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Temporal Association of Cannabis Use with Symptoms in Individuals at Clinical High Risk for Psychosis

Cheryl M Corcoran, MD¹, David Kimhy, PhD¹, Arielle Stanford, MD¹, Shamir Khan, PhD¹, Julie Walsh, BA¹, Judy Thompson, PhD¹, Scott Schobel, MD¹, Jill Harkavy-Friedman, PhD¹, Ray Goetz, MA¹, Tiziano Colibazzi, MD¹, Victoria Cressman, PhD¹, and Dolores Malaspina, MD^{1,2}

¹ Columbia University, Department of Psychiatry, New York, NY

² New York University, Department of Psychiatry, New York, NY

Abstract

Background—Cannabis use is reported to increase the risk for psychosis, but no prospective study has longitudinally examined drug use and symptoms concurrently in clinical high risk cases.

Method—We prospectively followed for up to 2 years 32 cases who met research criteria for prodromal psychosis to examine the relationship between substance use and clinical measures.

Results—Cases with a baseline history of cannabis use (41%) were older, but did not differ in clinical measures. Longitudinal assessments showed these cases had significantly more perceptual disturbances and worse functioning during epochs of increased cannabis use that were unexplained by concurrent use of other drugs or medications.

Conclusions—These data demonstrate that cannabis use may be a risk factor for the exacerbation of sub-threshold psychotic symptoms, specifically perceptual disturbances, in high risk cases.

INTRODUCTION

Cannabis misuse and psychotic disorders are highly comorbid (Regier et al., 1990; Cuffel et al., 1993; Kendler et al., 1996). Evidence suggests that cannabis misuse is not simply a consequence of psychotic illness, as it is prevalent even by the first episode of psychosis, with rates of approximately twenty to forty percent (Pencer et al., 2003; Van Mastrigt et al., 2003; Sevy et al., 2001). However, despite this marked comorbidity and increasing interest in cannabis use as a putative causal risk factor for psychosis and schizophrenia (Moore et al., 2007; Murray et al., 2007), little is known about the co-evolution of cannabis use and symptoms in teens and young adults at heightened risk for psychotic disorder. Understanding this relationship has potentially profound implications as cannabis is one of a few potentially modifiable risk factors of schizophrenia (Arseneault et al., 2004) with an estimated eight percent of the attributable risk for this disorder being accounted for by cannabis use.

Address for correspondence: CM Corcoran MD, New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York 10032 or email cc788@columbia.edu.

Need affiliations: list me as NYU and as Columbia (where I retain adjunct professor)

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In patients with established diagnoses of psychotic disorder, the temporal dynamics of the relationship of cannabis use to psychotic and other symptoms over weeks to months has been evaluated; these studies demonstrate a dose-dependent association of cannabis use with psychotic symptoms, adjusting for potential confounders such as exposures to other drugs, prescribed medications, and stress (Hides et al., 2006). In genetic high risk studies, cannabis use has been associated in cross-section with positive symptoms (Miller et al., 2001), and found to escalate in the months leading to an onset of frank psychosis (Miller et al., 2006). However, no prospective assessment of *both* cannabis use and symptoms *together* has yet been done in young people at elevated clinical risk for psychosis and schizophrenia, despite prevalent cannabis use in many prodromal samples (17% – 37.5%) (Phillips et al., 2002; Rosen et al., 2006; Haroun et al., 2006). Prodromal or clinical high-risk studies are inconclusive as to whether cannabis use at ascertainment can predict later psychosis (Phillips et al., 2002; Kristensen and Cadenhead, 2007), and discrepant results may be explained by a relative lack of interval data on cannabis use in these samples (Phillips et al., 2002).

The demonstration that cannabis use could exacerbate clinical symptoms in high risk subjects, independent of concurrent exposures to medications and other drugs, would have strong implications for early interventions. We hypothesized that cannabis use would be prevalent in our urban prodromal cohort (Hambrecht and Hafner, 1997; Kristensen and Cadenhead, 2007), and would be temporally linked to both psychotic and anxiety symptoms. Specifically, cannabis use was anticipated to fluctuate over time with perceptual disturbances or subthreshold hallucinatory symptoms, consistent with findings from challenge (D'Souza et al., 2004; Koethe et al., 2006), experience sampling (Verdoux et al., 2003) and epidemiologic (Thomas, 1996) studies. These same studies suggest that cannabis use would be related to symptoms of anxiety (Verdoux et al., 2003; D'Souza et al., 2004), which could exacerbate positive symptoms. While these relationships have been demonstrated in patients with established disorders (Hides et al., 2006), they have not been evaluated in a prodromal sample, who remain at heightened risk for psychotic disorder. In this study, we examined the dynamic relationships over time (up to 2 years) between clinical symptoms and drug use in an urban clinical high risk/prodromal sample with prevalent cannabis abuse. We hypothesized that cannabis use would be temporally associated with perceptual disturbances and anxiety.

