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Cannabis and Psychosis: *What Can Daily Diaries Tell Us About Who is Vulnerable?*

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ABSTRACT

The association between cannabis use and the initial development of psychotic symptoms has attracted increased interest over the past decade. In particular, researchers have attempted to elucidate whether cannabis use increases the risk of psychosis among vulnerable individuals or may just represent attempts to self-medicate distressing symptoms. While a growing literature suggests that cannabis use may contribute to the development of psychotic symptoms, these findings are based primarily on retrospective assessments that have limited ability to clarify the temporal link between cannabis use and psychotic symptoms. The authors review the literature regarding the link between cannabis use and psychotic symptoms; point out the limitations associated with retrospective assessments; and discuss advantages of incorporating daily diary methods, such as Experience Sampling Method (ESM), to study cannabis use and symptoms during daily functioning in "real world" environments. The authors also discuss potential future applications of ESM in research and clinical practice that may inform the identification of individuals vulnerable to develop psychotic symptoms, as well as the development of treatments that target this population.

FOCUS POINTS

- Psychosis onset has been associated with cannabis use.
- The causal relationship between cannabis and psychosis remain unclear.
- Retrospective assessments cannot determine the temporal direction of this link.
- Daily diaries can clarify the directionality of this link during "real world" daily functioning.

INTRODUCTION

The association between cannabis use and psychotic symptoms has attracted increased interest over the past decade.[1-3] A multifarious body of research has been conducted to characterize this link, including cohort, epidemiologic, challenge, and genetic studies. A primary focus of these inquiries has been the potential causal role cannabis use may play in the initial development of psychotic symptoms and schizophrenia. In particular, researchers have attempted to elucidate whether cannabis use increases risk of psychosis among vulnerable individuals or may just represent attempts to self-medicate distressing symptoms.[4] The increased interest in this link is rooted, in part, in cannabis being potentially one of a few modifiable risk factors of schizophrenia,[5] with an estimated 8% of the attributable risk for this disorder being accounted for by cannabis use.

Previous reports indicate that the prevalence of cannabis use

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in a first episode of psychosis (~20% to 40%)[6-8] is comparable to rates reported among individuals at high risk of psychosis (17% to 41%).[9-12] Cross-sectional studies in genetic high-risk individuals indicate a link between cannabis use and positive symptoms, with an increase in use and symptoms during the months leading to the development of frank psychosis.[13,14] Similarly, individuals with psychosis vulnerability were more likely to report abnormal perceptions and thought influence when they used cannabis[4,15] and were more likely to develop psychosis.[2,16] Evidence from challenge,[17,18] genetic,[19-21] and epidemiologic studies[22] provide further support for this link. However, the support for cannabis playing a causal role in the development of psychosis is not universal. Opponents of this position point to evidence of increased use of cannabis in the general population (eg, Australia) without corresponding elevations in cases of schizophrenia,[23] as well as a lack of association between cannabis use and later development of psychosis in some clinical high-risk cohort studies.[9] While a growing literature suggests that cannabis use may play a role in the development of psychosis, these findings are based primarily on retrospective assessments that have limited ability to clarify the temporal link between cannabis use and psychosis. The use of daily diary methods may potentially elucidate this link. Thus, the primary aims of this article are to review the literature regarding the link between cannabis use and psychotic symptoms; identify the limitations associated with retrospective assessments; and discuss advantages of incorporating daily diary methods, such as Experience Sampling Method (ESM), to study cannabis use and symptoms during daily functioning in "real world" environments.

LINK BETWEEN CANNABIS USE AND INITIAL DEVELOPMENT OF PSYCHOTIC SYMPTOMS: *METHODOLOGIC LIMITATIONS*

A growing body of literature suggests cannabis is associated with the initial development of psychotic symptoms. However, the literature remain inconclusive regarding the causal direction of this link due to numerous methodologic limitations. First, most studies to date in high-risk individuals have employed single assessments or cross-sectional designs. Thus, evidence of the co-evolution of cannabis use and symptoms over time remains unclear. Corcoran and colleagues[12] recently published the first prospective longitudinal report on cannabis use and symptoms in individuals at clinical high risk of psychosis. Subjects were assessed prospectively every three months for up to 2 years. Data indicated that periods characterized by increased cannabis use were associated with significantly more perceptual disturbances and worse functioning, controlling for medications and use of other drugs. However, the 3-month assessment intervals in this study did not permit time-lag analyses, precluding the evaluation of causality between cannabis use and symptoms.

