# Chapter 14
# The Interface of Cannabis Misuse and Schizophrenia-Spectrum Disorders

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**Abstract** This chapter provides an overview of the complex ways in which cannabis misuse intersects with schizophrenia-spectrum disorders. The centrally active constituents of *Cannabis sativa* are discussed, and the central endocannabinoid system is briefly reviewed. Information on cannabis use and misuse in the general population is provided, including the prevalence of use in general population samples and consequences of such use. Findings pertaining to cannabis misuse among individuals with schizophrenia-spectrum disorders are presented, along with an overview of the adverse effects of cannabis use in terms of symptoms, neurocognition, age at onset, and various aspects of the long-term course and outcomes. A discussion of the literature that suggests that cannabis use is a component cause of, or independent risk factor for, psychosis is given. Other potential mechanisms for the association are considered, including psychosis causing cannabis use or the existence of a shared diathesis that underlies both. To evaluate the literature suggesting that cannabis use, especially in early adolescence, is a component cause of schizophrenia-spectrum disorders, nine criteria for establishing causality are summarized. The chapter concludes with a brief discussion of treatment implications for clinicians and program developers, as well as prevention implications for researchers, public health officials, and policy-makers.

**Keywords** Cannabis · Endocannabinoid · Marijuana · Psychosis · Schizophrenia · Substance abuse

**Abbreviations**

| | |
|---|---|
| $\Delta^9$ -THC | Delta-9-tetrahydrocannabinol |
| CBD | Cannabidiol |
| CI | Confidence interval |

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| | |
|---|---|
| CNS | Central nervous system |
| OR | Odds ratio |
| US | United States |

## Introduction

Western societies have had a long and complex relationship with marijuana, or cannabis, at times tending to propagandize the adverse consequences of using the drug, and at other times and in other places striving to promote the drug as benign or even beneficial [1, 2]. Within the last two decades or so, however, there appears to have been a gradual accumulation of psychiatric and neurobiological evidence that cannabis use may in fact be detrimental in some mental health domains. This is true of the psychosis continuum, spanning from psychotic-like symptoms in the general population, to schizotypal personality traits, to the initial onset of psychotic disorders, to the long-term course of chronic psychotic illnesses. A general summary of the relevant research literature, as provided in this chapter, clearly indicates that cannabis use is intimately tied to psychosis in a number of ways. There is now convincing evidence that premorbid cannabis use is likely a component cause – part of a complex constellation of risk factors – of schizophrenia-spectrum disorders.

Researchers have repeatedly found themselves, after careful reviews of the extant literature, or upon completing rigorously conducted studies, concluding their articles with admonishments that policy-makers and public health officials should not ignore the clear signal of science indicating that cannabis use, especially in early adolescence, increases risk for psychotic disorders [3–7]. There has seemed to be a need to defend these results, which challenge widely held assumptions, and at times vocal insistence, that this "soft" drug is neither addictive nor harmful. Although its addictive potential is now quite clear (e.g., a cannabis withdrawal syndrome is now widely recognized [8]), there may indeed be some individuals in the population who experience few or no adverse consequences to occasional or light use. However, this chapter presents a case for cannabis use being detrimental in several respects for those with psychotic disorders or individuals with an underlying, latent vulnerability to developing such illnesses.

It would appear that the convergence of evidence is now such that society at large may be interested in learning more, as exemplified by the July 2010 article in *Time* magazine entitled "The Link Between Marijuana and Schizophrenia" [9]. This chapter attempts to present a balanced view of the complex interface; while recognizing that the associations between cannabis use and psychosis (and between psychosis and cannabis use) are undoubtedly multi-faceted, perhaps too complicated for a brief chapter to adequately portray even in the most general of ways. For this reason, many of the most pertinent references are provided. For a much more in-depth review of many of the topics covered in this brief chapter, the 2004 book *Marijuana and Madness: Psychiatry and Neurobiology*, by Castle and Murray [10] is highly recommended.

## The Plant, Methods of Intake, and Centrally Active Constituents

While it grows wild and is also cultivated worldwide, cannabis is native to central Asia, where it originally grew near riverbeds and on hillsides [11]. This flowering plant has been cultivated widely for centuries, valued for its ability to produce fibers, oil, and Δ-9-tetrahydrocannabinol ($\Delta^9$-THC) a substance producing euphoric effects. Although it has gone through substantial changes due to artificial selection, the domesticated cannabis plant has never become dependent on humans and strains have often escaped to grow wild. There are three known species, two of which – *Cannabis sativa* and *Cannabis indica* – are used to produce cannabis-based euphoric drugs [11, 12].

$\Delta^9$-THC is extracted from the cannabis plant in three different forms: herb, resin (or hashish), and oil [12]. The herb form consists of the flowering tops of the cannabis plant, which are dried and can be smoked in cigarette or cigar form (called joints and blunts) respectively, or in a variety of pipes. Approximately 79% of cannabis confiscations consist of the herb form, suggesting that this is the most prevalent form in use, and most cannabis herb seizures come from the United States (US; 60%) or Africa (30%) [12]. Cannabis resin, or hashish, is comprised of resin secretions from the female plant, made during the flowering phase of the plant's development. This form of cannabis is most popular in Europe, and is typically mixed with tobacco and smoked [12]. Cannabinoids can also be extracted from the herb or resin form into an oil or butter-based solution, which can then be used to make food products.

Although the plant produces over 60 cannabinoids, $\Delta^9$-THC is the psychoactive constituent that appears to be responsible for the euphoric effects of the substance [13]. This compound is lipid soluble and can activate cannabinoid receptors in various regions of the brain, as reviewed in more detail below. When consumed, $\Delta^9$-THC produces a euphoric effect or "high," but also may result in at least two other well defined psychological state changes: derealization of self and surroundings, and an anxious/depressive state [14]. Cannabis use can also result in perceptual changes, such that colors become brighter, music more vivid, and time appears to go faster [13]. Physiological effects include increased diastolic blood pressure; decreased body temperature [14]; an increased heart rate; greater expired carbon monoxide [15]; and in the long-term, respiratory problems and reduced lung tissue density [16]. Over the past 20 years, plant-breeding techniques have greatly increased the potency of cannabis products; whereas a typical "reefer" of the 1960s and 1970s contained approximately 10 mg of $\Delta^9$-THC, a modern-day "joint" made from potent subspecies may contain 150 mg, or even 300 mg if it is laced with hashish oil [13].

Of note, aside from the major psychotropic constituent of exogenous cannabinoids ($\Delta^9$-THC), there has been increasing interest in cannabidiol (CBD), which is thought to have anxiolytic properties, and perhaps even antipsychotic effects. That is, interestingly, the two main agents in ingested cannabis appear to have quite opposing actions: $\Delta^9$-THC is psychotomimetic, whereas CBD may have antipsychotic effects [17]. CBD, the second most abundant constituent of *Cannabis*

*sativa*, has weak partial antagonist properties at the $CB_1$ receptor (see below), inhibits the reuptake and hydrolysis of anandamide, and exhibits neuroprotective antioxidant activity [18]. This cannabinoid displays diverse pharmacologic actions (e.g., anticonvulsive, sedative, hypnotic, anti-inflammatory, neuroprotective, and possibly antipsychotic) without significant intrinsic activity on cannabinoid receptors; thus, it does not produce the psychotropic effects of $\Delta^9$-THC [19]. It has been suggested that CBD may have antipsychotic properties [20, 21], largely based on its effects in animal models of psychosis, findings from a small body of pre-clinical data, and results of very early clinical reports. Further research is needed, and the anxiolytic and other central nervous system (CNS)-related properties of CBD and other phytocannabinoids are being actively studied [19, 22].

