ABSTRACT

Schizophrenia is currently conceptualized as an illness that is caused by both genetic predispositions and exposure to stressors or environmental factors, particularly during early childhood and adolescence. This article focuses on one such environmental factor, cannabis use, especially use occurring prior to the onset of clinically evident psychiatric symptoms. Cannabis is commonly abused by adolescents and is the most abused illicit drug in the context of schizophrenia. Several first-episode studies document that the initiation of substance use and abuse typically precedes the onset of psychosis. This article highlights eight studies that characterize the impact of cannabis use on the age at onset of psychosis and three studies that provide early information on the impact of cannabis use on the age at onset of even earlier prodromal symptoms. Future research is needed to better characterize the impact of cannabis use on the onset of psychotic disorders and to determine if cannabis use increases the risk of developing a psychotic disorder, as several other studies suggest.

FOCUS POINTS

- Cannabis, or marijuana, is a drug that is commonly abused by adolescents and young adults; it is the most frequently abused illicit drug among people with schizophrenia or other psychotic disorders.
- Among people with comorbid substance abuse and schizophrenia or other psychotic disorders, substance use and abuse are typically initiated prior to the overt onset of the psychotic disorder.
- Some research suggests that cannabis use prior to onset may be associated with an earlier age at onset of psychosis, although it is difficult to establish whether this association is causal.
- Although additional research is needed, preliminary research suggests that cannabis use prior to any psychiatric symptoms may be associated with an earlier age at onset of the prodromal symptoms that commonly precede the onset of schizophrenia.

INTRODUCTION

Schizophrenia is currently conceptualized from the perspectives of the neurodevelopmental and diathesis-stress models. The neurodevelopmental model integrates altered pre- or perinatal brain development, adolescent developmental abnormalities, and potentially progressive processes that occur after illness onset. The diathesis-stress model suggests...
that symptomatic manifestations of the biologic vulnerability for schizophrenia are influenced by exposure to stressors or environmental factors. Based on these conceptualizations, the following points are fairly well accepted among schizophrenia researchers: First, the etiology of the disorder is most likely related to a number of genetic and early environmental risk factors. Second, later risk factors (during adolescence and young adulthood) and neurohormonal changes likely impact the manifestation of underlying vulnerability. Third, genes and environmental risk factors may interact to affect risk. Fourth, the sequential onset of symptoms usually occurs in a gradual fashion from the premorbid phase to the prodrome to the onset of full psychosis. Fifth, symptom onset, phenomenology, and course are highly heterogeneous. Last, both genetic and environmental factors contribute to this heterogeneity.

This article focuses on one such environmental factor, cannabis use, especially that which occurs prior to the onset of clinically evident psychotic symptoms. Although adolescent-onset cannabis use has been shown by epidemiologic research to be a risk factor (presumably a causal risk factor, or component cause) for schizophrenia, the present article examines this environmental factor in terms of its potential to adversely affect two key features of disease onset—age at onset of psychosis and age at onset of even earlier prodromal symptoms. This qualitative summary of the literature is not meant as a systematic review, but as a synthesis of select studies in this area.

**THE CROSSROADS OF SCHIZOPHRENIA AND CANNABIS USE**

Cannabis is the most commonly used illicit drug in the United States. According to the 2006 National Survey on Drug Use and Health, 45.4% of Americans ≥12 years of age have tried cannabis at least once. Among those ≥18 years of age with lifetime cannabis use, >50% report first using it between 12 and 17 years of age. Earlier onset of drug use has consistently been associated with greater risk of developing abuse and dependence. Cannabis use disorders occur in approximately 4% of the general US population, with a peak in the 18–29-year age range. Some 56% of those seen in treatment for cannabis abuse/dependence began using by 14 years of age, and 92% began by 18 years of age. Cannabis use is now considered a substantial public health problem by many, due to several reasons, as noted previously. First, US adolescents and young adults have very high rates of cannabis use. Second, cannabis dependence in youths predicts increased risks of using other illicit drugs and underperforming in school. Third, the cannabinoid content of smoked cannabis has increased substantially during recent decades, potentially resulting in a larger “dose” of psychoactive cannabinoids during drug use.