METHODS

The COPE Prodromal Research Program

The study was conducted at the Center of Prevention and Evaluation (COPE) prodromal research program at the New York State Psychiatric Institute at Columbia University Medical Center. This is an observational cohort study of help-seeking adolescents and young adults considered to be at heightened clinical risk for or prodromal to a nonaffective psychosis. Patients are ascertained generally through referrals from schools and clinicians in the New York metropolitan area and interested participants provide written informed consent (or assent if under 18, plus parental consent). Candidacy for the program is evaluated through interviews with patients and available family and other informants, and from information in available psychiatric and school records. Potential cases are reviewed at weekly meetings and input regarding their disposition is obtained from both research and clinical staff, including a senior child psychiatrist. Eligible cases are invited to enroll in the two year study, which includes a comprehensive baseline evaluation and quarterly assessments of exposures (use of drugs, alcohol and medications), clinical status (positive, negative, depressive, and anxiety symptoms), global function, and potential conversion to psychosis. Participants are offered treatment, including psychotherapy, family supportive education and targeted pharmacotherapy.

Inclusion and Exclusion Criteria

For study inclusion, the subjects must have been between the ages of 12 to 25, English-speaking, and have met criteria for at least one of three prodromal states, as assessed with the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003): 1) attenuated positive symptom syndrome; 2) genetic risk and deterioration syndrome; and/or 3) brief intermittent psychotic syndrome. Attenuated positive symptoms could not have occurred solely in the context of substance abuse or withdrawal (by history). Other exclusion criteria included a history of psychosis, serious risk of harm to self or others, major medical or neurological disorder, and mental retardation ($IQ < 70$, with functional impairment).

Structured Diagnostic Interviews

Structured diagnostic interviews differed by subject age. The Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime Version (K-SADS-PL) was used for patients ages twelve to fifteen years (Kaufman et al., 1997) and the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al 1994) was administered to patients 16 years of age and older. All interviews were conducted by psychiatrists and psychologists with advanced training in diagnosis, and diagnoses were established by consensus with experts on each of these measures. Both diagnostic interviews probe in detail DSM-IV Axis I psychotic, mood, anxiety, and substance use disorders.

Symptoms

Symptom severity was rated using the Scale of Prodromal Symptoms (SOPS) (Miller et al., 2003), which probes positive, negative, disorganized and general symptoms (with factors for positive, negative and disorganized; Hawkins et al., 2004). Positive symptoms include unusual thought content, suspiciousness, grandiosity, perceptual abnormalities and conceptual disorganization; these were rated from 0 (absent) to 6 (psychotic), with a prodromal range considered to lie between 3 and 5. The six negative symptom items also range from 0 to 6, yielding a range of 0 to 36 for total negative symptom score. Anxiety symptoms were evaluated using the Hamilton scale (Hamilton, 1976). The Structured Interview for Prodromal Syndromes includes the modified global assessment of function (mGAF), which has specific anchors within deciles from 0 to 100 (Miller et al., 2003). As described, symptoms and global function scores were evaluated at baseline and quarterly for up to two years. Reliability for the SIPS/SOPS was established with the Recognition and Prevention prodromal research group at Hillside Hospital (ICC's > 0.70 for individual scale items and 1.00 for syndrome ratings.) This is consistent with excellent to near excellent interrater reliability for individual SOPS items (Miller et al., 2003).

Substance Use and Abuse

Patterns of substance use were assessed at baseline and prospectively every three months. Baseline assessments included comprehensive diagnostic assessment of substance misuse disorders with the K-SADS-PL (Kaufman et al., 1999) or the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), depending on the age of the participant. At baseline, all members of the cohort were defined as users vs. nonusers: users were identified as those cases that had dependence diagnoses for tobacco or alcohol, or prior exposure to any other drug of abuse. For baseline and follow-up assessments, an inventory of recent substance use was used to elicit self-report of types and amounts of drugs used within the previous thirty days. Drugs included were alcohol, cannabis, benzodiazepines, other sedative/hypnotics, stimulants, phencyclidine, ketamine, other hallucinogens and other drugs (steroids, solvents/inhalants). Individuals who had never endorsed substance use were queried at follow-up as to whether they had used any substances since the last assessment including tobacco; if so, they were then re-identified as "users". Numbers of cigarettes smoked was not routinely assessed

prospectively. Participants were also queried as to concurrent use of antipsychotics or antidepressants.

