HHS Public Access

Author manuscript

Curr Addict Rep. Author manuscript; available in PMC 2015 June 01.

Published in final edited form as:

Curr Addict Rep. ; 1(2): 115–128. doi:10.1007/s40429-014-0018-7.

Impact of Cannabis Use on the Development of Psychotic Disorders

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Abstract

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

Keywords

Cannabis; psychotic disorders; psychosis; schizophrenia

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Conflict of Interest

Deepak Cyril D'Souza, Rajiv Radhakrishnan and Samuel T. Wilkinson have nothing to disclose.

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.

Introduction

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

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

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

Overview of Cannabis, Cannabinoids, and the Endocannabinoid System

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

The principal psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (THC). However, cannabis contains over 70 cannabinoids besides THC, including cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), cannabidivarin (CBDV),

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

Acute psychosis associated with intoxication

A link between cannabis intoxication and altered behavior including psychosis has long been recognized (27). In the 19th century, Moreau (de Tours) characterized transient hallucinations, paranoia, dissociative symptoms, thought disorganization and impairments in attention and memory reminiscent of psychotic symptoms seen in schizophrenia in the context of acute cannabis intoxication (reviewed in (28)). These phenomena have also been documented in numerous case-reports (reviewed in (28)) and estimated to occur in about 20%-50% of individuals who use cannabis (29, 30).

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

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

Cannabinoids have also been shown to induce abnormalities in electrophysiological indices of brain function that are also known to be present in schizophrenia and other neuropsychiatric disorders. THC reduces amplitude of the novelty P300a and target P300b,

measures of the automatic orientation of attention (P300a) and context updating (P300b) in healthy participants (38, 39) in a dose-dependent manner (40) without affecting processing speed. Furthermore, THC does not affect the N100, suggesting that cannabinoids do not have significant effects on early sensory registration (40). Self-monitoring is compromised in schizophrenia and contributes to deficits in insight (41). Error-related negativity (ERN), an event-related potential (ERP) component, is theorized to be related to error monitoring and has shown to be reduced in healthy volunteers exposed to THC (42). There is mounting evidence that disruptions in neural oscillations play a key role in the pathophysiology of psychosis (reviewed in (43)). Neural oscillations in the theta (θ; 4-7 Hz) and gamma (γ; 31-80 Hz) range are involved in sensory registration, the integration and binding of perceptual features, working memory, and conscious awareness (44-48), processes that are altered in psychosis. Studies in animals and hippocampal slices have provided evidence that cannabinoid agonists can disrupt synchronized neural oscillations at θ and γ frequencies (49-56). In humans, smoked cannabis was shown to disrupt θ band power; further, the degree of disruption correlates with working memory performance (57).

Functional neuroimaging studies with THC and CBD have revealed that they have opposing actions in neural networks involving the medial temporal and prefrontal cortices, regions that are rich in CB1 receptors. The networks recruited in these studies also recapitulate the pattern of activity seen in schizophrenia, thus making a case for the endocannabinoid hypothesis of schizophrenia (58-60). Individuals who experience acute psychotic symptoms induced by THC have a different pattern (medial temporal cortex and cerebellum) of brain activation compared to placebo, suggesting that these brain regions mediate THC-induced psychotic symptoms (61). THC attenuated activation in the left parahippocampal gyrus/fusiform gyrus, left middle temporal gyrus/superior temporal sulcus and right cerebellum/fusiform gyrus, and accentuated activation in right middle temporal gyrus in individuals who experienced transient psychotic symptoms (60).

Given the role of dopaminergic hyperactivity in the pathophysiology of positive symptoms, and prefrontal dopaminergic hypoactivity in the pathophysiology of negative symptoms and cognitive deficits (62, 63), a number of neuroreceptor imaging studies in humans have attempted to demonstrate THC-induced dopamine (DA) release. One small study showed reduced regional binding of the radiotracer [11C]raclopride suggestive of a very small increase in dopamine release following inhaled THC (64). However two other studies using comparable doses but different radiotracers failed to show any changes (65, 66). Similarly the effects of DA D2 antagonist antipsychotics on THC-induced effects have been mixed. The psychotomimetic effects of THC were not blocked by the dopamine receptor antagonist haloperidol (67) in healthy volunteers and THC was also shown to exacerbate psychotic symptoms in patients with chronic schizophrenia despite being on stable doses of antipsychotics (37). However, other studies suggest that haloperidol (68) and olanzapine (69) may attenuate THC-induced psychotomimetic effects in healthy volunteers. In a study using [18F]-fallypride, inhaled delta(9)-THC was associated with significant ligand displacement (dopamine release) in striatal subregions schizophrenic patients and their relatives but not in controls (62).