## The Central Endocannabinoid System

Whereas the major psychotropic constituent of exogenous cannabis is $\Delta^9$-THC, the major "endocannabinoid" (normal physiological compound that binds to the same receptors to which $\Delta^9$-THC binds) is anandamide. Although thousands of papers on the pharmacology and clinical effects of $\Delta^9$-THC and related compounds have been published since 1964 when $\Delta^9$-THC was identified [23], less is known about anandamide and related endocannabinoids. In 1988, specific, high-affinity cannabinoid binding sites were discovered in the rat brain [24], referred to as the $CB_1$ receptor. The peripheral $CB_2$ receptor was identified in mouse spleen several years later [25]. Thus, the $CB_1$ receptor is generally, though not exclusively, a "neuronal" receptor, whereas $CB_2$ is largely an "immune system" receptor [26]. After the discovery of the $CB_1$ receptor, it was assumed that the presence of a specific cannabinoid receptor in the CNS indicated the existence of endogenous cannabinoid ligands that activate such receptors [23]. Once identified [27], that compound was dubbed *anandamide* based on the Sanskrit word for bliss, and due to its chemical nature [23]. The discovery of other endocannabinoids that bind to the $CB_1$ receptor soon followed, though less is generally known about those ligands.

The biosynthesis and metabolism of anandamide and other endocannabinoids, such as 2-arachidonoyl glycerol, are now extensively understood [28, 29]. Anandamide is not stored in cells, but is rather formed mainly when needed, and it is inactivated in the brain by both reuptake and enzymatic hydrolysis [23]. Research on the endocannabinoid system has resulted in the identification of inhibitors of anandamide reuptake; compounds that block fatty acid amide hydrolase, the enzyme that hydrolyses anandamide; synthetic cannabinoids that are much more potent than $\Delta^9$-THC and related compounds; agonists specific to $CB_1$ or $CB_2$ receptors; and specific antagonists. As an example of the latter, rimonabant (SR141716) selectively blocks $CB_1$ receptors [30], and has been studied as a potential anti-obesity agent [31]. In fact, rimonabant has been approved in several countries as a medication to reduce body weight and improve cardiovascular risk factors in obese adults [18, 32]. Like CBD, rimonabant has recently been shown to have antipsychotic properties in

both animal and human models used to assess antipsychotic activity, as reviewed by Roser and colleagues [18].

$CB_1$ receptors are mainly located on presynaptic axons and nerve terminals, consistent with the role of endocannabinoids in modulating the release of diverse neurotransmitters. High densities of these receptors are located in the cerebral cortex (especially frontal regions), limbic forebrain (particularly in the hypothalamus and anterior cingulate cortex), hippocampus, basal ganglia, and cerebellum [33]. After endocannabinoids bind and activate $CB_1$ receptors, they are largely degraded by several enzymes, such as fatty acid amide hydrolase. Whereas exogenous cannabinoids (typified by $\Delta^9$-THC) cause a long-lasting activation of $CB_1$ receptors and thus a persistent inhibition of neurotransmitter release from nerve terminals that express such receptors, endocannabinoids (exemplified by anandamide) have inhibitory effects in a discrete local region for tens of seconds in response to particular patterns of afferent inputs [33].

It is likely that dysregulation of the central endocannabinoid system leads to specific symptoms or disorders, thus potentially contributing to the biological basis of some neurological and psychiatric illnesses [23]. In fact, several potential abnormalities in the endocannabinoid system have been reported among individuals with schizophrenia. For example, as presented in greater detail by Sundram and associates [34], Leweke and coworkers [35] found elevated levels of anandamide in the cerebrospinal fluid of 10 patients with schizophrenia compared to 11 controls. These elevated anandamide levels, which appear to be negatively correlated with psychotic symptoms, may point to a protective role, whereas the role of 2-arachidonoyl glycerol remains unclear [21]. Other examples of endocannabinoid abnormalities that have been reported in schizophrenia include an elevated density of $CB_1$ receptors in the prefrontal cortex in a post-mortem study involving 14 patients and 14 controls [36], and differences in a triplet repeat polymorphism in the $CB_1$ receptor gene among 242 Japanese patients and 296 controls [37]. Another preliminary study found that a single-base polymorphism in the $CB_1$ receptor gene was associated with varying risk of substance abuse among individuals with schizophrenia [38]. Of note, associations between genetic polymorphisms in the endocannabinoid system and schizophrenia have been quite mixed, as reviewed elsewhere [26, 39]. These and other studies [40–43] indicate possible endocannabinoid system alterations in schizophrenia that could be related not only to increased risk for schizophrenia, but also an elevated propensity for cannabis use [44].

Further research is needed to tease apart specific aspects of inherent dysregulation of the endocannabinoid system associated with schizophrenia from responses to exogenous cannabinoids or antipsychotic medications. D'Souza et al. [45] distinguished the "exogenous hypothesis," in which cannabinoids like $\Delta^9$-THC produce psychotic disorders by mechanisms extrinsic to the pathophysiology of naturally occurring psychoses, from the "endogenous hypothesis," in which components of the endocannabinoid system (like $CB_1$ receptors) are dysfunctional, contributing to the pathophysiology of schizophrenia (or some subtypes of this heterogeneous diagnostic category), perhaps unrelated to cannabinoid ingestion. Furthermore, they note the existence of diverse research findings that tentatively support both of these hypotheses.

## Cannabis Use and Misuse in the General Population

### *Prevalence of Cannabis Misuse in the General Population*

The first written recording on cannabis dates to 2727 BCE, when cannabis was used for medicinal purposes and was already reported to cause hallucinations if used in excess [1]. Cannabis has been used medicinally in various regions of the world since then, and its use came under debate as early as 900 CE; though it was not until the 1900s that governments started to outlaw its production and use [46]. Cannabis extracts were classified as a narcotic drug in the 1961 United Nations Single Convention on Narcotic Drugs, which served to update and standardize multi-lateral treaties on all narcotics, calling for participating countries to limit production, exportation, importation, distribution, possession, and use of cannabis exclusively to medical and scientific purposes [47]. Some 97 countries were represented in the original convention, and in total 184 have joined this treaty [48], making cannabis an illicit substance in most countries, though with varying degrees of prohibition and enforcement. While cannabis use is restricted or illegal in most areas, its production and use are not declining. For example, during the period from the late 1990s to 2006, there was a 10% increase in global cannabis consumption [12].

Currently, cannabis is the most widely used illicit drug worldwide. It is produced in at least 176 countries and consumed by approximately 4% of the world's population in a given year [12]. The annual prevalence of cannabis use is highest in Oceania (15.4%), followed by North America (10.3%), Africa (8.1%) and Western Europe (7.4%) [12]. Cannabis use is least prevalent in Asia (2.1%), Southeast Europe (2.3%) and South America (2.6%) [12]. Globally, cannabis use is associated with certain demographic characteristics, including male gender, a secondary or higher education, single or divorced marital status and a higher income [49]. The initiation of cannabis use typically occurs between the ages of 16 and 19 years, and in many areas of the world, younger adults are more likely to report having used the substance than are older adults, suggesting that the incidence of cannabis use may be increasing [49]. Interestingly, in recent years, younger women are much more likely to report having used cannabis than in previous years, effectively beginning to close the gender gap in younger cohorts [49].