Data analysis

The sample was assessed at baseline for exposure to and misuse of drugs. As mentioned, cohort members were defined as users if they had dependence diagnoses for alcohol or tobacco, or prior experimentation with any other drug of abuse. The subgroups of users and nonusers were compared as to demographics, prodromal and mood symptom severity, global function, and exposures to medications, using Student t-tests and chi-square for continuous and categorical variables, respectively. These subgroups were not expected to be different across any of these variables (Stirling et al., 2005).

Over the period of follow-up, any baseline nonusers who then had incident drug use were re-identified as “users”. It was expected based on previous literature that cannabis would be a commonly used drug (Hambrecht and Hafner, 2000; Kristensen and Cadenhead, 2007). Temporal relationships between cannabis use and symptoms (i.e. how use and symptoms covaried over time) were analyzed in the user subgroup using generalized estimating equation (GEE) regression models (Diggle et al., 1994) with the STATA 12.0 statistical package. GEE models account for correlations of repeated measures within individuals and enable the inclusion of all cases, even individuals who have not yet completed all scheduled assessments. Regression coefficients in GEE can be interpreted similarly to those in a standard linear regression model. Intraindividual correlation over time for each model is examined by a correlation matrix; in this study, an exchangeable correlation matrix provided the best fit for each GEE model constructed. GEE regression models were used to evaluate prospective data in the user subgroup for each drug that was used sufficiently frequently (i.e. > 10% of all observations in the dataset). Each GEE model tested the relationship of use of a specific drug to a specific contemporaneous clinical feature (i.e. total and specific positive symptoms, mood symptoms and function), examining first the crude association, and then adjusting for other contemporaneous covariates, such as use of alcohol, other drugs, and medications.

The predictor variables for each regression analysis were days of self-reported drug use in the preceding month, with models for cannabis and any other drugs used sufficiently frequently (as defined earlier). Dependent variables were anxiety and positive symptoms, specifically perceptual disturbances or subthreshold hallucinatory phenomena, and global function. Self-reported exposures to alcohol, other drugs, and medications were included as time-dependent covariates in serial models for each drug-symptom GEE regression model. Medication exposure was determined as yes/no for antipsychotic and antidepressant medications.

For longitudinal analyses, alpha was set at .05 for the hypothesized associations of cannabis use with perceptual disturbances and anxiety. Otherwise there were seven exploratory analyses: associations of drug use with function (Table 2) and five tests of association of cannabis use with total and other positive symptoms (Table 3) and one test of association of cocaine with total positive symptoms (Table 3). Adjusting for Bonferroni correction, the alpha set for these analyses were $.05/7 = .007$.

RESULTS

Baseline assessments

There were 32 consecutive prodromal cases, all of whom met attenuated positive symptom criteria for a prodromal syndrome; 25% also had functional decline and an affected first-degree family member, thereby meeting genetic risk criteria. Thirteen cases were categorized as drug users, i.e. tobacco or alcohol dependence or some experimentation with another drug of abuse.

A history of cannabis and alcohol use characterized all users, with two cases of cannabis abuse and six cases of cannabis dependence in remission (of whom two also had alcohol abuse in remission and another had cocaine abuse in remission). Experimentation was reported for hallucinogens ($n = 6$; 1–2 occasions), cocaine ($n = 2$; 1–5 occasions) and stimulants ($n = 1$; 10 occasions); experimentation occurred primarily in patients with a history of cannabis dependence. No patient endorsed any use of heroin, steroids, or inhalants. Other than for cannabis and tobacco, there were no other drug dependence diagnoses in the sample. Sixteen percent of the overall sample had smoked cigarettes, but only one was a current smoker at baseline assessment. (The low rates of smoking may be due to cigarettes being quite expensive (~\$8 per pack) for this relatively low income cohort.) Of note, rare sips or drinks of alcohol were endorsed by 32% of the nonuser group, who otherwise denied smoking or experimenting with any other drug.

The subgroups of drug users and nonusers were comparable in terms of demographics and clinical variables (Table 1). Both groups were primarily male and ethnically diverse, and had substantial functional impairment, with prevalent mood symptoms. Drug users were significantly older than nonusers. Users also had a higher IQ and a lower prevalence of family history of psychotic disorder, differences which were not statistically significant in this small sample.

Longitudinal analysis

There was no incident drug use observed in the nineteen cases identified as nonusers at baseline; hence, the subgroups of users and nonusers remained discrete over time (consistent with studies which show initiation of cannabis use typically precedes positive symptoms in the prodromal period i.e. Hambrecht and Hafner, 2000). Drug users had an average of 4.1 follow-up assessments, whereas nonusers had an average of 4.4 follow-up assessments.