Another limiting factor is the use of retrospective measures of cannabis use and symptoms. Such assessments are vulnerable to the influence of memory difficulties, affective states at assessment time, and cognitive biases and reframing. Even when prospective designs are used (eg, conducting assessments prospectively every 3 months for up to 2 years), these assessments are still based on the participants' retrospective recollection of cannabis use and symptoms from the past week, from the past month, or since the previous assessment. These difficulties are particularly critical given the substantial memory deficits experienced by many individuals at high risk for psychosis,[24,25] making the use of retrospective assessments potentially problematic in this population. This view is echoed in the preliminary assessment guidelines for the pharmaceutical industry published by the United States Food and Drug Administration.[26] Accordingly, Patient-Reported Outcome (PRO) instruments that:

> ...require patients to rely on memory, especially if they must recall over a period of time, or to average their response over a period of time may threaten the accuracy of the PRO data. It is usually better to construct items that ask patients to describe their current state than to ask them to compare their current state with an earlier period or to attempt to average their experiences over a period of time.[26] (p. 11)

A third limiting factor is rooted in the relatively brief impact period (minutes to hours) of Delta 9-tetrahydrocannabinol, the active ingredient of *Cannabis sativa*.[27] Retrospective assessments that are completed days, weeks, or even months after the actual cannabis use are limited in their ability to provide information about the co-evolution of mood, symptoms, and drug use over the brief periods before and after the actual cannabis use. As a result, the determination of the temporal link between mood, symptoms, and cannabis use remains unclear.

Finally, the use of retrospective assessments may provide only limited information about the social and environmental context associated with cannabis use, as well as motivation for use. Thus, the current literature based on retrospective assessments of cannabis use and symptoms may have limited ecological validity to determine the temporal relationship between cannabis use and development of psychotic symptoms.

DIARY METHODS

To overcome some of these difficulties, researchers have employed daily diary methods to study cannabis use and symptoms during daily functioning in "real world" environments. Diary methods such as ESM is an ecologically valid time sampling of self-reports developed to study the dynamic process of person-environment interactions.[28] Subjects in ESM studies are typically supplied with a digital wristwatch and booklets containing questionnaires about current mood, symptoms, activities, and social context. The subjects are instructed to complete a questionnaire upon hearing beeps from the wristwatches, which

are typically preprogrammed to beep randomly numerous times a day to elicit experience samples. ESM offers numerous advantages over retrospective assessments including: the ability to record experiences, behavior, and context using high time-resolution measurement (over minutes to hours) that permits time-lag analyses; assessment of current experiences with limited need of episodic memory input; the potential for inclusion of minor/transient experiences that may not be recalled later, but may still have an impact on mood and behavior; the ability to assess motivation *in vivo*; and the possibility to analyze in high time-resolution the daily fluctuations and patterns of change across activities, social contexts, and time of day.

Spearheaded by researchers from the Maastricht group,[28-31] ESM has been used extensively to study psychosis during the flow of daily functioning in individuals with schizophrenia spectrum disorders. More recently, the authors of this study demonstrated the feasibility and validity of using ESM with Palm computers in hospitalized individuals with schizophrenia[32] and in young people identified as at heightened clinical risk for psychosis,[33] allowing researchers to link these data to concurrent ambulatory physiologic measures.

A handful of attempts have been made to apply ESM to study cannabis use and psychosis. The Table lists peer-reviewed publications of studies using daily diary methods (such as ESM) to investigate cannabis use and psychosis.[20,21,34,35] Among individuals with established psychosis, ESM has been used to investigate the link between psychosis, cannabis use, and the functional polymorphism in the catechol-*O*-methyltransferase gene (COMT Val(158)Met).[20,21] Only two studies[34,35] to date have used ESM to elucidate the link between cannabis use and psychotic symptoms in individuals with psychosis proneness. Verdoux and colleagues[34] and Tournier and colleagues[35] investigated this link in undergraduate university students. They reported that subjects with high vulnerability for psychosis were more likely to report unusual perceptions, as well as feelings of thought influence compared to subjects with low vulnerability.[34] In contrast, cannabis use did not increase subsequent occurrences of psychotic experiences. Similarly, individuals with a diagnosis of agoraphobia were significantly more likely to use cannabis (regardless of state anxiety; however, overall, there was no evidence for anxiolytic or anxiogenic effect of cannabis use in this agoraphobia sample.[35] These findings were interpreted as inconsistent with the self-medication model.[34]