### *Consequences of Cannabis Misuse in the General Population*

#### Cannabis Abuse and Dependence

In the population at large, one of the most immediate consequences of cannabis use is that a portion of users develop a cannabis use disorder – currently described as cannabis abuse or cannabis dependence – such that they lose control over their cannabis use, neglect important areas of their lives, or put themselves or others in harm's way [50]. Data on the prevalence of cannabis use disorders is limited or

non-existent in many countries but is available in the US and Australia, two countries with relatively high rates of cannabis use. While the portion of the US population using cannabis remained stable at approximately 4% during the 1990s, the rate of cannabis use disorders increased from 1.2% in 1990–1991 to 1.5% in 2000–2001 [51]. In the US, the lifetime and 12-month prevalences of cannabis abuse (7.2 and 1.1%) exceed those of cannabis dependence (1.3 and 0.3%) [52]. Similar rates were reported in Australia, where 1.7% of respondents in a nationally representative household survey met criteria for a cannabis use disorder [53].

In the US, cannabis use disorders are more prevalent among those who are single, separated, divorced, or widowed, and rates vary by geographic region and ethnicity, with a higher prevalence among Native Americans and lower rates among African Americans, Asian Americans, and Hispanic Americans in comparison to Caucasians [52]. The mean ages at onset of cannabis abuse and dependence in a US sample were 19.3 and 19.0 years, with an average duration of 35.0 and 44.3 months, respectively [52]. In the US, treatment seeking is relatively low for cannabis abuse (9.8%) and dependence (34.7%) and is delayed by an average of 5.5 and 3.0 years, respectively, after onset of the disorder [52].

Cannabis use disorders are associated with high rates of psychiatric comorbidities. In a large, nationally representative sample in the US, a substantial portion of those with a cannabis use disorder in the past 12 months also had a current alcohol use disorder (57.6%), nicotine dependence (53.1%), a mood disorder (29.9%), an anxiety disorder (24.1%), and/or a lifetime history of a personality disorder (48.4%) [52]. In a similar study from Australia, those with a 12-month history of cannabis dependence were more likely to have an anxiety disorder (odds ratio (OR): 1.4), a positive screen for psychosis (OR: 2.8), or another drug use disorder (OR: 14.0), but were less likely to have a mood disorder (OR: 0.9), after adjusting for age, gender, educational attainment, marital status, employment status, and neuroticism [54]. Among those with cannabis dependence, the unadjusted rates of affective (13.6%) and anxiety (16.5%) disorders, a positive screen for psychosis (6.8%), and another drug use disorder (17.6%) were higher than among those with no cannabis use during the past year (6.2%, 5.4%, 0.7%, and 0.5%, respectively) [54].

### Impaired Academic Performance

Cannabis use and misuse are consistently associated with poor school performance in a wide range of adolescent and young adult samples. The intensity of cannabis use is correlated with lower grade point averages, less satisfaction with school, negative attitudes about school, and non-attendance [55]. In a study of three Australian cohorts, cannabis use at 15 years of age was predictive of school non-completion [56]. Multiple theories have been proposed to explain this association, including the ideas that cannabis induces an "amotivational syndrome," causes cognitive impairments, or is used mostly by those youths who have adopted an anti-conventional (e.g., rebellious) lifestyle [55]. The latter theory appears to have the strongest support [57, 58]. For instance, the effects of cannabis use on school attendance and

performance were reduced, but not altogether absent, when variables such as adolescents' tendency towards a social/delinquent lifestyle and family structure were controlled for [57]. A recent study found that low school performance at the age of 14 years is a predictor of frequent cannabis use in young adulthood, which suggests that this association may well be bi-directional [59].

### Criminal Behavior, Suicidality, and Unintentional Injuries

Societal impacts of cannabis use include associations with criminality, suicidality, and vehicular accidents [58, 60]. In a longitudinal study in New Zealand, the frequency of cannabis use correlated with higher instances of property/violent crime, even after controlling for adverse life events, deviant peer affiliations, school dropout, living situation, and other substance use [60]. An analysis of police records in the US revealed a positive association between self-reported cannabis use at the time of the offense and non-drug related violent, property, and income-producing crime, after controlling for other substance use [61]. Similarly, the use of marijuana or other drugs, peer use of illicit substances, and family members' use of illicit substances were each independently associated with a higher likelihood of committing violence among Colombian adolescents [62]. Suicidal ideation and suicide attempts are also associated with cannabis use, especially in young adolescents, though this effect is reduced and does not always remain significant after controlling for demographic and other relevant variables [60, 63, 64]. Also of concern, the effects of acute cannabis intoxication include cognitive and psychomotor impairments that reduce individuals' ability to operate a vehicle safely, especially when sustained attention is necessary [58]. In laboratory simulations, the effects of recreational doses result in an impairment that is comparable to blood alcohol levels of 0.07–0.10%, though in more realistic test settings, cannabis users appear to be aware of their impairment and are less likely to take risks than alcohol users [58].

### Impairments in Neurocognition

Cannabis use also affects cognitive functioning in multiple domains, such as short-term memory and attention [65], as well as working memory [66, 67]. These deficits also have been observed in animal studies [68, 69], and have been assessed using both electroencephalography [70] and functional magnetic resonance imaging [71] in addition to neuropsychological methods. The longer-term consequences on cognitive functioning are less clear. Long-term cannabis users performed more poorly than controls or short-term users in a measure of verbal learning, and made more errors than the other groups in a measure of verbal information processing [72]. In a Costa Rican sample, long-term cannabis use was associated with impairments in short-term memory, working memory, and attention, but only when comparing an older cohort of users with non-users; no differences between younger users and non-users were evident [73]. The association of long-term cannabis use with impaired learning and working memory has appeared to be replicated [71, 74]. However,

other studies have failed to detect long-term cognitive consequences of cannabis use [75].

### Psychotomimetic Effects and Psychiatric Symptoms

The psychotropic effects of cannabis on any particular individual vary somewhat in relation to diverse factors – strain of the plant, part of the plant ingested, route of administration, proportional content of $\Delta^9$-THC, dose consumed, previous experience, expectation of effect, personal characteristics of the individual, and the context in which the agent is taken [76] – but tend to be relatively consistent in terms of the typical euphoric effects mentioned above. Yet, cannabis intoxication can at times result in depersonalization and derealization, enhanced self-observation, disjointed speech, visual and auditory hallucinations (though usually poorly formed and short-lasting), and grandiose and paranoid ideation of nearly delusional proportions. Cannabis ingestion also has the potential to induce or alleviate anxiety, perhaps related to the dose taken and the proportional content of CBD. There is ongoing debate about whether long-term cannabis use induces a syndrome of amotivation reminiscent of the negative syndrome commonly observed in schizophrenia [58, 76]. Clearly, a number of the psychotropic effects of cannabis are recognizably similar to the signs and symptoms of schizophrenia and related psychotic disorders.

### Cannabis-Induced Psychosis

In a small subset of individuals who ingest the substance, a short-lasting psychotic syndrome may occur. These individuals would be diagnosed as having a cannabis-induced psychotic disorder if there is a clear temporal relation between heavy drug intake and the onset of psychotic symptoms, as well as rapid and complete resolution of symptoms after abstinence; furthermore, such a diagnosis assumes that the psychosis would not have occurred in the absence of cannabis use. A number of case reports of cannabis-induced psychosis can be found in the literature [77], though conclusions drawn from case reports are inherently limited. It remains debated as to the extent that cannabis use can cause a "cannabis psychosis" that is etiologically distinct from most schizophrenia-spectrum disorders.