The follow-up period varied among participants, according to when they entered the study. The thirteen users had a total of fifty-three assessments, with observations per patient ranging from 1 to 8 observations (1 ($n=3$), 2 ($n=1$), 3 ($n=2$), 4 ($n=1$), 5 ($n=2$), 6 ($n=2$), 8 ($n=2$)). All users at follow-up endorsed alcohol or cannabis use. Among users, alcohol use was endorsed in 77.4% of follow-up assessments, with a mean of 3.3 days of reported use (SD 4.2, range 0 – 20) reported for the prior month; in 68% of these assessments for which alcohol use was acknowledged, cannabis use was also endorsed. Cannabis use characterized 60% of follow-up observations, with a mean of 5.7 days (SD 5.1; range 1 – 21) reported for the prior month; in 90% of these assessments for which cannabis was endorsed, alcohol use was also endorsed. By contrast, cocaine use was endorsed for only 11.3% of observations, and was noted to be used only concurrently with alcohol and cannabis. Hallucinogen use was relatively rare, reported in 5.7% of observations. No other drug use was reported. Interval data on cigarette smoking was not systematically ascertained.

GEE regression models were developed to examine the main hypotheses of a temporal association of cannabis “dose” (reported days of recent use) with subacute perceptual disturbances and anxiety, accounting for the intraindividual correlation of repeated measures and exposures to other drugs and medications. As hypothesized, perceptual disturbances were temporally related to cannabis use, an association which could not be accounted for by concurrent exposures to alcohol, other drugs or antipsychotic medications (Table 2). Likewise, anxiety symptoms were greater with time-limited increases in cannabis use, although this association did not survive adjustment for concurrent exposure to medication (Table 2). Of note, among users, anxiety and perceptual disturbances were significantly temporally associated ($p < .001$). Global function was worse during quarters in which recent cannabis use was endorsed an effect also found for cocaine use (Table 2).

Posthoc analyses showed no temporal association of cannabis with other positive symptoms, either separately or as a total score, or of cocaine with positive symptoms (Table 3).

DISCUSSION

In this urban cohort of young people identified as prodromal for psychosis, self-reported cannabis use was prevalent, characterizing 41% of the sample; alcohol was also frequently used, whereas tobacco, stimulants and hallucinogens were less commonly used. Cannabis-using cases were significantly older, but were otherwise similar to other prodromal cases, including on severity of positive, negative and affective symptoms, and in level of functional impairment. It was only in longitudinal study that an association of cannabis use with symptoms was evident. Specifically, cannabis use was temporally associated with subthreshold hallucinatory phenomena, or perceptual disturbances, in a dose-dependent fashion, even when adjusting for exposure to alcohol, cocaine, or medications. No other drugs of abuse had a contemporaneous association with symptoms, though functional impairment was temporally associated with increased use of both cannabis and cocaine. Cannabis use also was related to time-limited increases in anxiety.

To our knowledge, this is the first study in prodromal or clinical high risk cases which closely examines episodic use of cannabis and its relationship to fluctuations over time in symptoms. Our repeated-measures design is very close to that of a longitudinal study in patients with recent-onset psychosis (Hides et al., 2006), in which contemporaneous exposures to stress, other drugs, and psychoactive medications were documented, yet could not explain an association of cannabis use and psychotic symptoms. (These authors aggregated unusual thought content, hallucinations, and conceptual disorganization, and so it is not known if any of these specific psychotic symptoms were associated with cannabis use.) Thus, our data add to this literature by demonstrating that temporal associations of cannabis use and psychotic-like symptoms occur even before the onset of frank psychotic symptoms in high risk individuals.

Of note, an association of cannabis exposure with symptom severity was not evident in cross-section at baseline, and associations only became evident when within-subject comparisons were made. In our study, users and nonusers were similar on demographic and clinical characteristics at baseline, as well as in conversion rates to psychosis. Their striking resemblance suggests that the positive symptoms observed among drug users are not simply a phenocopy of an emerging primary psychotic disorder. Our cohort also resembles those which have younger patients and less substance use, with prevalent mood and anxiety symptoms, serious impairment in global function and previous medication exposure (Preda et al., 2002; Lencz et al., 2004; Meyer et al., 2005). Nearly all prodromal patients have attenuated psychotic symptoms, and may develop these features as a consequence of different causal factors, consistent with heterogeneity. Therefore, it is not surprising that we found a trend toward greater prevalence of family history in those prodromal patients who had not experimented with drugs or smoked cigarettes or become dependent on alcohol. Overall, our prodromal cohort was very similar to that described in Kristensen and Cadenhead (2007), ascertained from an urban area in the US, comparable in age, patterns of drug use and conversion rates to psychosis. Their discrepant finding of greater symptom severity and higher conversion rates to psychosis among baseline cannabis users may be secondary to differences in ascertainment of prodromal subjects.

