factors. In the 2013 National Survey on Drug Use and Health, the self-reported age of first use among all US marijuana smokers was 16 years. Individuals affected by the diathesis would not be expected to start cannabis use later than this, but rather earlier, and to be more likely to use it more heavily than the typical cannabis user. Median age of onset of schizophrenia is in the early 20s for males and somewhat later for females [11]. Thus, among individuals who both use cannabis and become schizophrenic, we would expect the cannabis use to precede the diagnosis of schizophrenia. The appearance of one behavior before the other does not imply a causal relationship; it merely reflects the typical course of development of these behaviors. Let us call this alternative the "shared vulnerability" hypothesis. The vulnerability increases the chances of both cannabis use and psychosis, but the two behaviors emerge at different stages of development. In other words, early and heavy cannabis use may be viewed as one of several prodromal signs predicting an increased likelihood that schizophrenia will emerge at a later time. We will contrast this with the "cannabis as a contributing cause" hypothesis.

Literature Review

Our goal was to review recent research reports on cannabis and psychosis, with particular attention to how each report provides evidence relating to these two hypotheses. Two

primary kinds of data are brought to bear on this issue: studies done with schizophrenic patients and studies of first-episode psychosis. Hill's nine "viewpoints" will provide the structure for this review.

1. Strength

   Is the association between cannabis use and psychosis strong enough to warrant our attention? It could be argued that it is not. For example, the vast majority of cannabis users will never receive a diagnosis of a psychotic disorder. But, psychotic disorders are rare, and we should remember that over 90 % of cigarette smokers do not develop lung cancer, and over 90 % of women who consume two or more drinks per day during pregnancy will produce normal-appearing offspring. What is important in each of these cases is the risk ratios, which are approximately 10:1 relative to abstainers.

   The apparent relative risk for psychosis among users of cannabis has been reported to be about 2:1, and for heavier users as high as 6:1 [1, 18]. In addition, it has often been reported that cannabis users have an earlier onset of first-episode psychosis or schizophrenia [19–23]. Although not as strong as the relationship for tobacco and lung cancer or for maternal alcohol and birth defects, the association is strong enough to warrant further efforts to understand it. From a public health perspective, however, the potential contribution of cannabis use to schizophrenia appears to be quite small. A recent model of the "Global Burden of Disease" estimated that the number of "disability adjusted life years lost" due to the potential contribution of regular cannabis use or dependence to schizophrenia represented about 0.35 % of the total disability associated with cannabis, and only about 0.04 % of the total disability associated with schizophrenia [24••]. In other words, schizophrenia among cannabis users is much less important than the disability caused by cannabis dependence itself. These reviewers did not accept the premise that cannabis use increases the incidence of schizophrenia and based their findings only on the evidence that cannabis users have an earlier onset of the disorder, leading to the conclusion that cannabis use has marginal effects on the total disability burden of schizophrenia. We therefore conclude that efforts to understand the relationship should be motivated by an academic desire to better understand the nature of schizophrenia rather than by a belief that attempts to reduce cannabis use will reduce the burden of this disorder.

   Further, we point out that the existence of a correlation between cannabis use and psychosis as well as the earlier onset of psychosis in cannabis users is consistent with either the cannabis as a contributing cause or the shared vulnerability hypothesis.

2. Consistency

   Here, we are on solid ground. As described in the "Introduction," many studies from many populations over many years have reported that cannabis users have higher than average rates of schizophrenia. Again, this consistency does not favor either hypothesis.

3. Specificity

   By specificity, we mean to ask whether cannabis has a special relationship to the incidence of psychosis. We can ask the question in two ways: (1) Is the use of other substances also associated with psychotic illness? and (2) Do cannabis users also have higher than average rates of other psychiatric disorders? There is reason to question the causal hypothesis from both of these perspectives. First, it has long been known that schizophrenia is associated with higher rates of heavy tobacco smoking, and recent evidence continues to support this link [6, 25]. Indeed, the kinds of evidence linking psychotic illness and schizophrenia to the use of these two substances are remarkably similar, as have been the arguments about causality [26, 27•, 28]. Also, cannabis users are more likely to smoke tobacco, and tobacco smokers are more likely to use cannabis, meaning that separating these two relationships is difficult [29].