Some have argued that a cannabis-induced psychosis might in many instances be an early sign of schizophrenia rather than a distinct clinical entity [78]. In fact, in one study that followed patients treated for cannabis-induced psychosis in Denmark, nearly 50% received a diagnosis of a schizophrenia-spectrum disorder within a mean follow-up period of 5.9 years [79]. Crebbin and colleagues [80] reported that among 35 first-episode psychosis patients diagnosed with a drug-induced psychosis, one-third developed a schizophrenia-spectrum disorder within two years, and Caton and associates [81] found that one-quarter of early-phase psychosis patients diagnosed with substance-induced psychosis received a diagnosis of a primary psychotic disorder after just one year. Mathias and coworkers [82] noted that there exists a striking paucity of data on the outcome, treatment, and best practices for substance-induced psychotic disorders.

Of note, as discussed further below, clinical experience also suggests that heavy cannabis use among individuals with established psychotic disorders can be associated with short-term exacerbations of symptoms. Such observations are supported by results from a double-blind, randomized, placebo-controlled study of intravenous administration of $\Delta^9$-THC in 13 stable, antipsychotic-treated patients with schizophrenia, which documented transient increases in cognitive deficits, perceptual aberrations, positive and negative symptoms, and motor disturbances [83]. Thus, even though individuals with psychosis might perceive an immediate benefit of cannabis use (e.g., euphoric and anxiolytic effects), worsening of diverse symptom domains is likely.

## Cannabis Use and Misuse among Individuals with Schizophrenia-Spectrum Disorders

### *Broadly Defined Substance Abuse and Dependence in the Context of Schizophrenia-Spectrum Disorders*

It is widely recognized that the prevalence of nicotine, alcohol, and illicit drug use and misuse is elevated among individuals with schizophrenia-spectrum disorders. Cannabis is the most common drug of choice. For instance, cannabis was used by 88% of hospitalized first-episode psychosis patients who had used drugs in a sample from Atlanta, Georgia, US, followed by alcohol, hallucinogens, and cocaine [84]. A similar distribution of drug use was found in an Italian sample of individuals with schizophrenia in which, among the 43% who reported using illicit substances, all had used cannabis, followed by hallucinogens (19%), stimulants (17%), and opiates (8%) [85]. Similar trends were also evident in an Indian sample; again, cannabis was the most commonly used substance, followed by alcohol [86]. Comorbid substance abuse and dependence among individuals with schizophrenia-spectrum disorders are associated with higher rates of relapse, a greater severity of positive symptoms [87–91], depression, interpersonal conflict [92], an increased risk of and shorter time to relapse, and an increased likelihood of inpatient admission [93, 94]. Furthermore, these associations are evident already at the time of the first episode [95].

### *Prevalence of and Motivations for Cannabis Misuse Among Individuals with Schizophrenia-Spectrum Disorders*

An extensive literature review of worldwide epidemiological and clinical study samples estimated the 12-month and lifetime prevalences of cannabis use among individuals with psychosis to be 29.9 and 42.1%, respectively, with rates of cannabis misuse at 18.8% (12-month) and 22.5% (lifetime) [96]. While the literature is biased by reports from clinical samples, these rates are six or more times higher than those reported from the general population [12]. This high prevalence of cannabis use

has sparked interest in whether this represents an attempt to "self-medicate" among individuals with psychotic disorders. However, reported reasons for using cannabis in samples of individuals with schizophrenia and related disorders have not entirely supported this theory. For instance, in an Australian study on motivations for using cannabis, individuals with schizophrenia reported that boredom, social needs, poor sleep, anxiety and agitation, negative symptoms, and depression were the most important motivators of cannabis use [97]. A systematic literature review found that in diverse samples, individuals with schizophrenia most commonly report that their motivation is to enhance positive affect, relieve dysphoria, and facilitate social engagement [98] – motivations common to the general population – rather than to "self-medicate" specific psychotic symptoms. Furthermore, cannabis and other substance use is already highly prevalent among first-episode samples and retrospective studies document that the onset of cannabis use typically precedes the development of overt symptoms of schizophrenia [99].

## *Clinical Consequences of Cannabis Misuse Among Individuals with Schizophrenia-Spectrum Disorders*

The effects of cannabis misuse on clinical features of individuals with schizophrenia are varied, including both transient and lasting effects, in domains such as age at onset of symptoms, symptomatology, neurocognitive performance, psychosocial functioning, and long-term course and outcomes. These adverse consequences of cannabis use disorder comorbidities may be driven by detectable neuropathological changes [100, 101]. For example, Rais et al. [101] conducted a study in which magnetic resonance imaging scans were obtained in 51 patients with recent-onset schizophrenia and 31 healthy controls. As expected based on prior research, gray matter volume loss over the 5-year study period was greater in patients with schizophrenia; however, the 19 patients who used cannabis (but no other drugs) during this 5-year interval lost gray matter at nearly twice the rate of the 32 patients who had not used the drug since the baseline scan. Further research is required to elucidate the specific CNS mechanisms by which cannabis use is associated with the clinical consequence discussed briefly below.

### Effects on Positive and Negative Symptoms

While the literature is mixed, most evidence suggests that cannabis use is associated with greater levels of positive symptoms [94, 102, 103], though some have failed to replicate this effect [104]. In a double-blind, experimental setting, $\Delta^9$-THC was found to transiently increase positive symptoms in a sample of individuals with schizophrenia [83]. In a South African sample, frequent cannabis use was associated with increased hallucinations, delusions, thought disorder, and bizarre behaviors [105]. First-episode patients have reported increased auditory and visual hallucinations, and confusion; some patients also recount experiencing their particular

psychotic symptom during cannabis intoxication. However, other data suggest that positive symptoms do not differ according to cannabis use when other substances are also taken into account [106]; or that patients with schizophrenia with and without comorbid cannabis use, who are treated with atypical antipsychotic agents, do not differ in positive and negative symptom scores [107]. Bersani and colleagues [85] found that cannabis users in an Italian sample had lower rates of thought disorder, though this may be confounded by patients' ability to obtain the substance, which is undoubtedly partly dependent on intact cognitive and social functioning. Furthermore, while this group found that hallucinations were greater among those individuals who began using cannabis before the onset of schizophrenia, this association was not present when the comparison included those who initiated cannabis use after the onset of the illness.

There is less evidence to suggest that cannabis use exacerbates negative symptoms. D'Souza and associates [83] found that in the aforementioned double-blind, experimental setting with individuals with schizophrenia, administration of $\Delta^9$-THC resulted in a temporary increase in negative symptoms, such that participants appeared more blunted, less talkative, less spontaneous, and more internally preoccupied while under the influence of the substance. In a South African sample, increased avolition and apathy was observed among frequent cannabis users [105]. However, a number of studies have found that, even when adjusting for the effects of other drugs, lower, not higher, negative symptom scores are found in patients who use cannabis [85, 106]. Among first-episode patients in particular, those meeting criteria for comorbid cannabis dependence presented with significantly lower negative symptom scores at the time of first hospital admission [108]. The potential association between cannabis use and the absence of prominent negative symptoms is likely complex, as discussed previously [109]. Greater negative symptoms may impede social interactions necessary to initiate and maintain illegal drug use [110]. Because cannabis use is illegal in many countries, this substance is probably often more difficult to procure than alcohol, and individuals with prominent negative symptoms such as avolition, social isolation, and withdrawal likely would have some difficulty obtaining it [111]. Additionally, negative symptoms such as amotivation and anhedonia, may diminish the rewarding properties of drugs [112], making cannabis use less appealing to those with prominent negative symptoms.