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

Acute psychosis outlasting the period of intoxication

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

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

Cannabis and persistent psychotic disorders

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

One of the first studies that attempted to link cannabis exposure to schizophrenia was a longitudinal, 15-year cohort study of 45,570 Swedes (91). A dose-response relationship was observed between self-reported cannabis use at age 18 years and psychiatric hospitalization for schizophrenia over the ensuing 15 years (91). Zammit et al. replicated the findings in a subsequent analysis of these data (92), and furthermore showed that adjustment for potential

confounders such as psychiatric diagnosis, IQ score, degree of social integration, disturbed behavior in childhood, cigarette smoking and place of upbringing did not explain the association. The most recent follow-up of this cohort (see Table 1), found an increased risk for the development of schizophrenia in those who used cannabis compared to non-users (93). Notably, the risk for schizophrenia declined in the cannabis using group as follow up time increased suggesting a predisposing vulnerability such that those who are genetically vulnerable will develop schizophrenia within a certain window of time after exposure, while those who are not genetically vulnerable remain unaffected by exposure. A number of other large long-term and cross-sectional epidemiological studies, including the Dunedin cohort (94), the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (95), German Early Developmental Stages of Psychopathology (EDSP) Study (96) and the Christchurch Health and Development Study (97) have reported similar findings (reviewed in (28)).

Strength of association and consistency

Generally, the strength of the association between cannabis exposure and schizophrenia is modest but consistent. Meta-analyses have estimated odds ratios (ORs) of 1.41-2.34 (98-100). While the association between cannabis use and the later development of persistent psychotic disorders is consistent, it should be noted that methodological limitations may bias this association, including residual confounding, follow up bias, direction of causality, and difficulty discriminating between psychotic symptoms from acute intoxication and psychotic disorder at the time of assessment (101).

Temporal Relationship

Temporality is considered one of the more important criteria needed to establish causality. Establishing the temporal relationship between an environmental factor and schizophrenia may be particularly challenging in part because the onset of schizophrenia is difficult to establish. The emergence of positive symptoms may be the final step in the evolution of schizophrenia. Negative and cognitive symptoms are more difficult to recognize than positive psychotic symptoms, and often precede positive symptoms. This makes pinpointing the onset of illness and therefore establishing the temporal relationship between cannabis exposure and schizophrenia challenging.

Several recent retrospective studies have reported that in the majority of cases studied, cannabis use preceded the development of psychosis by a period of years in first-episode psychosis (FEP) patients with a history of cannabis exposure(102-104). Though these studies are limited by their retrospective approach the finding that cannabis use precedes psychosis onset has also been supported by the findings of a number of earlier longitudinal, prospective studies (105-108).

A number of studies also suggest that cannabis exposure is associated with an earlier and more abrupt onset of psychosis. A meta-analysis of 83 studies investigating the association between cannabis and psychosis found that cannabis users who develop psychotic disorders do so on average 2.7 years before those who do not use cannabis (109). Additional studies report a similar trend (110, 111).

Interestingly, data for the converse temporal relationship also exists. As such, it is again emphasized that most epidemiological studies have not taken into account negative and cognitive symptoms, which are thought to occur earlier than positive ones. A prospective study of a large population of Dutch teenagers with assessments of psychosis and marijuana use at ages 13, 16, and 19 showed a significant association between cannabis use and psychosis vulnerability across all time points (112). Notably, there was a bidirectional association; that is, psychosis vulnerability at ages 13 and 16 predicted cannabis use at ages 16 and 19, respectively.

Biological Gradient

Most large epidemiological studies have found a consistent biological gradient characterizing the cannabis-psychosis association (91, 93, 95, 97). In general, those who report heavier cannabis use have a higher risk of a psychosis outcome. A recent analysis of the National Epidemiologic Survey on Alcohol and Related Conditions data set supported the existence of a biological gradient (see Table 1) (113). Notwithstanding these findings, it should be noted that there are considerable limitations to assessing a dose-response effect of the cannabis-psychosis relationship. The concentration of THC in cannabis, which contributes to the dose of exposure, varies significantly; to our knowledge, no large epidemiological studies have attempted to measure or control for the variation in THC. Further, the concentration of CBD, which is believed to offset the pro-psychotic effects of THC (18), can also vary.