Unsurprisingly, given the aforementioned high population prevalence of cannabis use, cannabis is the most abused illicit drug in the context of schizophrenia. The Epidemiologic Catchment Area study found the lifetime prevalence of a cannabis use disorder in people with schizophrenia to be 19.7%. Many studies confirm high rates (20% to 70%) of cannabis use in patients with schizophrenia. Data from 53 studies of schizophrenia revealed that 12-month prevalence estimates of use and misuse of cannabis were 29% and 19%, and lifetime use and misuse estimates were 42% and 23%, respectively. Researchers report rates of cannabis misuse ranging from 15% to 65% in first-episode samples.

Several first-episode studies document that the initiation of substance use and abuse typically precedes the onset of psychosis, often by several years. When prodromal symptoms are taken into account, one German study of 232 patients with a first episode of psychosis found that 29.5% of those using drugs had a drug problem >1 year before the earliest sign of an emerging psychotic disorder. In an additional 34.6%, drug abuse emerged at the same time as the first symptoms. In a first-episode sample (n=133) from the Netherlands, among those patients who had used cannabis by the time of their first treatment contact, 64.3% reported initiating cannabis use before the onset of social and/or occupational dysfunction and 85.7% before the onset of psychosis. In a sample of 109 hospitalized patients with first-episode non-affective psychosis in the US, 79.8% had used cannabis at least once in the years prior to hospitalization (Compton MT, unpublished data, March 2009). While mean ages at the onset of prodromal symptoms and psychotic symptoms in that sample were 19.4±5.3 and 21.8±4.7 years, respectively, the mean age at first use of cannabis among the 87 who had used it was 15.8±4.0. These and other studies indicate a high prevalence of cannabis use occurring prior to the onset of psychiatric symptoms in people who develop a psychotic disorder.

Although numerous studies show that the initiation of substance use commonly precedes the onset of psychosis, this does not necessarily imply a directional or causal association. It is not surprising that substance use often precedes psychosis given that initiation of substance use usually occurs during adolescence. However, research establishing that early-course patients typically begin substance use prior to onset confirms temporality (ie, that exposure precedes outcome in a plausible way), which is one criterion in ultimately establishing a causal relationship. This article, which largely focuses on the possibility that pre-onset cannabis use may hasten onset of psychotic disorders, notes as important the substantial research showing that, among patients with comorbidity, substance use often precedes the manifestation of symptoms.
The biologic pathways linking cannabis use and psychosis are being actively studied. Numerous research findings, six of which are briefly described here, may demonstrate the biologic plausibility of pre-onset cannabis use impacting not only vulnerability for developing schizophrenia, but also the age at onset among those who do develop the disorder. First, exogenous cannabinoids (eg, marijuana) are extremely lipid soluble, accumulating in fatty tissues from which they are slowly released back into body compartments, including the brain, suggesting that even occasional cannabis use leads to long-term exposure of central receptors to cannabinoids. Second, exogenous and endogenous (eg, anandamide) cannabinoids exert their effects (such as modulating the release of neurotransmitters including glutamate, norepinephrine, and dopamine) by interactions with specific cannabinoid (CB1) receptors that are distributed in brain regions implicated in the pathophysiology of schizophrenia (including the cerebral cortex, limbic areas, basal ganglia, and thalamus). Third, cannabis increases mesolimbic dopaminergic transmission and inhibits glutamatergic release. Fourth, several studies have shown an increased CB1 receptor density in brain regions of interest in schizophrenia, including the dorsolateral prefrontal cortex and the anterior cingulate cortex, and elevated levels of endogenous cannabinoids in the blood and cerebrospinal fluid of patients with schizophrenia. Fifth, gene variants of the CB1 receptor may be associated with schizophrenia and risk of substance abuse in individuals with schizophrenia. However, other studies have not found an association with risk for schizophrenia, and a recent meta-analysis did not implicate these gene variants among 24 showing significant effects. Sixth, acute administration of cannabis causes both patients and controls to experience transient increases in cognitive impairments and schizophrenia-like positive and negative symptoms. It could be argued that these six points provide only a weak argument for a causal effect of cannabis on hastening onset. For example, the findings of increased CB1 receptor density in regions implicated in schizophrenia are not surprising given that CB1 receptors are relatively widely dispersed. However, when taken together, these findings do suggest biologic plausibility, which, like temporality, is one criterion for eventually demonstrating causality.