The use of other drugs was also evaluated. Alcohol use was common, but bore no relationship to symptoms or function. Cocaine use, far less frequent, was temporally associated with lower function only. Amphetamines and hallucinogens were not used sufficiently to be examined for relationships to clinical symptoms. The specific association of cannabis with symptoms may

be an issue of statistical power, as other drugs of abuse are also known to stimulate striatal dopamine. Consistent with our data, use of cannabis, but not alcohol or cocaine, was associated with psychosis in a similar prodromal cohort, and amphetamine use was too infrequent to evaluate (Kristensen and Cadenhead, 2007). Of interest, in that cohort, tobacco use was also a predictor of conversion to psychosis. Unfortunately, tobacco use was not prospectively assessed in the current study.

As hypothesized, cannabis use was temporally associated with specifically subthreshold hallucinatory symptoms, consistent with challenge (D'Souza et al., 2004; Koethe et al., 2006), experience sampling (Verdoux et al., 2003) and epidemiologic (Thomas, 1996) studies. This association held even when controlling for concurrent exposures to other drugs and medication. Hence it does not appear that cannabis, if contributing to the development of positive symptoms, does so only through increasing medication noncompliance or exposure to other drugs. However, the clinical relevance of perceptual disturbances *per se* as a specific predictor of psychotic disorder has not been established (Cannon et al., 2008; Yung et al., 2004).

Although cultural stereotypes and population sampling (Thomas, 1996) would suggest a temporal association of cannabis use with suspiciousness, this was not observed in this study. There are several possible explanations for this lack of association, including insufficient statistical power to detect a smaller effect. Alternatively, perceptual disturbances may be more discrete, salient and easily recalled. Suspiciousness is a more common characteristic of a putatively prodromal state, and its changes may be less likely to be noted or reported.

As hypothesized, cannabis use was related to increased anxiety, as has been demonstrated in experience sampling (Verdoux et al., 2003) and challenge (D'Souza et al., 2004) studies, though this effect did not survive controlling for use of psychiatric medication. Anxiety was highly temporally correlated with subthreshold hallucinatory phenomena, which is consistent either with anxiety mediating their association, or alternatively confounding their association (i.e. increased anxiety leads to both psychotic-like symptoms and increased use of cannabis). However, anecdotally, participants in the study reported that they typically used cannabis when they felt better and were in a social setting, with negative effects then consequent to use.

The probing for an association of cannabis use with subthreshold symptoms and function in prodromal patients was for "proof of principle", i.e. to test whether cannabis use and clinical variables covary over time in a clinically relevant well-characterized sample with minimal medication and illness duration effects, while considering other factors such as exposures to other drugs and medications. The design of this study is such that it can only determine association, not causation. However, it should be noted that there was no incident use of cannabis among baseline nonusers, which would be unlikely if psychotic-like symptoms were to lead to cannabis use. Also, as mentioned, patients reported using cannabis typically when prodromal symptoms were improved or remitted, and they were in social settings where cannabis was available. They reported accepting the offer of a joint to feel more at ease and be more effective socially. Increases in anxiety and positive symptoms subsequently occurred over the following few days.

There is sufficient evidence from the literature to support a psychotogenic role for cannabis, including challenge studies (D'Souza et al., 2004; Koethe et al., 2006) and experience sampling studies which employ time-lag analyses (Verdoux et al., 2003). In a case report of a "self-induced" challenge study, a drug-free schizophrenia patient surreptitiously smoked cannabis during a pause in PET imaging, and had a worsening of psychotic symptoms within hours (Voruganti et al., 2001). The mechanism of this increased psychosis after smoking cannabis in this patient was suggested by an immediate 20% decrease in striatal D2 receptor binding of

the radioligand on PET scan (consistent with increased endogenous dopamine). As mentioned, however, the clinical relevance of perceptual disturbances as a predictor of psychotic disorder has not been established (Yung et al., 2004; Cannon et al., 2008).

Cohort studies suggest an association of adolescent cannabis use with clinically relevant psychotic symptoms and diagnosis years later, as reviewed recently in Lancet (Moore et al., 2007). One report indicated that cannabis use initiated by age 15 was more strongly associated with schizophreniform disorder at age 26 than cannabis use initiated later, by age 18 (Arseneault et al., 2002). This finding has been interpreted to mean that there may be a critical developmental window during adolescence when cannabis exposure contributes to the etiology of schizophrenia. An alternative possibility, offered by the authors of this cohort study themselves, is that earlier onset of cannabis use may be associated with later more extensive use of cannabis, i.e. a larger dose. These two alternatives have very different implications for 1) our understanding of the pathophysiology of psychotic disorders and 2) for the possibility of intervening to prevent psychosis in putatively prodromal young people who already use cannabis.