Specificity

The specificity of the association between cannabis and psychosis is stronger than the associations between cannabis and other mental illnesses, and the associations between other substances and psychosis. For instance, cannabis exposure has a stronger association with psychosis outcomes than depression or anxiety outcomes (99). In relation to other substance use, conversion to schizophrenia was found to be highest with cannabis (46%) followed by amphetamines (30%), and alcohol (5%) in a large study (87), suggesting higher specificity of psychosis outcomes than for other substances. While there is a strong association between cigarette smoking and schizophrenia, there is little evidence to support the notion that cigarette smoking “causes” schizophrenia.

Biological Plausibility

The immediate effects of cannabinoids on DA, GABA and glutamate neurotransmission, may explain some of the acute cannabinoid-induced symptoms discussed above. However, the mechanism by which cannabinoid exposure results in schizophrenia has not yet been established. As discussed elsewhere (114), one hypothesis suggests that cannabinoid exposure alters brain development that most believe continues until the age of 25 (115). Factors that disrupt brain maturation or development may have long-term consequences. The endocannabinoid system is central to a number of neurodevelopmental processes including axon elongation, neurogenesis, neural maturation, neural specification, glia formation, and neuronal migration (116-124), processes that may be relevant to the neurodevelopmental hypothesis of schizophrenia. Excessive or non-physiologic perturbation of the endocannabinoid system in the rapidly changing brain, as is the case in adolescence,

may have far reaching consequences. This may be particularly true in the setting of already abnormal neurodevelopmental processes, as would likely be the case in individuals at risk for psychosis.

Window of Exposure

An emerging finding is that earlier exposure to cannabis is associated with a higher risk for psychosis outcome and that the risk declines when exposure is after late adolescence. Thus, those who begin using cannabis at a young age are at particularly high risk of developing schizophrenia (94, 103, 125)). One study reported that the association between cannabis and psychotic disorders was only significant when cannabis use began before age 14 (103). Another study found that, compared to cannabis users with onset after age 17, those who began use before age 17 had a significantly greater risk of positive symptoms (adjusted OR 9.5, p=0.0001), and a greater risk of auditory hallucinations (adjusted OR 8.5, p=0.003) (125). One interpretation of these findings is that cannabis exposure during critical periods of brain development may lead to long lasting consequences such as psychosis. Indeed, this hypothesis has received some support in animals studies showing that exposure to cannabinoids in adolescence has more deleterious effects than exposure in adulthood (126-130).

Alternatively, Stefanis et al. found a consistent lag of 7-8 years between age of onset of cannabis use and the age of onset of psychosis in a retrospective study of 997 individuals (ages 12-19 years at time of onset of cannabis). This suggests that cumulative exposure to cannabis may be more relevant than age at onset of cannabis, with earlier cannabis use resulting in greater cumulative exposure (131).

Another important theme is that cannabis use is associated with an earlier age of onset of psychosis – by 2.7 years in one meta-analysis (Large et al., 2011). This association appears to be somewhat specific, since tobacco use, which is also highly prevalent in psychotic disorders, is not associated with an earlier onset of psychosis (Myles et al., 2012).

Cannabis and Cognitive and Negative Symptoms

Cognitive Symptoms

Cognitive deficits, a core feature of schizophrenia (132), include deficits in memory, attention, executive functioning vocabulary, visuospatial skills and learning (133). There are several parallels between the cognitive deficits observed in schizophrenia and the cognitive deficits associated with cannabis exposure.

In controlled laboratory experiments cannabis and cannabinoids have been shown to produce transient, dose-related cognitive deficits (reviewed in (28)) including impairments in working memory, short term memory and attention. These cognitive deficits bear some resemblance to the cognitive deficits of schizophrenia. Whether chronic exposure to cannabis is associated with persistent cognitive deficits remains controversial (reviewed in (135)). In chronic cannabis users, one study found no persistent cognitive deficits after 28 days of confirmed abstinence (134), while other studies have shown that the time to full recovery ranges from weeks to months of abstinence (135-137). Another study found

persistent deficits despite almost two years of abstinence (85, 138). In a recent review (139) among studies in which cognitive testing was performed 3 weeks or later after the last use of cannabis, there was considerable variability in whether deficits were found on measures of attention/concentration (134, 136, 138, 140-145), decision-making/ risk-taking (146), response inhibition (136, 140-142, 145), working memory (144) and verbal memory (134, 141, 142). Most studies found impairment on reasoning/problem-solving task (136, 141, 142, 145) (140).