Having provided some evidence supporting potential biologic plausibility, the remainder of this article focuses on two themes—the potential impact of early-course cannabis use on both the age at onset of psychotic symptoms and the age at onset of even earlier prodromal symptoms. Age at onset of the prodrome and psychosis are critical variables to understand because they are important prognostic factors. An earlier age at onset is associated with a higher degree of cognitive impairment, increased severity of psychosocial and functional disability, more severe symptoms and behavioral deterioration, less responsiveness to antipsychotics, decreased ability to tolerate discontinuation of medication, and greater likelihood of rehospitalization. Given extensive literature connecting earlier onset with poorer course and outcomes, discovering potentially modifiable determinants of age at onset is crucial. Could pre-onset cannabis use in adolescence be one such determinant?

THE IMPACT OF PRE-PsyCHOTIC CANNABIS USE ON THE AGE AT ONSET OF PSYCHOSIS

At least eight studies, generally collecting cross-sectional or retrospective information from individuals with a recent onset of psychosis, have examined the potential impact of cannabis use on the age at onset of psychosis. These studies, discussed briefly here, are also summarized in the Table (Compton MT, unpublished data, March 2009). Although numerous older studies explored the relationship between substance abuse and psychosis, Hombrecht and Häfner were perhaps the first to study the exact timing of the onset of substance use and symptoms in first-episode psychosis. In the Age, Beginning, and Course (ABC) schizophrenia study, they found that the mean age at onset of the first negative symptom, first positive symptom, and first admission were lower in the 32% who had abused drugs prior to admission than in those who had not. The mean ages at first positive and negative symptoms were each 5.7 years younger for those with a history of drug abuse than for those with no substance abuse history (21.1 compared to 26.8, and 24.3 compared to 30.0, respectively). Among those who reported a history of drug abuse, the mean age at onset of drug abuse was 18.6 years, or 1.5 and 5.7 years before the mean age at onset of the first negative and first positive symptoms. However, the analysis of age at onset was not restricted to those who had initiated drug abuse specifically before, rather than during or after, the onset of illness. In addition, the independent effects of particular substances of abuse were not considered (although 90% of those abusing drugs in the sample had abused cannabis, 63% had used other drugs as well). Finally, the study did not examine the impact of drug use before it reached the threshold of drug abuse.

Among a sample of patients in New York State with a first episode of either affective or non-affective psychosis (n=541), symptom onset among men and women was examined by Rabinowitz and colleagues in three groups: those with no lifetime substance use disorder diagnosis, those in remission or with mild substance use, and those with current moderate-to-severe substance abuse at the time of admission. Females with current moderate-to-severe substance abuse were 6 years younger at the onset of first psychotic symptoms than their counterparts with no lifetime substance use. No significant impact on the age at onset was observed for males. However,
the inclusion of patients with affective as well as non-affective psychoses introduces heterogeneity in the expected age at onset, disease mechanisms, gender distribution, and rates of comorbid substance abuse. Nonetheless, this study is notable for accounting for the severity of substance use.