While these findings[35] shed light as to the temporal link between cannabis use and psychosis, the study included a non-clinical sample of college students. No study to date has used ESM to characterize prospectively in high time-resolution the temporal link between cannabis use and positive symptoms during the flow of daily functioning among individuals at clinical high risk for psychosis. Such a study may offer unique and vital information that may not be possible to collect using retrospective assessments. Such a study will permit the conduct of time-lag analyses that will shed light about the directionality of the cannabis use—positive symptom link, informing causality; will allow the collection of data as to motivation for use within close temporal proximity to time of use; and

TABLE

PEER-REVIEWED PUBLICATIONS OF USE OF DAILY DIARY METHODS TO INVESTIGATE CANNABIS USE AND PSYCHOSIS[20,21,34,35]

Year	Study	Population	N	Duration	Sampling Frequency (per day)	Outcome
2003	Verdoux et al[34]	College students	79	7 days	5 times	Subjects with high vulnerability for psychosis were more likely to report unusual perceptions as well as feelings of thought influence than subjects with low vulnerability for psychosis. They also were less likely to experience enhanced feelings of pleasure associated with cannabis.
2003	Tournier et al[35]	College students	79	7 days	5 times	There was no significant association between the level of state anxiety and cannabis use. However, a diagnosis of agoraphobia was significantly associated with increased likelihood of cannabis use, independent of state anxiety and other confounding factors.
2008	Henquet et al[20]	Individuals with psychotic disorder	31 P 25 HC	6 days	12 times	Individuals with the COMT Val(158)Met Val allele, but not subjects with the Met/Met genotype, showed an increase in hallucinations after cannabis exposure, conditional on prior evidence of psychometric psychosis liability.
2008	Van Winkel et al[21]	Individuals with psychotic disorder	31 P 25 HC	6 days	12 times	A significant interaction between COMT(Val158Met) genotype and stress was found for patients, but not for healthy controls. Similarly, a significant interaction between COMT(Val158Met) genotype and stress was also apparent, with Met/Met patients showing the largest increase in psychotic experiences in reaction to stress.

P=psychotic patients; HC=healthy controls; COMT=catechol-*O*-methyltransferase.

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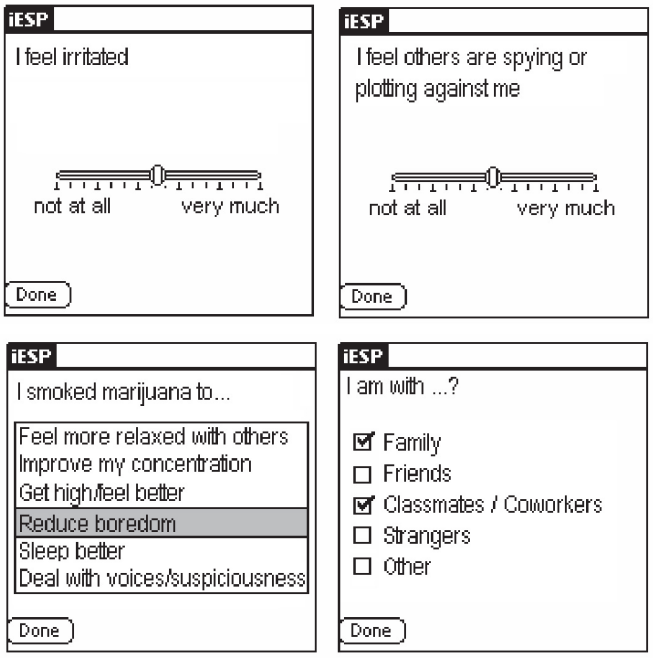
will provide information about the social and environmental context of cannabis use in the flow of daily functioning in this population. Understanding the motivation for and context in which individuals at clinical high risk for psychosis use cannabis could inform the development of preventive interventions to reduce exposure, and delay or possibly prevent psychosis onset. Numerous investigators, notably Barrowclough and colleagues,[36] have demonstrated the safety and efficacy of psychological treatments aimed at reducing the use of cannabis and other drugs in patients with schizophrenia, including first-episode patients.[37,38] Treatments include motivational models,[39] cognitive-behavioral therapy (CBT), family intervention,[36] and antipsychotics.[9] With an understanding of motives for use, these programs for first-episode dual-diagnosis patients could be piloted in substance-using prodromal patients. Miller and colleagues[40] is currently developing a study using ESM with Palm computers in a sample of urban, help-seeking adolescents and young adults who have been determined to be at clinical high-risk for psychosis using the Structured Interview for Prodromal Syndromes and Scale of Prodromal Symptoms–the diagnostic "gold standard" in psychosis high-risk research. Figure 1 presents screen shots of questions to be presented on the Palm computers as part of this study.