   Beyond that, people with psychosis tend to use alcohol heavily and often have higher rates of stimulant and opioid use [30, 31•, 32, 33••, 34•]. It may be that cannabis use is more common than the use of other illicit drugs among schizophrenic populations (e.g., [31•], but this is perhaps due to the fact that cannabis is the most widely used illicit drug in the general population. In many cases, alcohol use disorder is found about as frequently as cannabis use disorder [31•, 32, 33••, 34•].

   The other perspective on specificity also falls short, in that cannabis use has been associated with a variety of other psychiatric disorders, including depression, anxiety, bipolar disorder, and antisocial personality disorder [34•, 35–38].

   The shared vulnerability model does not call for the same degree of specificity, since it does not depend upon a specific pharmacological action of cannabis to produce a unique sensitivity to psychosis. All we really know is that, more often than chance, the people who develop certain mental disorders are the same people who are more likely to use various psychoactive drugs. Thus, the apparent lack of specificity for the cannabis-psychosis relationship favors the shared vulnerability model (Table 1).

4. Temporality

   Longitudinal studies have typically reported that cannabis use precedes the first evidence of psychosis [39••],

Table 1 Studies relating to the issue of specificity (Hill criterion 3)

Study	Participants	Measures	Results
Sara et al. 2014 [31•]	13,624 people diagnosed with schizophrenia	SUDs	29 % cannabis UD; 26 % alcohol UD; 14 % stimulant UD
Auther et al. 2015 [32]	370 people at clinical high risk for psychosis	2+-year follow-up for conversion to psychosis	Cannabis abuse/disorder associated with conversion rate, but not after controlling for alcohol use
Hartz et al. 2014 [33••]	9131 people with severe psychotic illness vs 10,311 controls	Levels of substance use	Odds ratio for daily smoking 5.11; "recreational" drugs 4.62; alcohol > 4 drinks/day 3.96; cannabis > 21 times/year 3.47
Nesvag et al. 2015 [34•]	From Norwegian patients register: 9002 with schizophrenia, 15,000 bipolar; 87,540 depressive	5-year prevalence of comorbid SUD	Schiz: 14.8 % polysubstance, 7.6 % stimulants, 6.7 % cannabis, 4.3 % opiates, and 3.3 % sedatives Bipolar: 5.8 % poly, 4.6 % sedative, 3.3 % cannabis, 2.6 % stimulants, and 2.1 % opiates
Lagerberg et al. 2015 [37]	324 people with bipolar disorder	Age at onset of bipolar	"Dose-response" relationship with level of cannabis use
Fernandez-Calderon et al. 2015 [30]	4102 therapeutic community clients with multiple SUDs	Comorbidity of psychiatric disorders	In the cluster of alcohol/cannabis/cocaine; 12 % psychotic, 11 % mood, and 9 % anxiety
Guillem et al. 2015 [38]	207 cannabis users	Comorbid psychiatric disorders	53.2 % anxiety disorder, 38.1 % mood disorder, and 4.8 % psychotic disorder

and much emphasis has been placed on these findings. If one considers only the two simplest direct-causation alternatives, either that cannabis is a contributing cause for psychosis or that the mental disorder develops and then cannabis is used as a form of "self-medication," then the evidence clearly favors the cannabis as a contributing cause hypothesis. Indeed, just such an analysis was recently used to conclude that tobacco use causes schizophrenia [26]. But we should take care not to fall victim to the classic logical fallacy, *post hoc ergo propter hoc*. The occurrence of one event before another may be necessary to impute causation, but it is not sufficient. The shared vulnerability model allows these two forms of behavior to emerge at different times simply because the typical age of the first use of cannabis occurs five or more years before the typical age of the first psychotic episode. With shared vulnerability as a plausible alternative, temporality provides no special support for a causal explanation.

5. Biological Gradient

The cannabis as a contributing cause hypothesis would predict that psychosis should be more likely in heavier users of cannabis due to increased exposure to cannabinoid chemicals. Recent reports add to the already-existing literature demonstrating that heavier users are at greater risk [6, 40]. Under experimental controls, the demonstration of a dose-response relationship is powerful evidence of a specific pharmacological effect, because other variables are controlled and only dose is manipulated. However, a naturally occurring gradient of cannabis use does not merely represent increased chemical exposure but includes increased likelihood of a wide variety of associated confounding variables. The shared vulnerability hypothesis views heavy use of cannabis and early use of cannabis as potential signs (along with early and heavy use of tobacco and alcohol) of an increasing burden of vulnerability in those individuals, which may also place them at greater risk for psychosis or some other psychiatric disorder. This can produce what appears to be a dose-response relationship in the absence of any direct causal effect of cannabinoid chemicals. Since we have already pointed out the relative lack of specificity of the cannabis-psychosis relationship, these so-called dose-response relationships are consistent with either hypothesis.