In the Calgary Early Psychosis Program, which assesses and treats patients with a recent onset of psychosis, 44% of 357 consecutively admitted patients had substance abuse or dependence in the previous year.\(^7\) In this sample, Van Mastrigt and colleagues\(^8\) found that patients who had misused cannabis (or cannabis and alcohol) were younger and had an earlier age at onset of positive psychotic symptoms than non-users or those who misused alcohol only or alcohol and other drugs. These findings suggest that a link may exist between cannabis use and age at onset of psychosis, and that this effect may be related to the cannabis, per se, as opposed to personality traits or other vulnerabilities that lead to a substance use disorder, given that misuse of other substances did not carry the same association. However, without data on the age at first cannabis use or abuse, or on the onset of prodromal or negative symptoms, it is not possible to establish the directionality of the association between cannabis use and the age at onset of symptoms.

Veen and colleagues\(^3\) used an incidence cohort of patients in the Netherlands to examine the independent influences of gender and cannabis use on early course features. The sample (\(n=133\)) included natives of the Netherlands, first- and second-generation immigrants from Surinam and Morocco, and individuals from other racial/ethnic groups. Patients who used cannabis (\(n=70\)) had an earlier median age at onset compared to the 63 patients not using cannabis. In a multiple regression analysis, male cannabis users (\(n=55\)) were found to have had their first psychotic episode a mean of 6.9 years earlier than 37 male nonusers. Cannabis use was a stronger predictor of age at first psychotic episode than gender. However, the study did not control for the effects of family history or the use of other substances (eg, alcohol, cocaine). Furthermore, the study treated cannabis use as categorical/dichotomous variable (which is true of most studies conducted to date) and therefore could not examine potential dose-effect relationships.

Mauri and colleagues\(^4\) retrospectively studied 285 first-episode patients in Italy and found that patients abusing cannabis had an earlier age at onset compared with those who did not abuse cannabis, though it is unclear how onset was operationalized. Further, this comparison failed to control for

### TABLE

**A SUMMARY OF EIGHT STUDIES EXAMINING THE POTENTIAL IMPACT OF PRE-ONSET CANNABIS USE ON AGE AT ONSET OF PSYCHOSIS\(^{28,34,38,42,43,70,71}\)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Location</th>
<th>Sample Size and Diagnoses</th>
<th>Main Findings Regarding Substance Use and Age at Onset of Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Hambrecht and Häfner(^28)</td>
<td>Mannheim, Germany</td>
<td>232; schizophrenia or a paranoid disorder</td>
<td>Drug abuse was associated with a lower age at first sign, first positive symptom, and first negative symptom of schizophrenia. The onset of drug abuse typically preceded the first positive and negative symptoms, but preceded the first sign in only 27.6% of cases.</td>
</tr>
<tr>
<td>1998</td>
<td>Rabinowitz et al(^8)</td>
<td>New York, United States</td>
<td>541; first-episode affective or non-affective psychoses</td>
<td>Females with current moderate-to-severe substance use had an earlier age at onset of psychotic symptoms than those with no history of substance abuse. This association was not found among males in the sample.</td>
</tr>
<tr>
<td>2004</td>
<td>Van Mastrigt et al(^8)</td>
<td>Calgary, Canada</td>
<td>357; consecutive admissions to an early psychosis program</td>
<td>Cannabis use at entry was associated with a younger age at onset of psychosis. Those who used cannabis (or cannabis and alcohol) had a younger age at onset of psychosis (when the first positive symptom emerged) than non-users, alcohol-only users, and multi-drug users.</td>
</tr>
<tr>
<td>2004</td>
<td>Veen et al(^3)</td>
<td>The Hague, Netherlands</td>
<td>133; first-episode non-affective psychosis</td>
<td>Prior cannabis abuse was associated with an earlier age at onset of both social and occupational dysfunction and psychosis. However, when controlling for gender, this association only remained significant for the onset of psychosis.</td>
</tr>
<tr>
<td>2006</td>
<td>Mauri et al(^4)</td>
<td>Milan, Italy</td>
<td>285; first-episode schizophrenia</td>
<td>Among those with cannabis abuse, the mean age at onset of psychosis was significantly lower (24.0±6.3) than that of patients not using cannabis (26.8±6.5).</td>
</tr>
<tr>
<td>2006</td>
<td>Barnes et al(^4)</td>
<td>London, United Kingdom</td>
<td>152; first-episode psychosis</td>
<td>Cannabis use and gender had independent effects on age at onset, after adjusting for the use of alcohol and other drugs. Cannabis use was significantly associated with an earlier age at onset, with an average decrease of 5 years.</td>
</tr>
<tr>
<td>2008</td>
<td>González-Pinto et al(^1)</td>
<td>Vitoria, Spain</td>
<td>131; first-episode affective or non-affective psychoses</td>
<td>Higher levels of cannabis use were associated with a younger age at onset (7.8.5 and 12 years, respectively) for those with cannabis use, abuse, and dependence. By comparison, gender and other substance use had little effect on age at onset.</td>
</tr>
<tr>
<td>2009</td>
<td>Compton et al, unpublished data</td>
<td>Atlanta, Georgia, United States</td>
<td>109; first-episode non-affective psychosis</td>
<td>Progression to daily cannabis and daily tobacco use were associated with an earlier age at onset of psychosis (the level of frequency of use was treated as a time-dependent covariate).</td>
</tr>
</tbody>
</table>