Cannabis intake may exacerbate affective and other types of symptoms beyond the positive and negative domains. There have been mixed reports about the impact of cannabis use on depressed mood among individuals with schizophrenia-spectrum disorders [86, 92]. Comorbid cannabis use disorders were associated with suicide attempts in a French sample of schizophrenia patients [113]. Furthermore, when compared with controls, both putatively prodromal adolescents and first-episode patients reported feeling more anxious and depressed during periods of cannabis use, with long-term effects including depression, less control over thoughts, and social problems [114]. In the double-blind experiment with individuals with schizophrenia, administration of $\Delta^9$-THC resulted in transient but clinically significant increases in a variety of symptoms, including somatic concerns, feelings of guilt, tension, uncooperativeness, unusual thought content, poor attention, and

preoccupation [83]. Additionally, an increase in perceptual alterations was observed, such that after consuming cannabis, participants appeared more "spaced out," and were more likely to behave in an unusual way or need redirection [83].

### Effects on Neurocognition

The literature on cannabis use and cognition in the context of schizophrenia is mixed. Acute cannabis intoxication appears to cause cognitive impairment among individuals with schizophrenia, much like in the general population. In the double-blind experiment conducted by D'Souza and coworkers [83], participants with schizophrenia exhibited increased impairments in verbal learning, but not in verbal fluency, following administration of $\Delta^9$-THC. However, in terms of long-term cognition, the association appears to be entirely reversed by some accounts. In a recent sample, patients with a comorbid cannabis use disorder demonstrated significantly better performance on measures of processing speed, verbal fluency, and verbal learning and memory [104]. A recent literature review found that, of 23 available studies in schizophrenia, 14 reported that cannabis users had better cognitive functioning than non-users, eight studies reported no or minimal differences in the two groups, and one study reported poorer cognitive functioning among the cannabis-using group [115]. A recent first-episode study found a few specific deficits among cannabis users, but greater generalized cognitive deficits among non-users [116]. This seemingly paradoxical finding could be explained by the aforementioned idea that cognitive abilities either directly or indirectly enhance individuals' ability to obtain illicit substances.

### Effects on the Age at Onset and Mode of Onset of Psychosis

Regarding age at onset of psychosis, while most studies to date have reported differences between drug users and non-users without reference to the specific substances used, several have tested for an association between cannabis use specifically and the age at onset of psychotic symptoms. As reviewed by Compton & Ramsay [99], several studies have found that cannabis users/misusers had an earlier age at onset of psychosis than non-users [88, 89, 103, 117]. Recently, this was replicated in a South African sample [105]. Furthermore, González-Pinto et al. [118] extended this finding by demonstrating that cannabis use, abuse, and dependence were associated with a 7-, 8.5-, and 12-year decrease in the age at onset of psychosis, though the sample included patients with both nonaffective and affective psychoses. Compton and colleagues [7], in the US, found that an early progression to frequent premorbid cannabis use was associated with earlier ages at onset of prodromal symptoms and psychotic symptoms. By contrast, in a sample of 125 men with schizophrenia, those who had used cannabis did not have a significantly younger age at onset of symptoms than non-users [85]. Recently, Sevy and associates [119] found that compared to non-substance-abusing first-episode patients, those with a cannabis use disorder had an earlier age at onset of positive symptoms, though this association did not

persist when controlling for several other demographic and clinical variables, such as gender and premorbid adjustment.

Aside from age at onset of psychosis, there is also some evidence that the mode of onset of psychosis – how rapidly frank psychotic symptoms evolve – may differ in psychoses with comorbid cannabis use compared to those developing in the absence of cannabis use. Specifically, a more acute mode of onset has been noted among individuals with a psychotic disorder in the context of cannabis use [120, 121] (Compton MT, Broussard B, Ramsay CE, Stewart T, submitted for publication).

#### Effects on Long-Term Course and Outcomes

Numerous studies indicate that comorbid cannabis use, like the use of other illicit drugs, is associated with a poorer course of illness, including a greater number of relapses and hospitalizations. For instance, among outpatients in the Netherlands, those who reported using cannabis had their first relapse sooner and a greater number of relapses over the course of a year [122]. Similarly, in a South African study, those who used cannabis >20 times per year had a greater number of relapses and hospitalizations than those who did not [105]. By contrast, comorbid cannabis abuse or dependence was not associated with a greater number of hospitalizations or increased medication dosages in a French study [113]. Nonetheless, a systematic literature review found that cannabis use is quite consistently associated with increased risk of relapse and medication nonadherence [123].

## Cannabis Use as a Cause of Schizophrenia-Spectrum Disorders: The Ongoing Debate

### *Studies Implicating Cannabis Use in Adolescence as a Component Cause*

Several large-scale epidemiological studies lend credence to the assertion that cannabis use may be a "component cause" of schizophrenia. In a sentinel study involving over 50,000 Swedish conscripts, Andréasson and coworkers [124] found a dose-response relationship between cannabis use at conscription (at the age of 18 years) and schizophrenia diagnoses some 15 years later. Nearly two decades later, a follow-up of the same study showed that cannabis users were more likely than nonusers to be diagnosed with schizophrenia some 27 years later, even when controlling for a number of potential confounding variables [123].

In the Netherlands, a study of more than 4,000 individuals in the general population found that those using cannabis at baseline were nearly three times more likely to manifest psychotic symptoms at 3-year follow-up compared to individuals not using the drug, even after controlling for several potential confounders [125]. An apparent dose-response relationship was also observed. In a general population birth cohort of over 1,000 individuals in New Zealand, those using cannabis at the ages of

15 and 18 had higher rates of psychotic symptoms at age 26 compared to non-users, and the effect was stronger for earlier use [126]. In terms of specificity, the risk was specific to cannabis use as opposed to use of other drugs, and early cannabis use did not predict later depression. In a prospective birth cohort of nearly 4,000 individuals in Australia, McGrath et al. [127] found that early initiation of cannabis use (before about 15 years of age) was associated with an increased risk of nonaffective psychosis, scoring in the highest quartile of the Peters et al. [128] Delusions Inventory, and the presence of delusions. Furthermore, this association persisted when assessed among sibling pairs, thereby reducing the likelihood that the association was driven by residual confounding due to unmeasured shared genetic and/or environmental influences. Although a number of important limitations of such studies have been pointed out [129], the epidemiological evidence generally supports cannabis use as a component cause of schizophrenia and related psychotic disorders.

Given the accumulating literature, Arseneault and colleagues [4] reviewed five studies that included well defined samples drawn from population-based registers or cohorts and controlled for diverse potential confounders [3, 124–126, 130], and computed a pooled OR of 2.3 (95% confidence interval (CI), 1.7–2.9). Also in 2004, Smit and associates [5] reviewed five population-based, longitudinal studies (four of which were included in the aforementioned review) [3, 125, 126, 130, 131] in order to address five hypotheses about the relationship between cannabis use and schizophrenia: the self-medication hypothesis, the co-occurring drug use hypothesis, the confounding hypothesis, the interaction hypothesis, and the etiological hypothesis. They concluded that the first two could be eliminated, that more research is needed to rule out potential confounding effects, and that the latter two hypotheses (cannabis use increases risk but particularly in vulnerable individuals, and cannabis use makes its own unique contribution to the risk for schizophrenia) were both partly supported by the studies they reviewed. Weiser and Noy [44] pointed out that an alternative explanation is that pathology of the cannabinoid system in patients with schizophrenia may be associated with both increased rates of cannabis use and an increased risk for schizophrenia, without cannabis being a causal factor for schizophrenia.