In the current study, we observed not only that positive and anxiety symptoms worsen during times of increased cannabis use, but that they improved or even remitted when young people ceased use. The prodromal period is often assumed to be marked by an insidious decline, yet remissions (Haroun et al, 2006) and fluctuations in symptoms do occur. We have demonstrated that cannabis use and positive symptoms fluctuate together over time. Ebbs and flows of positive symptoms may track exposures to other mutable risk and protective factors. Hence, an understanding of why these clinical high risk young people use cannabis could inform the development of preventive interventions to reduce exposure and delay or possibly prevent psychosis onset.

Strengths and Limitations

The longitudinal design of this study is its strength, as it enabled the discovery of an association between cannabis use and clinical features only when differences between subjects could be accounted for in analysis. Further, the use of time-dependent covariates addressed the problem of potential confounds (i.e. alcohol, other drugs, medications). In addition, cases were diagnosed using rigorous criteria and drop out rates were low. The study sample was ethnically diverse, which adds to the generalizability of our findings.

Limitations include a small sample size with possible Type 2 error for detecting associations of use of different drugs with clinical characteristics. The minimum detectable beta is 0.4 in this study, for standard errors of $\sim .10$ (see table 2) and a variance inflation factor of two (given a mean of 4 repeated measures and an ICC of 0.3 for anxiety and perceptual disturbances, obtained using xtreg in STATA). Also, the specificity of associations to a prodromal cohort is unclear, as there were no normal controls. Assessment of drug use depended on self-report and was not confirmed by urine toxicology. However, in a similar prodromal cohort, urine toxicology did not reveal any covert use of cannabis (Kristensen and Cadenhead, 2007). Unfortunately, tobacco use was not prospectively assessed. Also, unlike the study of recent onset psychosis (Hides et al., 2006), in which patients were assessed weekly, the three month interval in the current study did not permit time-lag analyses to explore causal direction between cannabis use and symptoms. Other limitations include no systematic assessment of motives for drug use.

Future directions

A larger study would further clarify the association of cannabis and other drug use with specific symptoms and function in young people at heightened risk for psychosis. Systematic

assessment of motivations for use could inform the development of interventions to reduce drug use in these high-risk adolescents and young adults. Biological assays could shed light on putative markers of vulnerability to the psychotogenic effects of cannabis, such as allelic variants of the catechol-O-methyl transferase (COMT) gene (Caspi et al., 2005; Henquet et al., 2006). Mechanisms could be evaluated through PET imaging of striatal dopamine in conjunction with challenge studies in clinical high risk patients.

Conclusion

This is the first study to prospectively evaluate temporal associations of cannabis and other drug use with symptoms and function in a clinical high risk cohort of young people. As hypothesized, cannabis use was temporally associated with anxiety and positive symptoms, specifically subthreshold hallucinatory phenomena. Adjustment for potential concurrent confounders such as exposures to other drugs and medications did not change the association of cannabis with this positive symptom. Fluctuations in symptoms tracked changes in cannabis use, which suggests that cannabis has psychotogenic effects in a putatively prodromal sample. Cannabis use may be a potentially modifiable proximal risk factor for clinically relevant psychotic symptoms. Understanding motivations for its use in these vulnerable young people can inform the development of preventive interventions. Further, a close temporal correlation of cannabis use and symptoms in a high-risk cohort informs theories of pathophysiology, and offers evidence contrary to that expected with a hypothesis of a critical developmental window for cannabis exposure.

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References

- Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. *Br J Psychiatry* 2004;184:110–117. [PubMed: 14754822]
- Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* 2002;325:1212–1213. [PubMed: 12446537]
- Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T, Heinssen R. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry* 2008;65(1):28–37. [PubMed: 18180426]
- Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol Psychiatry* 2005;57(10):1117–1127. [PubMed: 15866551]
- Cuffel BJ, Heithoff KA, Lawson W. Correlates of patterns of substance abuse among patients with schizophrenia. *Hosp Community Psychiatry* 1993;44(3):247–251. [PubMed: 8444435]
- Diggle, PJ.; Liang, KY.; Zeger, SL. *Analysis of Longitudinal Data*. Oxford: Clarendon Press; 1994.