the influence of gender, and only 18% of females had used substances compared to 44% of males. Additionally, much of the data were obtained by retrospectively reviewing medical records (which are presumably less thorough and accurate than formal research assessments). 56% of patients having used drugs were multi-drug abusers (and this apparently was not controlled for), and the amount and duration of substance use was not considered.

In London, Barnes and colleagues assessed 152 first-episode patients and found that those reporting past substance use were significantly younger at the onset of psychotic symptoms compared with those who had not used substances. In a linear regression, use of any substances other than cannabis was not significantly related to age at onset, though gender and cannabis use were. The age at onset of psychosis was on average 4.2 years older for women and 5 years younger for participants using cannabis, adjusting for the other variables. In this study, like most others, cannabis was the most prevalently used illicit substance, and, therefore, detecting an effect of cannabis may be easier than finding effects of other drugs, given issues of statistical power. Unfortunately, inquiries about past substance use did not include detailed assessment of the frequency and quantity of drugs taken, and it is unclear whether the initiation of cannabis use in fact preceded the onset of symptoms in the patients included in the analysis.

González-Pinto and colleagues found, among 131 first-episode patients in Spain, a significant, gradual reduction in age at onset as the level of use of cannabis increased—a decrement of 7, 8.5, and 12 years for patients with cannabis use, abuse, and dependence, respectively. The effect was not explained by the use of other drugs or gender. However, the study included patients with affective psychosis, who would be expected to have a later age at onset, and likely a lower prevalence of comorbid cannabis use. In addition, the study did not take into account the duration of cannabis use and it is not clear exactly how age at onset was operationalized.

Recently, Compton and colleagues (Compton MT, unpublished data, March 2009) examined the impact of prior cannabis use on the age at onset of psychosis in 109 patients hospitalized for a first episode of psychosis. This group found that both daily cannabis and daily tobacco use occurring before onset of psychosis had a significant effect on the risk of onset of psychosis (hazard ratios of 2.0 and 1.8, respectively, P<.05), when the level of frequency of use was treated as a time-dependent covariate in Cox regressions (ie, progression to daily use was associated with a higher risk of onset). Of note, cannabis and tobacco use were highly correlated (eg, having ever used nicotine was highly associated with having ever used cannabis, \( \chi^2=25.5, P<.001 \) [Compton MT, unpublished data, March 2009]) and therefore may not represent two independent risk factors. A gender by progression to daily cannabis use interaction was observed—progression to daily use was related to a much larger increased relative risk for onset of psychosis in females (hazard ratio=5.1) than in males (hazard ratio=3.4). Although this study took into account the frequency of cannabis use (ie, never, ever but not weekly use, weekly but not daily use, or daily use), it did not assess quantity of use and did not gather detailed information on patterns of use.