6. Plausibility

Is there a plausible biological explanation for the relationship between cannabis use and psychosis? One way to approach this is to look for biological effects of cannabis exposure that can then plausibly be linked to psychosis. There has been considerable research effort aimed at providing evidence for such a biological pathway. A number of different hypotheses have been explored based on effects on dopamine systems [41], endocannabinoid systems [42–44], brain volume [45–47], gray matter density [15], cortical maturation [48], hippocampal shape [49], or various functional properties of the brain [50–53]. No consistent results have been obtained that would increase the plausibility of a pharmacological mechanism for causation (Table 2). Particular attention should be paid to studies demonstrating altered functioning of the endocannabinoid systems in psychosis, in light of an earlier review proposing that genetic factors contributing to schizophrenia might operate in some individuals via such

Table 2 Studies relating to the issue of plausibility (Hill criterion 6)

Investigators	Hypothesis tested	Participants	Findings	Caveats
Bioque et al. 2013	The endocannabinoid system is disrupted in the first episode of psychosis patients	Patients with a first episode of psychosis, $N = 95$ Controls, $N = 90$	Reduced expression of the endocannabinoid synthesis enzymes and an increased expression of the degradative ones observed in patients with a first episode of psychosis	Nearly all of the patients were taking antipsychotic medications No information provided on other drug use of participants Amount or recency of cannabis use not controlled No significant difference observed between the groups on cannabinoid receptor activity
Bossong et al. 2006	THC causes a release of dopamine throughout the striatum	Data were combined from two studies, $N = 19$	Decreased D2/D3 binding potential only in the limbic striatum. This implies that THC produced an increase in dopamine release, but effect was modest (3.7 % reduction) and did not occur throughout the striatum	Studies employed different routes of drug administration Only one THC dose examined
Epstein and Kumra 2015	(1) The magnitude of cortical thinning would be altered in individuals who met criteria for cannabis use disorder across heteromodal association cortex regions; and (2) the magnitude of these alterations would be related to the amount of cannabis consumed	Adolescents with early-onset schizophrenia: • Cannabis use disorder, $N = 11$ • Non-cannabis use disorder, $N = 17$ Controls: • Cannabis use disorder, $N = 17$ • Non-cannabis use disorder, $N = 34$	Greater lifetime exposure to cannabis was associated with greater cortical thickness in the left and right superior frontal gyri, left pars opercularis, right pars triangularis, right supramarginal, and left inferior parietal cortex	Small number of participants studied The influence of drug use other than cannabis not controlled The influence of other psychiatric disorder not controlled
Fischer et al. 2014	Dysregulated brain reward circuit underpin cannabis use in schizophrenic patients	Patients with schizophrenia and cannabis use disorder, $N = 12$ Controls, $N = 12$	Smoked cannabis and oral THC administration increased brain reward circuit connectivity	All patients were taking antipsychotic medication The influence of drug use other than cannabis not controlled Small number of participants studied Controls had higher levels of education
Greenwood et al. 2014	The study investigated mismatch negativity amplitude reduction in chronic cannabis users relative to controls	Near-daily cannabis users, $N = 39$ Controls, $N = 42$	The mismatch negativity amplitude frequency was reduced in cannabis users	Cannabis users were abstinent for less than 24 h The influence of drug use other than cannabis not controlled Controls had higher IQ and levels of education
Haller et al. 2013	Study investigated whether chronic use of cannabis induces structural brain changes that may be responsible for the	50 patients with a first episode psychosis:	Cannabis consumption was not related to alterations in gray or white matter in first-episode psychosis	All patients were taking antipsychotic medication

Table 2 (continued)

