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Brief report

Cannabis abuse and risk for psychosis in a prodromal sample

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Abstract

The goal of the present study was to examine the rate of cannabis use among participants in the Cognitive Assessment and Risk Evaluation (CARE) Program, a longitudinal program for individuals who are "at risk" for developing a psychotic disorder. Cannabis abuse was assessed in 48 individuals identified as at risk for psychosis based on subsyndromal psychotic symptoms and/or family history. At 1 year follow-up, 6 of the 48 (12.5%) at risk subjects had made the transition to psychosis. Of the 32 subjects who had no use or minimal cannabis use, one subject (3.1%) converted to psychosis. Of the 16 subjects who met criteria for cannabis abuse/dependence, five (31.3%) converted to psychosis. The results show a significant association between cannabis abuse and conversion to psychosis in this sample. Nicotine use was also found to be significantly associated with later conversion. The significant associations between cannabis and nicotine abuse and conversion to psychosis in individuals at risk for schizophrenia suggest that early identification and intervention programs should screen for and provide education about the deleterious effects of these substances.

Keywords: Prodrome; Marijuana; Schizophrenia; Substance use; At risk; Nicotine

1. Introduction

Epidemiological studies have shown an association between cannabis abuse and psychosis (Andreasson et al., 1987; Regier et al., 1990; Hambrecht and Hafner, 1996; Cantwell et al., 1999; Arseneault et al., 2002; Zammit et al., 2002). Recent literature reviews and meta-analyses (Arseneault et al., 2004; Semple et al., 2005) suggest that cannabis "use" (not necessarily "abuse" or "misuse") confers an overall two to three-fold increase in the relative risk for later schizophrenia. Additionally, the risk of developing schizophrenia increases with heavier (Smit et al., 2004) and earlier cannabis use (Arseneault et al., 2002).

Cannabis abuse may be responsible for one to two new cases of schizophrenia per 1000 people per year while the vast majority of cannabis abusers will not proceed to frank psychosis (Weiser et al., 2005). It is possible that cannabis use confers a greater risk for the later development of a psychotic illness in individuals who are already "at risk" for schizophrenia based on the presence of subsyndromal psychotic symptoms, a family history of schizophrenia and/or a recent deterioration in global functioning (Haroun et al., 2006).

The goal of the present study was to examine the rate of cannabis use among participants in the Cognitive Assessment and Risk Evaluation (CARE) Program, a longitudinal program for individuals who are at risk for developing a psychotic disorder. The primary aim of the

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CARE Program is to predict which individuals are at greatest risk for developing psychosis using a combination of clinical, familial and vulnerability marker risk assessment. Haroun et al. (2006) previously reported on a subset of the sample used in this report and showed that those individuals who developed psychosis had significantly higher clinical ratings at baseline (delusional-like experiences, suspiciousness and thought disorder). The converted group was more likely to have taken an antipsychotic agent and less likely to have a family history of psychosis in a first-degree relative. Additionally, the group who converted to psychosis was more likely to have a history of substance abuse or dependence.

The current report further explores the association of substance abuse to conversion to psychosis in this sample. We hypothesized that a history of cannabis use would increase the risk for psychosis because of the above-mentioned studies.

2. Methods

2.1. Participants

Participants included 48 (26M/22F) individuals between the ages of 12 and 30 (mean age = 18.6 years, S.D. = 4.2) who met the CARE criteria (Seeber and Cadenhead, 2005) for being at risk for schizophrenia and had participated in the study for a minimum of 1 year. All subjects were administered the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003) and met at least one of three at-risk states, as described in Table 1. The original sample, recruited between 2000 and 2005, included 62 subjects, but 13 were lost to follow-up before 1 year, and one was missing cannabis use history.

Subjects with a history of a DSM-IV psychotic disorder (psychotic mood disorder or schizophrenia), a neurological disorder or a serious head injury were excluded. Subjects who met DSM-IV criteria for drug or alcohol dependence at the time of initial evaluation were excluded because of the risk of affecting psychophysiological and neuropsychological test measures. Sixteen subjects reported a lifetime history of cannabis abuse ($n = 15$) or dependence in remission ($n = 1$). Of those who had a cannabis abuse or dependence history, five also met criteria for alcohol abuse and two for alcohol dependence in remission. Two of these subjects (who had misused both cannabis and alcohol) also had a history of amphetamine abuse or dependence. One subject who did not meet cannabis abuse or dependence met DSM-IV criteria for alcohol dependence in remission. Eight of the 48 subjects smoked cigarettes (amount of nicotine smoked ranged from 0.125 to 1.5 packs per day). Subjects who used illicit drugs (with the exception of cannabis) within 30 days of the initial assessment were excluded. Seven subjects reported having used cannabis in the month before to the initial assessment, and all denied intoxication at time of evaluation.