### Impact of Pre-prodrome Cannabis Use on the Age at Onset of the Prodrome

While the previously reviewed studies suggest, through various analytic designs, that cannabis use may be associated with a younger age at onset of psychotic symptoms, only a few groups have attempted to determine if cannabis use is associated with a younger age at onset of prodromal symptoms. The prodrome is the syndromal period commonly comprised of non-specific psychiatric symptoms, emerging attenuated positive symptoms, negative symptoms, and psychosocial decline—commonly lasting several months to a few years—that precedes the emergence of frank psychosis in most patients. One critique of the literature is that the possible influence of cannabis use on prodromal symptoms has not been adequately explored. Doing so could shed light on the competing hypotheses that substance use precipitates or hastens onset of the illness versus that very early, subtle symptoms of the illness make patients vulnerable to substance use.

Hambrecht and Hälner conducted one of very few studies that included an analysis of prodromal symptoms in relation to substance use. In 232 first-episode patients from the ABC schizophrenia study, they found that the mean age at onset of the first sign was lower in the 32% who had abused drugs prior to admission than in those who had not. First signs included the first negative, positive, or non-specific psychiatric symptom if it occurred continuously until the onset of psychosis. In this way, the “first sign” represented the onset of the prodrome, if a prodrome had occurred, or psychosis, if there had been no prodrome. The age at first-sign onset was 7.2 years younger among those who had abused drugs than among those who had no history of drug or alcohol abuse (18.5 compared to 25.7 years).

In the report by Veen and colleagues, the relationship between prior cannabis use and the age at onset of the first sign of social or occupational dysfunction, which could be considered a proxy for the age at onset of the prodrome, was examined. In this cohort, the median age at onset was 18.1 years among patients using cannabis, as compared to 27.7 years in those not using cannabis. However, in a linear regression, gender was a more important predictor of age at onset, and after controlling for this variable, cannabis use was not a significant predictor. This study did not use a precise indicator of the
onset of the prodrome, but it is noteworthy for its analysis of the effect of prior cannabis use on onset. Like their analysis of age at onset of psychosis, Veen and colleagues\textsuperscript{43} did not control for family history or other substance abuse, and they treated cannabis use as a categorical variable.

Similar to their findings pertaining to age at onset of psychosis, Compton and colleagues (Compton MT, unpublished data, March 2009) examined the impact of prior cannabis use on the age at onset of illness/prodromal symptoms in 109 hospitalized first-episode patients. When considering the level of frequency of use as a time-dependent covariate in Cox regressions, both daily cannabis and tobacco use had a significant effect on the risk of onset of the symptoms (which represented the onset of the prodrome in 70% of the sample), hastening onset (hazard ratios=2.1 and 1.8, respectively). As noted above, although this analysis accounted for the frequency of cannabis use, other methodologic limitations make the results preliminary, requiring further research.

\textbf{DISCUSSION AND UNANSWERED QUESTIONS}

In summary, several studies suggest that cannabis use among first-episode patients prior to onset may be associated with an earlier age at onset of positive psychotic symptoms. Much less is known about potential associations between pre-prodromal cannabis use and the onset of prodromal symptoms. The Figure depicts hypothesized symptom development and the accumulation of functional impairment in the early course of schizophrenia in patients with a history of cannabis use compared to those without a history of cannabis use. Further research is needed to show whether pre-onset cannabis use is in fact an independent risk factor for developing a psychotic disorder or for an earlier emergence of symptoms among those who do develop a disorder. Support for the psychotogenic properties of cannabis during a prodromal period comes from