Investigators	Hypothesis tested	Participants	Findings	Caveats
	cognitive and psychological disturbances in schizophrenia	Cannabis users, $N = 33$ Non-drug using controls, $N = 17$		Small number of participants studied
Herzig et al. 2015	Study investigated whether functional hemispheric asymmetry for language is attenuated in cannabis users with and without first-episode psychosis	Patients with a first episode of psychosis: • Cannabis users, $N = 11$ • Nonusers, $N = 18$ Controls: • Cannabis users, $N = 38$ • Nonusers, $N = 52$	Cannabis use associated with balancing rather than exacerbating uncommon hemispheric laterality patterns	The influence of drug use other than cannabis not controlled Equal and small group sizes
Koenders et al. 2015	Schizophrenic patients would show decreased regional brain volumes compared with healthy controls in regions previously found to be related to schizophrenia	Schizophrenic patients: • Cannabis use disorder, $N = 80$ • Nonuse disorder, $N = 33$ Non-drug using controls, $N = 84$	Patients with schizophrenia (with or without a CUD) had smaller volumes of most brain regions (amygdala, putamen, insula, parahippocampus, and fusiform gyrus) than healthy controls, and differences in cortical volume were mainly driven by cortical thinning	No associations between age at onset and frequency of use with regional gray matter volumes were found The influence of drug use other than cannabis not controlled
Malchow et al. 2013	Study investigated the association between cannabis abuse and psychopathological symptoms, brain morphology, and neuronal integrity in subcortical brain regions of schizophrenic patients	Patients with a first episode of psychosis, $N = 47$ Controls, $N = 30$	Cannabis use was associated with smaller brain volume in several regions compared with controls	Controls had higher levels of education Schizophrenic patients were younger Cannabis history information unreliable Small number of participants studied
Monteleone et al. 2013	Cortisol awakening response is blunted in cannabis-using schizophrenic patients	Schizophrenic patients: • Cannabis users, $N = 16$ • Non-cannabis users, $N = 12$ Controls, $N = 15$	Cortisol awakening response was blunted in schizophrenic patients who used cannabis	Cannabis history information unreliable and not confirmed by biological measure Small number of participants studied The influence on cortisol levels was not determined
Onwuameze et al. 2013	Patients with specific MAPK14 genotypes are more vulnerable to the effects of heavy marijuana misuse and would show greater brain volume deficits than patients without marijuana misuse	Patients with schizophrenia-spectrum disorders: Cannabis use disorder, $N = 52$ Non-cannabis use disorder, $N = 183$	In heavy marijuana users, specific allelic combinations of cannabinoid-related genes were associated with smaller WM brain volumes	Non-patient group not examined Small number of participants studied The influence of drug use other than cannabis not controlled

Table 2 (continued)

Investigators	Hypothesis tested	Participants	Findings	Caveats
Solowij et al. 2013	Cannabis use would alter hippocampal pathology typically observed in schizophrenia	Patients with schizophrenia: • Near-daily cannabis users, $N=8$ • Non-cannabis users, $N=9$ Controls: • Near-daily cannabis users, $N=15$ • Non-cannabis users, $N=16$	Hippocampal differences were observed among the groups	Controls had higher levels of education Small number of participants studied No measure of hippocampal pathology was assessed
Suarez-Pinilla et al. 2015	Study investigated whether three cannabinoid receptor variants were associated with changes in brain volumes, body mass index, or psychopathological scores	First-episode psychosis patients, $N=65$	Specific cannabinoid receptor polymorphisms were associated with smaller caudate and thalamic volume	The influence of antipsychotic medication unknown Small number of participants studied
Volk et al. 2014	Study investigated cannabinoid binding levels in deceased schizophrenia patients	Patients with schizophrenia, $N=21$ Controls, $N=9$	Schizophrenic patients had 8 % higher binding to cannabinoid receptors in the prefrontal cortex	The influence of antipsychotic medication unknown Small number of participants studied

a mechanism [54]. If we eventually learn that altered endocannabinoid functioning is a predictor of the later appearance of schizophrenia, this might provide an important clue to the shared vulnerability, in that such genetically induced alterations could potentially influence both schizophrenia and cannabis use. On the other hand, alterations in endocannabinoid functioning have been associated with anxiety, PTSD, and depression and might be a consequence of the emotional stress associated with active psychosis [55].