A systematic review of 11 studies examining the relationship between cannabis use and psychosis (among which seven were included in a meta-analysis) found a pooled OR of 2.9 (95% CI: 2.4–3.6), suggesting that cannabis use is an independent risk factor both for psychosis per se and the development of psychotic symptoms in non-clinical samples [6]. Two years later, a systematic review of 35 studies revealed an increased risk of any psychotic outcome (independent of transient intoxication effects) in individuals who had ever used cannabis, with a pooled adjusted OR of 1.4 (95% confidence interval, 1.2–1.6), and results were consistent with a dose-response effect [132]. Given these large studies, reviews, and meta-analyses, there have been increasingly confident assertions in the field that cannabis use is a component cause; however, a number of limitations in the diverse studies conducted to date must be recognized. These include the diversity of operationalizations of psychosis outcomes, the fact that measures of cannabis use are usually based on self-report and not complemented by objective biological assays, potential confounding by the

effects of other concurrently used drugs, and difficulty in ruling out the possibility that prodromal manifestations of schizophrenia precede cannabis use [4, 133].

The apparent "causal" effect that is suggested by the replicated association could have three different directionalities. Cannabis use may cause psychosis, or in those individuals with underlying vulnerabilities in particular. Alternatively, psychosis may make individuals more likely to use cannabis. Finally, a shared diathesis may underlie both outcomes. The first theory – increasingly viewed as a likely explanation – is explored in more depth below through a consideration of criteria for establishing causality. Potential evidence for the second and third theory is given below under "coherence and consideration of alternative explanations."

## *Criteria for Establishing Causality*

Published in 1965, Austin Bradford Hill's criteria for establishing a causal effect have been used widely in epidemiological inquiries [134]. These criteria are often used as a checklist for establishing causality, though Hill himself did not intend them to be used in this way [134]. Hofler [134] provides a thorough description of Hill's criteria and their application in current research. Arseneault and coworkers [129] outlined an extensive review of the definitions of a cause in relation to cannabis use potentially causing schizophrenia, as well as an exposition of three key criteria for establishing causality: *association* (the cause and the disease appear together), *temporal priority* (the putative cause is present before the disease), and *direction* (changes in the putative cause lead to changes in the outcome, as opposed to being driven by a confounding third variable). In the sections that follow, Hill's criteria, along with a brief summary of each in relation to the link between cannabis use and psychosis, are given.

### Strength

*A strong association is more likely to have a causal component than is a modest association.* Cannabis use has a relatively weak but consistent association with psychotic disorders, on a similar scale to other known single environmental risk factors. Perhaps the most compelling reason to consider cannabis as a potential cause of schizophrenia is that multiple prospective studies have found cannabis use to be associated with a greater odds of developing psychosis, as discussed above. A review of seven prospective studies noted that this effect persisted after the studies controlled for various potential confounding factors such as intelligence, psychiatric symptoms at baseline, and sociodemographic variables [135]. While this effect is replicated in longitudinal studies, it is arguably relatively weak compared to the causal risk factors implicated in some other human health conditions. Yet, other well established environmental risk factors for schizophrenia have similar effect sizes, including obstetric complications during birth (OR: 2.0, CI: 1.6–2.4) [136], and a history of sexual abuse (adjusted OR: 2.9, CI: 1.3–6.4) [137]. Therefore, cannabis use is plausible as one of many component causes that, in concert, may result in

the development of schizophrenia-spectrum disorders. Though it may be a relatively small added risk for individuals who are not otherwise vulnerable, cannabis consumption is widely prevalent in the general population and could therefore be implicated in a fairly large number of cases.

### Consistency

*A relationship is observed repeatedly.* Although the variation of psychosis-related outcomes that have been examined in relation to cannabis use may be seen as a methodological limitation across the body of extant studies, it also provides for a confirmation of consistency of the observed association. In addition to being associated with schizophrenia, more broadly defined psychotic disorders, and psychotic symptoms, cannabis use has also been associated with greater schizotypy among undergraduate college students [138–141] as well as symptoms consistent with the prodrome among adolescents [142].

### Specificity

*A factor influences specifically a particular outcome or population.* Arseneault et al. [4, 129] pointed out several studies that indicate both specificity of the exposure (cannabis use as opposed to use of other drugs) and specificity of the outcome (schizophrenia and other psychosis-related outcomes as opposed to other domains of psychiatric disorders). However, further research is clearly needed regarding both aspects of specificity. As noted above, a number of psychosis-related outcomes have been examined, as opposed to a single, specific outcome (e.g., hallucinations). Furthermore, given the variability in active constituents of ingested cannabis, along with differences in their biological effects, research will need to further disentangle the causal influences of specific compounds.

### Temporality

*The factor must precede the outcome it is assumed to affect.* In most studies that have examined the temporal sequencing of cannabis use and psychosis, first-episode patients report initiating cannabis use before the onset of psychotic symptoms, oftentimes by several years [85, 99]. Several studies have found that the majority of individuals with a recent-onset psychosis report initiating use even before the first sign of the prodrome [7, 99]. If cannabis use is typically initiated or increased after the onset of schizophrenia, it may be considered a consequence of the disorder, rather than a cause of it. This would fit better into the argument that individuals with schizophrenia-spectrum disorders use cannabis to "self-medicate" or reduce particular symptoms that are distressing [88].

One complicating factor is that in order to determine a temporal association, the onset of schizophrenia must be defined. The most obvious point of reference may be the onset of positive symptoms such as delusions, hallucinations, or disorganization. However, some would argue that the onset of the prodrome may be

a more valid reference point for studies of causality, as this represents a period of distinct changes that are later recognized as the early signs of an emerging disorder. Furthermore, premorbid deficits are widely recognized, and a retrospective study using home videos found increased neuromotor abnormalities in children as compared to their siblings, starting as early as infancy [143]. These findings, along with evidence that pregnancy and birth complications, season of birth, and early developmental delays are risk factors for developing schizophrenia [144], suggest that the later development of the disorder could be related to genetic and environmental vulnerabilities that have existed from birth. These factors make a determination of temporality an ongoing challenge.

**Biological Gradient**

*The outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory*. Larger doses or longer exposure to cannabis – especially in early adolescence – appear to be associated with a higher risk of psychosis and a hastened onset of psychosis. Most studies to date compare patients in dichotomized groups, either by the presence or absence of cannabis use beyond a certain threshold or by the presence or absence of a cannabis use disorder. However, in a prospective study, Henquet and colleagues [145] found a dose-response relationship between cannabis use and psychotic outcomes, with ORs of developing psychosis progressively increasing with frequency of use, ranging from 1.0 (CI: 0.5–1.9) among those using cannabis once a month or less, to 2.6 (CI: 1.5–4.3) among daily users. As noted previously, González-Pinto and associates [118] documented a decrease in age at onset of psychosis (nonaffective or affective) of 7, 8.5, and 12 years, respectively, in individuals with cannabis use, abuse, and dependence, when compared with non-users.