\textbf{FIGURE}

\textbf{SYMPTOM DEVELOPMENT AND THE ACCUMULATION OF FUNCTIONAL IMPAIRMENT IN THE EARLY COURSE OF SCHIZOPHRENIA IN THOSE WITH A HISTORY OF CANNABIS USE (LEFT), COMPARED TO THOSE WITHOUT A HISTORY OF CANNABIS USE (RIGHT)}

The curves represent the development of symptoms over time, from premorbid social and academic impairments, to the development of prodromal symptoms, to the onset (and resolution, with treatment) of frank psychotic symptoms. The width of the curve represents the accumulation of functional impairment at each stage. Based on the early evidence available, it is postulated that first-episode patients with a history of cannabis use are likely to have an earlier age at illness onset, as represented by the left-shift of the curve. Some evidence also suggests those using cannabis will accumulate more functional impairment even during the premorbid phase and then throughout the early course of the illness, with a higher likelihood of school drop-out and incarceration, a greater severity of positive symptoms, and poorer response to therapy.

the finding that perceptual disturbances fluctuate over time with cannabis use in a clinical high-risk cohort. As stated above, an earlier age at onset of psychosis is a poor prognostic indicator. If further research proves a link between adolescent, pre-onset cannabis use and age at onset, then decreasing cannabis use among adolescents may delay the onset of psychosis among those destined to develop a psychotic disorder. Some have argued that there now exists sufficient evidence to inform the public that using cannabis could increase the risk of developing a psychotic illness; this may be especially relevant for at-risk groups. Programs to decrease cannabis use may be particularly beneficial in adolescents identified as being at very high risk for psychosis, by virtue of a positive family history or by being identified as potentially prodromal or at “ultra-high risk” based on emerging psychiatric symptoms and functional decline. Just as decreasing cannabis use has been suggested as a potential preventive intervention to reduce the incidence of schizophrenia, reducing cannabis use also could delay onset among those who do, nonetheless, develop the disorder.

Numerous unanswered questions should be the focus of ongoing research. First, given the high comorbidity between cannabis abuse and the abuse of other addictive substances, especially nicotine and alcohol, the independent effects of pre-onset cannabis use, as well as pre-onset nicotine, alcohol, and other drug use, should be examined. Although the neurobiologic feasibility of the cannabis/psychosis link was pointed out above, it must be recognized that alcohol and other drugs impact upon dopaminergic, glutamatergic, and other neurotransmitter systems affected by schizophrenia. Regarding potential effects of alcohol and cannabis, for example, on psychosis risk, the same neural structures are indeed affected by both substances, at least at a global level (mesolimbic dopamine pathways and the central reward system in general), though alcohol and cannabis exert their effects partly through different receptors (ie, γ-aminobutyric acid-ergic/glutamatergic and cannabinoid receptors, respectively). Some evidence suggests that alcohol may exert modulatory actions in the endogenous cannabinoid system. In addition to cannabis and alcohol, nicotine use is also a critical variable to examine for a couple of reasons: Cigarette smoking is highly prevalent in individuals with schizophrenia and there is increasing interest in the literature in biologic links between the central nicotinic system and schizophrenia. However, though such elucidation of single-drug effects would be beneficial, it must be emphasized, as noted above, that the independent effects of each substance will be difficult to parse given the high degree of comorbidity across substances, especially cannabis, alcohol, and nicotine. Relatively large sample sizes likely will be necessary to examine independent effects.

A second direction for future research pertains to the issue of causality versus association. Like any observational study, the studies described here cannot rule out the possibility of reverse causality, in which the disease processes associated with the later development of psychosis render an individual more susceptible to the initiation of substance use and abuse earlier in life. Even if further research indicates that pre-onset cannabis use is associated with an earlier age at onset, sorting out whether the cannabis use causes an earlier onset or is a marker of a disease process or subtype associated with earlier onset will be challenging. Similar questions pertain to the link between cannabis use and risk of developing schizophrenia—causality remains difficult to prove, and a shared diathesis for both psychotic illnesses and substance abuse may be at play.