Genetic studies have also failed to provide a consistent set of results that can help us to understand the cannabis-psychosis relationship. For example, a study on genetic variation in the COMT gene in a group of schizophrenic patients found a greater percentage of cannabis users in those expressing the Val/Val genotype. This can be interpreted either as suggesting that this genotype makes the individual more sensitive to the psychosis-causing effect of cannabis (cannabis as a contributing cause hypothesis) or that this genotype contributes to a shared vulnerability (shared vulnerability hypothesis). Another study on large gene deletions, said to be associated with schizophrenia [56], found that schizophrenic patients with these deletions had lower rates of cannabis use. One interpretation would be that this genetic variation makes a causal contribution to schizophrenia that is independent of the contribution made by cannabis use (cannabis as a contributing cause hypothesis). Another interpretation is that cannabis use shares less vulnerability from this particular genetic variation. Other studies have found no interaction between genetic risk for schizophrenia and the use of cannabis [57]. In any case, we are faced with a bewildering variety of potential genetic variations that are candidates for studying. One recent family-based study identified over 8000 single nucleotide polymorphisms that are statistically associated with schizophrenia [58]. Overall, the search for a biological pathway by which cannabis might exert a long-term deleterious effect has gone down many roads, but none has emerged as a truly likely explanation, which is what would be required to provide support to the causal hypothesis. The brain is a very complicated organ, and it might be that such a pathway does exist and someday its discovery will provide that support. We believe it to be likely that there is no biological pathway from cannabis use to psychosis, since the shared vulnerability hypothesis does not require one.

7. Coherence

Does one or the other of these hypotheses provide a better fit with all the other things we know about both psychosis and cannabis use? Perhaps, the biggest difference in the predictions based on these two ideas goes back to the issue of specificity. Under the cannabis as a contributing cause hypothesis, exposure to cannabinoid chemicals should result in a specific increase in the incidence of psychosis. The

shared vulnerability hypothesis predicts that whenever we find an association between cannabis and psychosis, we are also likely to see associations with certain kinds of substance use, as we have already reviewed, and also with other behavioral indicators of developmental vulnerability. For example, schizophrenic patients who tested positive for recent use of cannabis, cocaine, or methamphetamine had higher childhood adversity scores, a measure of premorbid behavioral problems [4].

Data from three recent family-based studies have shed light on some of the possible shared vulnerability between cannabis use and psychosis. In a Swedish national registry study [39••], a clear association was found between cannabis use and schizophrenia, but the majority of this relationship disappeared after controlling for familial relationships. Because much (but not all) of the vulnerability for schizophrenia may be inherited, the shared vulnerability hypothesis is coherent with this finding. Any residual, non-familial linkage between cannabis and psychosis could be due to non-inherited influences on vulnerability, such as season of birth, infections, or birth trauma. In an Australian twin study [59], greater genetic risk for schizophrenia, based on multiple single nucleotide polymorphisms, was found to be associated with greater use of cannabis, implying that both schizophrenia and psychosis can be associated with some of the same genetic risk factors. Finally, US researchers interviewed relatives of psychotic and non-psychotic individuals who were either heavy cannabis users or had no history of cannabis or other illicit drug use. A measure of "morbid risk of schizophrenia" was elevated in the families of psychotic patients regardless of cannabis use. The authors concluded that "having an increased familial morbid risk for schizophrenia may be the underlying basis for schizophrenia in cannabis users and not cannabis use by itself" [60••]. These family studies provide strong evidence supporting the shared vulnerability hypothesis over cannabis as a contributing cause.

Three studies on transition to psychosis or schizophrenia offer what at first appear to be conflicting results. North American adolescents identified as at "clinical high risk" for psychosis based on prodromal signs were followed for 4 years [61]. Level of cannabis use was not related to the frequency of receiving a diagnosis of psychosis (nor was tobacco or cocaine use). This clearly fails to support the hypothesis that cannabis is a contributing cause, but what does it say about shared vulnerability? We might suggest that most of the shared vulnerability was already captured within the high-risk group. A similar study in England found no influence of lifetime cannabis use on transition to psychosis, but increased risk in those who initiated use before age 15. The greater risk with earlier use is consistent with the shared vulnerability hypothesis, but the causal hypothesis can also accommodate these results if cannabis exposure at a younger age is more damaging than later exposure [62]. A somewhat different approach examined patients admitted for "substance-induced psychosis" [63•]. In the case of cannabis, these are acute episodes attributed to the short-term toxic effects of unusually high doses. In the Finnish national registry, the 8-year cumulative risk of receiving a diagnosis of schizophrenia was 46 % for cannabis-induced psychosis, compared to 30 % for amphetamine-induced psychosis and only 5 % for alcohol-induced psychosis. Although this result might appear to provide strong support for cannabis as a contributing cause, a likely alternative explanation is that cannabis-induced psychosis is not common among cannabis users and is more likely to appear in those already at risk for schizophrenia. This is consistent with the Finnish data, in which alcohol-induced psychosis was reported over 100 times more often than cannabis-induced psychosis, and stimulant-induced psychosis was 6.6 times more likely [63•] even though cannabis use is presumably much more common than amphetamine use in Finland.