Recently, a number of important studies have contributed to the evidence for an association between cannabis use and persistent cognitive impairment. One notable study was a follow up from the Dunedin cohort, where cannabis use was assessed via interviews at ages 18, 21, 26, 32, and 38 years of age and neuropsychological testing was performed at ages 13 and 38. Neurocognitive decline in numerous domains, including processing speed, memory, executive functioning, and verbal comprehension was shown in cannabis users. Deficits were most notable among those who began use in adolescence and heavy users. Overall, the study estimated a loss of 8 IQ points attributable to cannabis use, which did not reverse even after cessation of cannabis (147).

In another recent study, Fontes et al. investigated the neurocognitive performance of chronic cannabis users (n = 104) and healthy controls (n = 44). Cannabis users who began using before age 15 performed worse than controls in measures of sustained attention, impulse control, and executive functioning (148). Importantly, this study did not account for the possibility of residual effects of acute cannabis intoxication from subjects' last use of cannabis.

Negative Symptoms

Cannabis use, especially when chronic and heavy, has been associated with an "amotivational syndrome," (85, 149-152) which is characterized by numerous negative symptoms, including a lack of motivation, a loss of arousal, apathy, lethargy, and impaired social functioning (153). Most of the existing literature describing this phenomenon is decades old. Symptoms of the cannabis associated "amotivational" syndrome bear resemblance to the negative symptoms of schizophrenia (amotivation, apathy, social withdrawal, disinterest in blunted affect, etc). However, earlier studies have suggested that confounding variables—such as other substance abuse, poverty, or other psychiatric disorders—may explain this "amotivational syndrome" (154).

In contrast, some studies suggest that schizophrenia patients who use cannabis have fewer negative symptoms compared to those who do not (155, 156). This evidence, however, is limited due to the cross-sectional design of these studies.

In conclusions, while considerable research has focused on an association between cannabis exposure and positive symptoms, there is some evidence to suggest that cannabis exposure is also associated with negative symptoms, which like positive symptoms and cognitive deficits represent the 3 main domains of symptoms of schizophrenia.

Genetic Studies

A number of candidate genes have been studied as interacting with cannabis exposure to confer a higher risk for schizophrenia (see Table 2). Catechol-O-Methyltransferase (COMT) is an enzyme that metabolizes dopamine in the prefrontal cortex; individuals with the Val/Val genotype at locus 158/108 have a higher metabolic activity of this enzyme (and thus lower level of prefrontal cortical dopamine) relative to those with the Met/Met polymorphism (157). Early reports (158) suggested that individuals with the Val/Val(158) COMT genotype were 10 times more likely to develop psychosis than those with the Met/Met genotype. Subsequent data, however, has yielded mixed results (159-161), with a recent 2-year longitudinal study showing no differences in the risk for developing psychosis among COMT polymorphisms (see Table 2) (162). Likewise, Estrada et al. found no overall greater risk for psychosis in association with cannabis among all genotypes of COMT (163). However, this study did find that the Val/Val genotype is associated with the earliest age of onset of psychosis (see Table 2). Finally, Costas et al. showed that schizophrenia patients who were Met homozygotes had higher rates of lifetime cannabis relative to Val homozygotes (164). These data were in contrast to the earliest report of a COMT gene by cannabis exposure interaction reported Caspi et al. (158).

While recent studies of COMT genotype moderating the psychosis-cannabis association have been mixed, there has been a surge of interest in AKT1, which codes for a phosphorylating enzyme that has been shown to be activated by cannabinoid receptors (165). In a sample of psychotic patients, their unaffected siblings, and unrelated controls, Van Winkel found a 2-fold higher incidence of C/C genotype in patients with daily cannabis use history. Furthermore, individuals with a C/C genotype had a higher chance of being diagnosed with psychotic disorder relative to siblings and unrelated controls (see Table 2) (161). Daily cannabis users with the C/C genotype have been found to be at significantly higher risk of being diagnosed with psychotic disorder relative to T/T genotypes (odds ratio 7.23). Also, individuals with the C/C genotypes who used cannabis had a higher risk of psychotic disorder than individuals who did not use cannabis (odds ratio 2.18) (166). Other investigators (167) have shown that those with the C/C AKT1 genotype who use cannabis showed poorer sustained attention than those with the T/T genotype. This was true even when cannabis use was remote (>12 months prior to testing). Recently, preliminary evidence has shown that another single-nucleotide polymorphism of the AKT1 gene (SNP rs1130233) may moderate the acute psychosis-cannabis interaction (168).