- D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 2004;29(8):1558–1572. [PubMed: 15173844]
- Hambrecht M, Häfner H. Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. *Aust N Z J Psychiatry* 2000;34(3):468–75. [PubMed: 10881971]
- Hamilton, M. Hamilton Anxiety Scale. In: Guy, W., editor. *ECDEU Assessment Manual for Psychopharmacology*. NIMH; Rockville, MD: 1976.
- Haroun N, Dunn L, Haroun ACadenhead KS. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. *Schizophr Bull* 2006;32(1):166–78. [PubMed: 16207892]
- Hawkins KA, McGlashan TH, Quinlan D, Miller TJ, Perkins DO, Zipursky RB, Addington J, Woods SW. Factorial structure of the Scale of Prodromal Symptoms. *Schizophr Res* 2004;68(2–3):339–47. [PubMed: 15099615]
- Henquet C, Rosa A, Krabbendam L, Papiol S, Fananas L, Drukker M, Ramaekers JG, van Os J. An Experimental Study of Catechol-O-Methyltransferase Val(158)Met Moderation of Delta-9-Tetrahydrocannabinol-Induced Effects on Psychosis and Cognition. *Neuropsychopharmacology* 2006;31(12):2748–57. [PubMed: 16936704]
- Hides L, Dawe S, Kavanagh DJ, Young RM. Psychotic symptom and cannabis relapse in recent-onset psychosis. Prospective study. *Br J Psychiatry* 2006;189:137–143. [PubMed: 16880483]
- Haroun N, Dunn L, Haroun ACadenhead KS. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. *Schizophr Bull* 2006;32:166–178. [PubMed: 16207892]
- Lencz T, Smith CW, Auther A, Correll CU, Cornblatt B. Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. *Schizophr Res* 2004;68(1):37–48. [PubMed: 15037338]
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980–8. [PubMed: 9204677]
- Kendler KS, Gallagher TJ, Abelson JM, Kessler RC. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample. The National Comorbidity Survey. *Arch Gen Psychiatry* 1996;53(11):1022–1031. [PubMed: 8911225]
- Kristensen K, Cadenhead KS. Cannabis abuse and risk for psychosis in a prodromal sample. *Psychiatry Res* 2007;15(1–2):151–4. [PubMed: 17383738]
- Koethe D, Gerth CW, Neatby MA, Haensel A, Thies M, Schneider U, Emrich HM, Klosterkötter J, Schultze-Lutter F, Leweke FM. Disturbances of visual information processing in early states of psychosis and experimental delta-9-tetrahydrocannabinol altered states of consciousness. *Schizophr Res* 2006;88(1–3):142–50. [PubMed: 17005373]
- Lencz T, Smith CW, Auther A, Correll CU, Cornblatt B. Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. *Schizophr Res* 2004;68:37–48. [PubMed: 15037338]
- Meyer SE, Bearden CE, Lux SR, Gordon JL, Johnson JK, O'Brien MP, Niendam TA, Loewy RL, Ventura J, Cannon TD. The psychosis prodrome in adolescent patients viewed through the lens of DSM-IV. *J Child Adolesc Psychopharmacol* 2005;15(3):434–51. [PubMed: 16092909]
- Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, McFarlane W, Perkins DO, Pearlson GD, Woods SW. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull* 2003;29(4):703–15. [PubMed: 14989408]
- Miller P, Lawrie SM, Hodges A, Clafferty R, Cosway R, Johnstone EC. Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 2001;36(7):338–42. [PubMed: 11606002]

- Miller PM, Johnstone EC, Lawrie SM, Owens DGC. Substance use, psychiatric symptoms and the onset of schizophrenic illness. *Journal of Substance Abuse* 2006;11(2):101–113.
- Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007;370:319–28. [PubMed: 17662880]
- Murray RM, Morrison PD, Henquet C, Di Forti M. Cannabis, the mind and society: the hash realities. *Nat Rev Neurosci* 2007;8(11):885–95. [PubMed: 17925811]
- Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry* 1994;51(11):849–859. [PubMed: 7944874]
- Pencer A, Addington J. Substance use and cognition in early psychosis. *J Psychiatry Neurosci* 2003;28(1):48–54. [PubMed: 12587850]
- Phillips LJ, Curry C, Yung AR, Yuen HP, Adlard S, McGorry PD. Cannabis use is not associated with the development of psychosis in an ‘ultra’ high-risk group. *Aust N Z J Psychiatry* 2002;36(6):800–806. [PubMed: 12406123]
- Preda A, Miller TJ, Rosen JL, Somjee L, McGlashan TH, Woods SW. Treatment histories of patients with a syndrome putatively prodromal to schizophrenia. *Psychiatr Serv* 2002;53(3):342–344. [PubMed: 11875232]
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990;264(19):2511–2518. [PubMed: 2232018]
- Rosen JL, Miller TJ, D’Andrea JT, McGlashan TH, Woods SW. Comorbid diagnoses in patients meeting criteria for the schizophrenia prodrome. *Schizophr Res* 2006;85:124–131. [PubMed: 16650735]
- Sevy S, Robinson DG, Holloway S, Alvir JM, Woerner MG, Bilder R, Goldman R, Lieberman J, Kane J. Correlates of substance misuse in patients with first-episode schizophrenia and schizoaffective disorder. *Acta Psychiatr Scand* 2001;104(5):367–374. [PubMed: 11722318]
- Stirling J, Lewis S, Hopkins R, White C. Cannabis use prior to first onset psychosis predicts spared neurocognition at 10-year follow-up. *Schizophr Res* 2005;75:135–137. [PubMed: 15820332]
- Thomas H. A community survey of adverse effects of cannabis use. *Drug Alcohol Depend* 1996;42(3):201–20. [PubMed: 8912803]
- Van Mastrigt S, Addington J, Addington D. Substance misuse at presentation to an early psychosis program. *Soc Psychiatry Epidemiol* 2003;156(4):319–327.
- Verdoux H, Gindre C, Sorbara F, Tournier M, Swendsen JD. Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. *Psychol Med* 2003;33(1):23–32. [PubMed: 12537033]
- Voruganti LN, Slomka P, Zabel P, Mattar A, Awad AG. Cannabis induced dopamine release: an in-vivo SPECT study. *Psychiatry Res* 2001;107(3):173–177. [PubMed: 11566433]
- Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res* 2004;67(2–3):131–42. [PubMed: 14984872]