FIGURE 1

SCREEN SHOTS OF QUESTIONS PRESENTED AS PART OF AN ESM WITH PALM COMPUTER STUDY OF CANNABIS USE AND PSYCHOSIS IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS



ESM=Experience Sampling Method.

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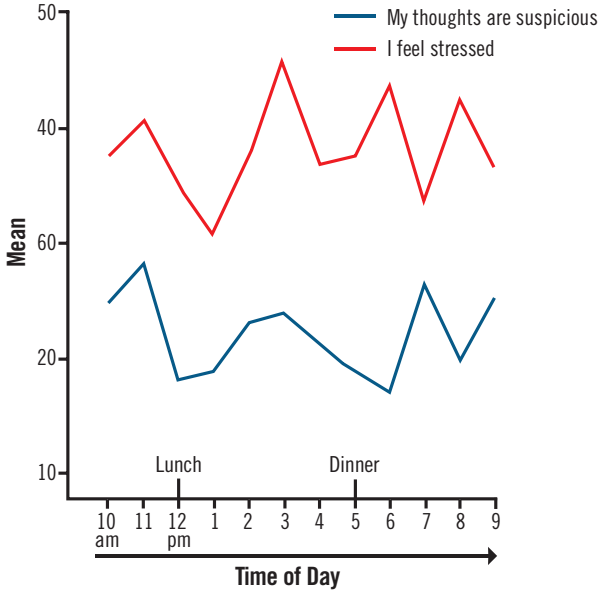
Daily diary methods such as ESM may also be used as a tool to identify in treatment the clinical correlates of psychosis, including cannabis use, during the flow of daily functioning in individuals at high risk of psychosis. Kimhy and colleagues[32] has used ESM with Palm computers to collect information about stress and psychotic symptoms in hospitalized psychotic patients as part of their daily functioning. For example, Figure 2 presents the mean ratings of subjective stress and suspiciousness across time of day in this population. Such information may allow identifying associations between stress, symptoms, and specific activities or social context (in this example, lunch and dinner time on the unit). In this case, lunch and dinner times on the inpatient unit are temporally linked with lower ratings stress and suspiciousness by patients. In particular, use of ESM may elucidate the link between cannabis use and exacerbation of attenuated psychotic symptoms that may not be recognized or recalled retrospectively by patients during treatment session. As such, they may allow clinicians to identify individuals in whom the use of cannabis may increase psychotic symptoms. Kimhy and Corcoran[33] recently published a case report in which ESM with a Palm computer was incorporated into CBT with an individual at clinical high risk of psychosis. The authors of this article are currently developing software for mobile devices that will allow data collection and homework completion as part of CBT treatment.

FIGURE 2

MEAN RATINGS OF SUBJECTIVE STRESS AND SUSPICIOUSNESS ACROSS TIME OF DAY IN HOSPITALIZED PSYCHOTIC PATIENTS



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CONCLUSION

The use of daily diary methods offers a novel and unique way to gather information on the temporal link between cannabis use and psychosis; motivation for use; and the clinical, social and environmental correlates of psychosis. As such, they may inform the discussion about the putative causal role of cannabis use on the initial development of psychosis and schizophrenia. ***PP***

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