Recent studies have identified other candidate genes as playing a role in moderating the association between cannabis use and psychosis, including BDNF (169) and DAT1 (168), which codes for a dopamine transporter that removes synaptic dopamine in striatal regions. In conclusion, there is emerging, but not robust evidence of specific genetic polymorphisms interacting with cannabis exposure to confer a higher risk for the development of schizophrenia.

An emerging literature suggests that a history of childhood abuse may confer a higher risk of psychosis in individuals who use cannabis (170, 171). In a longitudinal study, Konings and colleagues showed an interactive effect of history of childhood abuse and cannabis use in

the development of psychosis (172). Importantly, this study did not demonstrate that individuals with a prior history of child abuse were more likely to subsequently use cannabis. An interactive effect between childhood abuse and cannabis use on the development of psychosis was not supported in a recent study of a large set of individuals (N=1923) followed longitudinally (173). Vinkers et al. showed a three-way interaction between cannabis use, *COMT* genotype, and childhood abuse in moderating the risk for psychosis. Those who had Val/Val genotype were more likely to develop psychotic experiences when they had a history of cannabis use and childhood abuse than individuals with the Met/Met genotype (174); a replication sample showed similar results but did not reach statistical significance. In a cross-sectional study, Alemany et al. similarly reported that individuals who had the Val/Val genotype and who had been exposed to childhood abuse were vulnerable to the psychosis-inducing effects of cannabis (175).

In summary, the specific genes *COMT* and *AKT1*, as well as a history of childhood abuse, may moderate the interaction between cannabis and psychosis. However, more research, especially of a prospective and longitudinal nature, is needed to better characterize the roles that these factors may play.

Conclusions

In summary, exposure to cannabis is associated with a number of distinct syndromes, including (1) acute psychosis associated with cannabis intoxication, (2) acute psychosis that lasts beyond the period of acute intoxication, and (3) persistent psychotic disorders. Given the changing legal status of cannabis in the United States and elsewhere, research on the association of cannabis and psychosis (especially persistent psychotic disorders) has profound implications for public health and policy. As evidenced above, the cannabis-psychosis relationship fulfills many but not all of the traditional criteria for causality. The strength of association is modest but consistent; the relationship is biologically plausible, exhibits a dose-response effect, and, in most studies, persistent psychosis is preceded by cannabis use (though few studies have taken into account the time of onset of negative symptoms).

Similar to tobacco use and lung cancer, not everyone who has been exposed to cannabis develops a persistent psychotic disorder such as schizophrenia and not everyone diagnosed with schizophrenia has been exposed to cannabis. Therefore cannabis exposure is neither necessary nor sufficient to “cause” a persistent psychotic disorder such as schizophrenia. More likely, cannabis may be a component cause that, in concert with known (specific genetic polymorphisms or history of childhood abuse) and unknown factors, contributes to the risk of schizophrenia.

As the pathophysiology of schizophrenia remains poorly understood, the role of cannabinoid exposure in contributing to the development of this disorder is significant and warrants further study. Additionally, further work is necessary to identify the factors that moderate cannabis-associated psychosis, especially with respect to persistent psychosis. Such research will lead to greater understanding of the biological mechanisms underlying individual vulnerability. The cumulative literature to date indicates that individuals with a family

history of schizophrenia, individuals with prodromal symptoms, and individuals who have experienced discreet episodes of psychosis related to cannabis should be discouraged from using cannabis and cannabinoids.

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- * important
- ** very important