Third, regarding a potential impact of cannabis use on prodromal symptomatology, it is possible that cannabis use causes prodrome-like (but not definitively prodromal) symptoms in patients who later develop a psychotic disorder. That is, cannabis use in adolescence among patients who later develop a psychotic disorder may lead to apathy, academic problems, and other prodromal-appearing difficulties, though such problems may not necessarily be inherent to the schizophrenia process or may not alter the course of the developing psychotic disorder in a way that conveys long-term course implications. A number of studies suggest that cannabis use is associated with schizotypal features in people who may or may not develop schizophrenia. Furthermore, in a recent study involving 6,330 adolescents (15–16 years of age) in a Finnish prospective birth cohort, the 356 (5.6%) participants who had used cannabis endorsed a higher mean number of “prodromal” symptoms, and a dose-response relationship was evident. However, actual prodromal symptoms can only be confirmed retrospectively; it remains to be determined through further longitudinal research whether or not the symptoms assessed in that study actually represented a prodrome.

A fourth important issue requiring further, more methodologically rigorous research, relates to the measurement of substance use in relation to ages at onset of prodromal and psychotic symptoms. As noted above, not all prior studies commented on (in fact, most did not) or restricted the analyses to those whose drug use/abuse preceded the onset of psychotic and/or prodromal symptoms, which is critical to the research question. To advance the field in this area, future research should carefully examine the timing of the initiation of cannabis use and the development of psychotic symptoms as well as earlier prodromal symptoms using well-defined operationalizations of onset. Such retrospective measurement is admittedly a difficult task. Comprehensive assessments of cannabis and other substance use with reliable and valid retrospective measures that incorporate calendars, timelines, and significant life events should be used to gather data on amount, duration, frequency, and patterns of use, thus allowing for...
the examination of temporal relationships and potential dose effects. Additionally, because the limited research in this area to date has generally consisted of cross-sectional and retrospective studies, other research designs, including case-control and longitudinal studies, would be beneficial.

Fifth, relevant covariates, including gender and family history, must be examined when studying age at onset. The fact that a gender is a predictor of age at onset is one of the most consistent findings in schizophrenia research.87,88 For example, results from the ABC schizophrenia study indicate that women are 3–4 years older than men at illness onset, as defined by the onset of positive symptoms, negative symptoms, or psychosocial impairment.99,100 Family history of schizophrenia is also associated with an earlier age at onset.91–94 and should be assessed as a covariate. It should be noted, however, that even if future studies are more rigorous, it may still be difficult to establish with certainty that cannabis use hastens onset and that all relevant covariates have been taken into account. Confounding (the distortion of an apparent effect of cannabis use on risk brought about by an association with other significant risk factors) must be seriously considered.

These five issues, among others, suggest a need for further research to substantiate the early reports that pre-onset cannabis use, typically occurring in adolescence, may be associated with (and perhaps even causative of) an earlier age at onset. This line of research—in addition to ongoing research on the neurobiologic interface between cannabinoid systems and the neurocircuitry involved in schizophrenia, cannabis use as a potential component cause of schizophrenia, and the influence of cannabis use on symptom and neurocognitive profiles—may advance the field in terms of both further elucidating psychotic disorders and informing future preventive interventions.

CONCLUSION

Several first-episode studies show that the initiation of substance use and abuse typically precedes the onset of psychosis, often by several years. Studies reviewed also suggest that cannabis use among first-episode patients prior to onset may be associated with an earlier age at onset of positive psychotic symptoms. Much less is known about potential associations between pre-prodromal cannabis use and the onset of prodromal symptoms, though preliminary evidence suggests that an association may be present. Future research should examine the effects of cannabis, independent of other substances used; establish the causal direction of these associations; clarify whether prodrome-like symptoms observed during concurrent cannabis use are, indeed, related to the subsequent psychosis; include more rigorous research design; and control for all significant covariates such as gender and family history. PP

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