**Biological Plausibility**

*The observed association can be plausibly explained by substantive (e.g., biological) explanations.* As outlined elsewhere [45, 83], there are several possible mechanisms by which $\Delta^9$-THC might increase or cause de novo positive, negative, and cognitive symptoms of schizophrenia. For example, the effect of cannabinoids on increasing mesolimbic dopaminergic activity may explain the fact that positive symptoms can be induced by $\Delta^9$-THC in controlled pharmacological studies [45]. In terms of specific phenotypes (or endophenotypes), the administration of $\Delta^9$-THC in healthy volunteers results in an impairment in visual information processing that is similar to impairments observed in individuals with schizophrenia or those who are at high risk of developing the disorder [146]. As noted in the above brief overview of the endocannabinoid system, researchers are avidly studying a number of aspects of the endocannabinoid ligands, the $CB_1$ receptor, and genetic polymorphisms that could further elucidate the biological plausibility of the link between cannabis and psychosis. Several useful reviews of the potential neuropsychological and biological plausibility of the cannabis–psychosis link – a topic beyond the purview of this chapter – are available in the recent literature [67, 147–152].

### Experiment

*Causation is more likely if evidence is based on randomized experiments.* As previously suggested, experimental administration of $\Delta^9$-THC supports the notion that this agent induces diverse experiences similar to those observed in schizophrenia. Furthermore, emerging experimental evidence from animal and human studies indicates that $CB_1$ receptor antagonists (including rimonabant and CBD) may exert antipsychotic effects. Ongoing research may find further experimental, rather than observational, support for cannabis use as component cause of schizophrenia-spectrum disorders.

### Analogy/Coherence with Existing Theory and Knowledge

*For analogous exposures and outcomes, an effect has already been shown*. The fact that an environmental exposure may cause psychiatric symptoms or disorders is not a novel concept, and that such effects may be more likely among individuals already predisposed to the psychiatric disorder is not surprising. Thus, the increasingly agreed upon notion that cannabis consumption during a critical period of brain development [153, 154] could serve as a component cause of later psychiatric illness through effects on key neurobiological systems is coherent with both the widely accepted neurodevelopmental theory and diathesis-stress model of schizophrenia. Diverse environmental risk factors, ranging from apparently sufficient causes (e.g., *Treponema pallidum* causing the general paresis stage of neurosyphilis) to other presumed component causes (e.g., obstetric complications) are known to be associated with the onset of psychosis, and exposure to a psychoactive ingested drug is analogous to such risk factors in modern conceptions of complex disease causation.

### Coherence and Consideration of Alternate Explanations

*A causal conclusion should not fundamentally contradict present substantive knowledge.* While substantial evidence supports the theory that cannabis may have a causal effect in schizophrenia, not all research supports this notion, and other plausible theories have been proposed to explain the association. A valid concern was raised by Degenhardt and coworkers [155], who found that the incidence of schizophrenia – and the age at onset of incident cases – in Australia did not change with trends in cannabis use, as would be expected using mathematical models. The data appeared to fit better with the hypothesis that cannabis use hastens the onset in those with pre-existing vulnerabilities or is associated with psychosis either through reverse causality or a shared diathesis.

Regarding reverse causality, the alternate explanation commonly put forth (in arguments that cannabis use is not a component cause of schizophrenia) is that psychosis may be a risk factor for cannabis use. Bersani et al. [85] proposed that cannabis consumption may represent an effort to "self-medicate" in some, particularly to reduce negative, rather than positive, symptoms. (Of note, Tucker [95] suggested that the "self-medication" terminology is misleading as drugs of abuse

are generally inappropriate as medications and they do not appear to be associated with effective treatment outcomes.) Henquet and colleagues [135] dispute this as an explanation for the association between cannabis and psychosis, noting that prospective studies find cannabis associated with the later development of psychosis, even when those individuals with early indicators of vulnerability are excluded.

As mentioned above, yet another compelling alternate explanation is that the connection between cannabis use and psychosis may be explained by a shared diathesis. A cohort study in the Netherlands found that cannabis use in youth predicted future psychotic symptoms, and that psychotic symptoms in those who had never previously used cannabis predicted future cannabis use [156]. Such findings might indicate a shared diathesis. Henquet and associates [145] found that the association with cannabis use is substantially greater among adolescents with previously established vulnerability to psychosis. However, in this prospective study, psychosis proneness in early adolescence did not predict the initiation of cannabis use. Thus, some, but not all, evidence suggests a bidirectional effect, which may be underpinned by a shared genetic diathesis for both cannabis use and psychosis.

## *The Balance of the Evidence: Cannabis Use Appears to Be a Component Cause*

Taken together, the extant evidence suggests that premorbid cannabis use is a component cause of schizophrenia (rather than being a necessary cause or a sufficient cause), meaning that it probably contributes – in conjunction with other factors – to forming a complex causal constellation, along with other component causes, that leads to the disorder [4, 129, 133]. In general, the evidence suggests that cannabis use doubles the risk of developing schizophrenia in the long term [4]. However, as pointed out by McGrath and coworkers [127], the relationship is probably not strictly unidirectional; individuals who are vulnerable to developing psychotic disorders may be more likely to initiate cannabis use, which could then subsequently contribute to an increased risk of disorder.

One of many unanswered questions pertains to why only a small portion of individuals using cannabis develop psychotic symptoms or schizophrenia [133]. Most importantly, cannabis use is conceptualized as a component cause, rather than a sufficient cause. Thus, cannabis use may act in conjunction with genetic susceptibilities or with other environmental risk factors. The former is exemplified by the hallmark finding of Caspi et al. [157] that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis; specifically, carriers of the valine allele were most likely to develop psychotic symptoms and to develop schizophreniform disorder if they had used cannabis, but cannabis use had no such adverse influence on those with two copies of the methionine allele. Of note, recent evidence

suggests that this same gene-environment interaction may be associated with the age at onset of psychosis among first-episode patients [158]. Regarding potential interactions with other environmental risk factors, Harley and colleagues [159] reported that, in a sample of 211 adolescents between 12 and 15 years of age, both cannabis use and childhood traumatic experiences were significantly associated with the risk of experiencing psychotic symptoms; however, the presence of both early cannabis use and childhood trauma increased the risk beyond that posed by either risk factor alone, indicating a greater-than-additive interaction.

Of note, a major limitation to the ability of researchers to address the debate on cannabis use as a potential causal factor in schizophrenia-spectrum disorders is the widely recognized phenomenologic, and likely etiologic, heterogeneity of these disorders. Without valid groupings of patients into etiologically homogenous subsets, studies designed to elucidate causal associations are made more difficult.

## Treatment and Prevention Implications Pertaining to the Interface of Cannabis Misuse and Schizophrenia-Spectrum Disorders

### *Treatment Implications*

In general community samples of individuals with cannabis use disorders, cognitive-behavioral therapies and motivational interviewing techniques have proven beneficial [160, 161]. There is also some evidence for the effectiveness of contingency management (e.g., providing monetary-based reinforcement contingent on documented abstinence). Research on pharmacological approaches is nascent [161]. In general, the evidence base on the management of cannabis abuse and dependence in the general population is largely lacking, and the same is true of such treatments specifically among individuals with schizophrenia-spectrum disorders. Freedman [162] noted that the cumulative data suggest that cannabis use conveys long-term adverse consequences, and that patients with psychotic disorders and their families therefore need to understand these negative effects and be encouraged to engage in treatment for cannabis abuse and dependence.

The high rates of cannabis and other drug use among those with psychotic disorders suggests that all such patients should be screened, and those with a substance abuse or dependence diagnosis should be offered integrated treatment (as opposed to sequential or parallel treatments for the dual diagnoses) [163]. James and Castle [164] reviewed approaches to screening, assessing, and treating cannabis abuse and dependence in people with psychotic disorders. They note that as part of the detailed assessment process, the nature and degree of drug use, impact on illness, reasons for use, past treatments, and motivations to change should be considered. In addition to cognitive-behavioral therapies and motivational interviewing techniques, elements of the 12-step philosophy, psychoeducation, harm reduction, skills training, and

relapse prevention have also been used [164]. Several recent reports have reviewed the literature on the treatment of cannabis misuse among people with psychotic disorders [165, 166].