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Table 1

–Recent Epidemiological Studies

Reference and Study Design	Methods/Follow Up	Sample Size	Follow Up	Result
Meier et al 2012 Longitudinal, prospective	Cannabis use assessed at ages 18, 21, 26, 32, and 38	1,037 subjects from general population	38 years	Decline in neuropsychological functioning in processing speed, memory, executive functioning, verbal comprehension
(Dunedin cohort)	Neuropsychological testing at ages 13 and 38			8-point IQ decline in subjects with cannabis-dependence, onset in adolescence
Manrique-Garcia et al 2012 Longitudinal, prospective (Swedish military cohort)	Annonymous survey at time of conscription (ages 18-19 for 93%) Interview and psychological assessment after 35 years	50,087 military conscripts (mandated), 93% were ages 18-19 at initiation of service	35 years	The adjusted OR for the development of schizophrenia: 3.7 (95% CI 2.3-5.8) in subjects who used cannabis >50 times v. non-users 1.8 (95% CI 1.3-2.5) in subjects ever using cannabis v. non-users
Davis et al 2013 Cross sectional analysis (NESARC data set)	Face-to-face, computer-assisted interview focusing on DSM-IV diagnoses	34,653 adults from general population	NA	The adjusted OR for schizotypal features: 2.02 (95% CI 1.69-2.42) in subjects with lifetime cannabis use 2.83 (95% CI 2.33-3.43) in subjects with lifetime cannabis abuse 7.32 (95% CI 5.51-9.72) in subjects with lifetime cannabis dependence
				The adjusted OR for psychotic disorder: 1.27 (95% CI 1.03-1.57) in subjects with lifetime cannabis use 1.79 (95% CI 1.35-2.38) in subjects with lifetime cannabis abuse 3.69 (95% CI 2.49-5.47) in subjects with lifetime cannabis dependence
Kuepper, van Os, et al 2011 Longitudinal, prospective (German early development stages of psychopathology study)	Cannabis use and psychosis assessed at baseline, 3.5, and 8.4 years using CIDI	1,923 adolescents/ young adults (ages 14-24 at baseline) from general population	10 years	OR for psychotic symptoms at 8.4y follow up: 1.5 (95% CI 1.1-21) in subjects with lifetime cannabis use at 3.5y 1.9, (95% CI 1.1-3.1) in subjects with new cannabis use at 3.5y
				OR for cannabis use at 8.4y based on cannabis use at 3.5y: 0.8 (95% CI 0.6-1.2)
				OR for persistent psychosis based on cannabis at baseline and 3.5y: OR 2.2 (95% CI 1.2-4.2)

OR = odds ratio; CI = confidence interval; CIDI = composite international diagnostic interview

Table 2

Studies of the Genetic × Cannabis Interaction

Gene/locus	Study	Study Design	Sample Size	Follow up	Results
COMT/rs4680	Caspi et al 2005	Longitudinal, prospective (Dunedin cohort)	803	26 years	OR of developing psychotic disorder: 10.9 (2.2-54.1, 95% CI) for Val/Val genotype 2.5 (0.78-8.2, 95% CI) for Val/Met allele 1.1 (0.21-5.4, 95% CI) for Met/Met allele
COMT/rs4680	Zammit, Owens et al 2011	Longitudinal (Avon cohort)	2630	2 years	OR of psychosis in cannabis users: 1.56 (1.05-2.31, 95% CI) with Met/Met genotype 1.47(0.85-2.26, 95% CI) with Val/Val genotype 1.68 (1.23-2.28, 95% CI) with Met/Val genotype OR 1.0 (0.73-1.36, 95% CI) of cannabis x COMT interaction
COMT/rs4680	Costas et al 2011	Case-only, cross-sectional analysis	748	NA	OR 2.07 (1.27-3.26, 95% CI) of history of cannabis use in schizophrenia patients with Met/Met genotype v. Val/Val genotype
COMT/rs4680	Estrada et al2011	Case-control, cross-sectional analysis	80 inpatients with schizophrenia	NA	No difference in genotypes between diagnosis groups or between cannabis users and non-users
			77 inpatients with non-psychotic psychiatric illness		AOP was 15.46 (SD 1.09) for Val/Val cannabis users AOP was 17.12 (SD 2.9) for Val/Met cannabis users AOP was 18.78 (4.01) for Met/Met cannabis users
					For effect of genotype on AOP, beta = 1.66, SE = 0.78, p = 0.04
AKT1/rs2494732	van Winkel 2011	Cross-sectional analysis	801 subjects with psychosis	NA	RR 1.90 ($p < 0.01$) of C/C genotype in daily cannabis users - Case-only analysis
			740 unaffected Siblings		OR 1.96 (1.09-3.53, 95% CI) of being diagnosed with psychotic disorder in C/C allele subjects - Case-sibling analysis
			419 controls		OR 2.08 (0.92-4.67, 95% CI) of being diagnosed with psychotic disorder in C/C allele subjects - Case-control analysis

Gene/locus	Study	Study Design	Sample Size	Follow up	Results
AKT1/rs2494732	DiForte et al 2012	Case-control, cross-sectional analysis	489 subjects	NA	OR 7.23 (1.37-38.12, 95% CI) of psychotic disorder in C/C genotype subjects with daily cannabis use v. T/T genotype
			278 controls		OR 2.18 (1.12-4.31, 95% CI) of psychotic disorder in C/C genotype subjects with history of cannabis use

OR = odds ratio; RR = relative risk; CI = confidence interval; AOP = age of onset of psychosis; SE = standard error