Overall, taking a broad look at other things we know about both cannabis use and psychosis, we find considerable support for the shared vulnerability hypothesis. Those results that appear to support cannabis as a contributing cause are less convincing when viewed from a broad perspective.

8. Experiment

We have already said that controlled experiments to address this question might never be done. However, there have been opportunities to conduct semi-experimental analyses of the issue. Gage et al. [2] recently pointed out that in the UK, there has been at least a 10-fold increase in cannabis use since the 1970s. The cannabis as a contributing cause hypothesis would predict that such a large change in cannabis use would result in increased psychosis, yet data on first admissions for schizophrenia show no increase, and perhaps a slight decrease, over that time. Also, in the UK, there was a relaxation of regulation of cannabis in 2004, followed by a return to the previous more restricted classification in 2009. Although it is doubtful that these regulatory changes had much impact on actual usage of cannabis, hospital admissions for "cannabis psychosis" decreased after relaxation and increased after more stringent controls were returned, exactly opposite to what one would have predicted [64].

Two actual experiments have been conducted on the utility of providing treatment for cannabis use in psychotic patients with comorbid cannabis dependence. In the Danish study [65], 102 psychotic outpatients with cannabis use disorder were randomly assigned to treatment as usual, or usual treatment plus motivational interviewing and cognitive behavioral therapy focused on cannabis use. Over the 6-month study period, the experimental group had significantly more admissions to emergency care than the treatment as usual group. A similar study in Ireland [66••]

followed 88 outpatients over a 1-year period and found that motivational interviewing/cognitive behavior therapy had no effect on cannabis use or on positive or negative symptoms of psychosis. Taken together, these studies suggest that efforts to reduce cannabis use in psychotic patients achieve little, and that even if very large reductions in cannabis use could be achieved, there might not be a concomitant reduction in the incidence of psychosis.

9. Analogy

One thing that would increase the plausibility of the cannabis as a contributing cause hypothesis would be if there were another known toxic agent that was already accepted to be a cause of schizophrenia. No toxic agent is listed among the risk and prognostic factors in the DSM-5 [11]. There has been some interest in prenatal lead exposure as a possible contributor [67], based on considerably less evidence than has been provided for cannabis.

The closest analogies we can find are for tobacco and stimulant drugs, which also have been associated with schizophrenia [26, 31•] and which have been subject to the same questions about causality.

In contrast, there are several non-drug behavioral factors that can be associated with schizophrenia as in the shared vulnerability model. Poor early school performance, which we have already seen, is a predictor of cannabis use, has been associated with later development of schizophrenia [68], and has the level of violence among young criminals [69] and being arrested for arson [70]. In none of these cases do we assume that these activities cause the later appearance of psychosis, but rather that there is some shared vulnerability.

Conclusion

The numerous studies that have been conducted based on the tentative assumption that cannabis use might cause an increased risk for psychosis have not provided us with either a better insight into how cannabis actually produces such an effect or with an effective method for reducing the risk of psychosis by reducing cannabis use. We believe this is probably because cannabis does not in itself cause such an increase. Rather, our review of the evidence leads us to conclude that both early use of cannabis and heavy use of cannabis are more likely in individuals with a vulnerability to a variety of other problem behaviors, such as early or heavy use of cigarettes or alcohol, use of other illicit drugs, and poor school performance. In some individuals, the same vulnerability also results in increased risk for psychosis or some other mental disorder.

Future research studies that "put on blinders" and focus exclusively on the cannabis-psychosis association will therefore not be of much value to us in our efforts to better understand psychosis and how and why it occurs. Studies that examine whether certain patterns of substance use and other problem behaviors are more predictive of psychosis or of major depressive or bipolar disorders might provide interesting insight, as could genetic or familial studies that examine shared risks for these different problem behaviors and mental disorders.

It has been argued that even if we are uncertain that cannabis actually causes psychosis, it is better to err on the side of caution and warn cannabis users, psychiatric patients, and the general public about this potential danger of cannabis use [2]. However, those adolescents most at risk for beginning cannabis use are already suspicious about official warning messages when it is perfectly clear that cannabis use is not approved by the general society. If we wish scientists to be taken seriously when we do discover real and substantial dangers, then we believe it would be better to avoid behaving like "the boy who cried wolf."

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of impotance,
- •• Of major importance

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