Given that cannabis misuse commonly begins and escalates during adolescence and young adulthood, particular attention must be given to cannabis abuse and dependence among individuals with first-episode or early-course psychotic disorders. As noted above, the rates of cannabis misuse are high, and ages at initiation of use are early, among first-episode patients. For example, in Melbourne, Victoria, Australia, Hinton and associates [167] documented that 88.5% of 130 first-episode patients reported a lifetime history of cannabis use, and 73.8% were already regular users. Similarly, in Atlanta, Georgia, US, Stewart and coworkers [84] found that 79.8% of 109 first-episode patients had previously used cannabis, and that 60.6% had used it on a weekly or daily basis. In those two first-episode cohorts, the mean age of initiation of regular use was 16.7 and 16.5 years, respectively (with an earlier age of first use). These figures are of importance given that early initiation and regular use of cannabis in adolescence are known to be risk factors for later problematic cannabis and other drug use, lower educational attainment, criminal behavior, and other adverse consequences in general population samples [161]. Also as noted previously, use of cannabis in the context of schizophrenia-spectrum disorders, even among first-episode samples, is associated with poor medication adherence, greater severity of positive symptoms, and higher risk of relapse [168–170].

These and other findings point to a serious need for specialized cannabis misuse treatment services for first-episode patients. Yet, remarkably little is known about efficacious treatment approaches in this population. In a naturalistic study of a comprehensive, community-based, early intervention service, Hinton et al. [167] found a significant reduction in cannabis use during the initial few months of treatment, despite the fact that the service provided only educative feedback with respect to substance use (e.g., highlighting potential complications of continued use and recommending abstinence). The authors suggested that such indications of reductions in cannabis use during the early treatment of first-episode psychosis should engender optimism that readiness to change may be especially salient in the period following initial diagnosis. Other highly regarded specialized early intervention programs have described experiences with an integrated approach to reduce substance use in individuals experiencing a first episode of psychosis [171].

Given the dearth of specifically designed treatments for cannabis abuse and dependence for first-episode patients, existing approaches typically include components such as motivational enhancement, psychoeducation, skills training and support, and taking into account the stage of recovery [95]. In Australia, Edwards and colleagues [172] tested a cannabis-focused intervention (an individually delivered, cognitive-behavioral, harm-minimization approach involving 10 weekly sessions) in 23 first-episode patients compared to a psychoeducational control condition in 24 patients. They found that both conditions were associated with reductions in

cannabis use at the end of treatment and at 6-months post-intervention, suggesting that relatively simple interventions may be beneficial, but that further research is needed on specialized approaches.

## *Prevention Implications*

In light of the fact that premorbid/adolescent cannabis use appears to be a component cause of schizophrenia-spectrum disorders, several authors have suggested prevention implications. Arseneault and associates [129] noted that although the majority of young people who use cannabis do so without serious consequences, a vulnerable minority will experience harmful outcomes, and that cannabis use among psychologically vulnerable young adolescents should be strongly discouraged by parents, teachers, and health professionals. Furthermore, they note that policy-makers should concentrate on public health measures to delay the initiation of cannabis use given that the youngest cannabis users appear to be most at risk. In their systematic review, Moore and coworkers [132] suggested that there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life. In doing so, they noted that even though one's individual lifetime risk of a psychotic disorder – even among those who use cannabis regularly – is likely to be low, cannabis use probably has a substantial effect on psychotic disorders at the population level because exposure to the drug is so common.

As pointed out previously [7], in light of the rapid growth in research that aims to prospectively identify samples in an ultra-high risk state, or potentially prodromal syndrome, indicated preventive interventions using both psychopharmacologic (e.g., low-dose atypical antipsychotic agents) and psychotherapeutic (e.g., cognitive-behavioral therapy) modalities could benefit from also testing whether the prevention and treatment of cannabis use would delay conversion to a psychotic disorder. The possibility of delaying onset of psychosis, by reducing premorbid or prodromal cannabis use among those at high genetic or psychometric risk, could result in substantial improvements in outcomes (in addition to ameliorating problems associated with cannabis use disorders once a psychotic disorder is clearly present). Although data on cannabis use among ultra-high risk or potentially prodromal samples is very limited, one study involving 48 such individuals found that at 1-year follow-up, only one of 32 subjects who had no or minimal cannabis use had converted to psychosis (3.1%), compared to five of 16 (31.3%) who met criteria for cannabis abuse or dependence [173]. Though very preliminary and in need of replication in larger samples, such results suggest that preventing or treating cannabis use in such individuals could delay, or perhaps even avert altogether, the onset of psychosis.

Despite these findings and a multitude of calls for preventive approaches, the evidence base pertaining to primary or secondary prevention of cannabis use disorders among individuals with latent or overt schizophrenia-spectrum disorders is

virtually nonexistent. Given the extent of the comorbidity, and the public health burden posed by cannabis and other drug misuse, focused development and research is clearly needed.

## Conclusions and Future Directions

The world's most commonly abused illicit substance appears to have a number of unique associations with schizophrenia-spectrum disorders. This chapter has provided an overview of some of the key aspects of the interface: both exogenous and endogenous hypotheses have been put forth concerning the role of cannabis and the endocannabinoid system in schizophrenia; the potential for cannabis use to induce psychotic symptoms or syndromes has been long recognized; there are high rates of cannabis misuse among patients with first-episode and chronic psychotic disorders; such use is associated with diverse clinical consequences; and increasing evidence suggests a causal association between premorbid cannabis use and psychotic outcomes. A number of future directions for research are evident, only a few of which are mentioned here, in addition to many others that can be gleaned from the foregoing sections of this chapter.

First, given the fact that ingested cannabis contains varying levels of diverse constituents, and that some of these may have opposing effects (e.g., $\Delta^9$-THC and CBD, which appear to have psychotomimetic and antipsychotic properties, respectively), it is crucial for the field to further examine the effects of specific phytocannabinoids. For example, in the first study of its kind, Morgan and Curran [17] found that individuals with evidence of $\Delta^9$-THC only in their hair samples had higher rates of unusual experiences (a dimension of psychosis-proneness that may be considered an analogue of hallucinations and delusions) compared to those with no cannabinoids or a combination of both $\Delta^9$-THC and CBD in their hair samples. Such findings clearly have important implications for research into the link between cannabis use and psychosis.

Second, continued research on the endocannabinoid system, and on naturally occurring or synthetic agents that interact with this system, will undoubtedly lead to advances in the field's understanding of the complex link between cannabis use and psychotic disorders. As demonstrated by early studies of rimonabant, such agents may hold promise for the treatment of psychotic disorders, other psychiatric disorders, and general medical conditions. Third, although cannabis use, especially in early adolescence, is now generally considered to be a component cause of schizophrenia-spectrum disorders, further research is warranted on the other potential direction of causality (i.e., psychotic and other types of symptoms leading to initiation or escalation of cannabis use) and on the bidirectional and shared diathesis hypotheses. Another area for future research pertains to the great need to develop more effective interventions for the treatment – and ultimately primary prevention – of cannabis use disorders, especially among those with, or predisposed to, schizophrenia and related psychotic disorders.

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