TABLE 1
BASELINE COMPARISON OF DRUG USERS AND NONUSERS

Characteristic	Users (N = 13)	Nonusers (N = 19)
Age [*]	20.9 (2.8)	17.4 (3.4)
Sex (% male)	84.6%	78.9%
Ethnicity (% White)	46.2%	42.1%
Family history of psychosis (%) [‡]	7.7%	36.8%
IQ (Full scale) [‡]	108.4 (18.1)	94.8 (21.7)
SIPS/SOPS positive symptoms	15.3 (4.2)	12.7 (4.6)
Unusual thought content	4.2 (1.4)	3.5 (1.0)
Suspiciousness	3.2 (1.3)	2.7 (1.3)
Grandiosity [‡]	2.5 (1.6)	1.5 (1.5)
Perceptual abnormalities	2.8 (2.0)	2.7 (1.7)
Conceptual disorganization	2.6 (1.5)	2.3 (1.5)
SIPS/SOPS negative symptoms	11.9 (4.7)	14.6 (6.5)
Depression	10.5 (6.5)	10.2 (5.8)
Anxiety	6.9 (4.4)	8.5 (5.8)
Global function (GAF)	44.3 (8.6)	44.4 (6.1)
Antipsychotic use at baseline	30.8%	31.6%
Antidepressant use at baseline	23.1%	47.4%

^{*} p < .01

[‡] .05 < p < .10

TABLE 2
HYPOTHESIS-DRIVEN LONGITUDINAL ANALYSES

Perceptual disturbances			Anxiety		Global Function	
	β (se)	p	β (se)	p	β (se)	p
Crude model						
Cannabis use	.10 (.05)	.06	.33 (0.14)	.017	-.74 (0.27)	.006
Between-subject	1.41 (.33)	< .001	4.50 (0.98)	< .001	52.25 (2.25)	< .001
Full model						
Cannabis use	.13 (.05)	.07	.13 (0.13)	.31	-.64 (0.26)	.016
Alcohol use	-.07 (.05)	.21	.02 (0.15)	.89	.64 (0.27)	.017
Cocaine use	-.17 (.27)	.52	.19 (0.82)	.82	-3.03 (1.33)	.02
Antipsychotic	.75 (.52)	.15	1.15 (1.28)	.37	.35 (2.91)	.90
Antidepressant	-1.20 (.64)	.06	5.41 (1.19)	< .001	-5.49 (4.07)	.18
Anxiety	.15 (.05)	.002			-0.69 (0.24)	.004
Between-subject	.69 (.39)	.08	2.95 (0.32)	< .001	55.80 (2.45)	< .001
Crude model						
Cannabis use						
Between-subject						
Full model						
Cannabis use						
Alcohol use						
Cocaine use						
Antipsychotic						
Antidepressant						
Anxiety						
Between-subject						

TABLE 3
EXPLORATORY LONGITUDINAL ANALYSES

Scale of Prodromal Symptoms(with modified GAF)	Cannabis	
	β (se)	p
Total Positive Symptoms	.06 (.16)	.69
Overvalued Ideas	.003(.05)	.96
Suspiciousness	-.02 (.04)	.58
Grandiosity	.01 (.04)	.77
Conceptual Disorganization	.03 (.04)	.48
	Cocaine	
	β (se)	p
Total Positive Symptoms	-.27 (.95)	.78