Subjects were recruited through health services, public schools and colleges in the community of San Diego and were seen in the CARE Program, which is located within the Outpatient Psychiatry Clinic at UCSD. All subjects signed written informed consent (UCSD IRB#050650) to participate in a 2-year longitudinal study after the procedures were fully explained.

2.2. Procedure

All potential subjects were given a preliminary screen in which presenting symptoms were assessed and/or entry criteria were reviewed. Demographic information including age, education, family history of psychiatric illness, medical history, psychiatric history and medication history was also obtained. Subjects who met the preliminary entry criteria received a more extensive intake diagnostic interview. The SIPS was used to assess prodromal symptoms. The Structured

Table 1
Criteria for at risk states in the Cognitive Assessment and Risk Evaluation (CARE) Program

At risk groups
Brief psychosis group
●Severity scale score of 6 on one item P1–P5 [a] or D1–D4 [b] from the SIPS.
●Frequency <1 h and <3–6×/week or >1 h and <2×/week.
●Each episode of symptoms is present for less than 1 week, and symptoms spontaneously remit on every occasion.
●Symptoms began or worsened in the last year.
Subsyndromal group
●Severity scale score of 3–5 on one item P1–P5 or D1–D4 from the SIPS.
●Frequency at least 1× in the past month.
●Symptoms began or worsened in the last year.
Genetic risk and deterioration group
●Family history of psychosis in first-degree relative OR schizotypal personality disorder in identified subject.
●Deterioration in functioning and/or mood, anxiety or deficit symptoms.
●Symptoms began or worsened in the last year.

[a] P1–P5 — Psychosis items 1 through 5 from the Structured Interview for Prodromal Symptoms (SIPS).
[b] D1–D5 — Disorganized items 1 through 5 from the SIPS.

Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1995) or the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL) (if under 18) (Kaufman et al., 1996) was used to assess Axis I disorders, including substance use disorders. The Family History RDC (Andreasen et al., 1977) was used to determine family psychiatric history.

Study participants received clinical assessment interviews on a monthly basis to determine whether they were beginning to show signs of psychosis or other symptoms, including substance use. Participation in this study did not preclude individuals from receiving psychotropic or antipsychotic treatment. If study participants showed symptoms that caused significant distress and/or affected current functioning (e.g. school, work, family, peer relations), they were referred for additional services (e.g. individual or group psychotherapy, medication consultation with a psychiatrist) (Haroun et al., 2006).

The 48 subjects were divided into two groups based on lifetime cannabis use: 1) those with no cannabis use or minimal use without impairment ($n=32$) or 2) those who met criteria for abuse or dependence in remission, per DSM-IV criteria ($n=16$). During subsequent monthly clinical assessment interviews, subjects were asked about any drug use since the last contact. All subjects received a urine toxicology screen at initial testing and at 6-month testing intervals. Six subjects tested positive for cannabis during the course of the study and all of those were in Group 2.

2.3. Statistical analysis

Statistical analyses were performed using SPSS 10.0 for Windows. Non-parametric statistics were used to assess the relationship of cannabis abuse to risk for developing psychosis within 1 year. Demographic data were compared by *t*-tests. Discrete variables were analyzed using Fisher's Exact Test. Results were considered statistically significant when the corresponding *P*-value was 0.05 or less by two-tailed analysis.

3. Results

Groups 1 and 2 did not differ significantly in education, baseline SIPS ratings, family history of psychosis in a first-degree relative, abuse of other drugs or use of antipsychotic medication at baseline. Males were significantly more likely than females to abuse cannabis (Fisher's Exact Test $P=0.013$). Those who abused cannabis were significantly older than those who had little or no cannabis use (mean age=20.6 (S.D.=3.0) versus mean age=17.6 (S.D.=4.4), respectively, $t[46]=-2.409$, $P=0.02$).

At 1-year follow-up, six of the 48 (12.5%) at-risk subjects had made the transition to psychosis. Of those who became psychotic, three met criteria for schizophrenia, two for schizoaffective disorder, and one for bipolar mania with psychotic features (Haroun et al., 2006). Of the 32 subjects who had no use or minimal cannabis use (Group 1), one subject (3.1%) converted to psychosis. Of the 16 subjects who met criteria for cannabis abuse/dependence (Group 2), five (31.3%) converted to psychosis. The results show a significant association between cannabis abuse and conversion to psychosis in this sample (Fisher's Exact Test $P=0.012$). Three of the six subjects who tested positive for cannabis during the course of the study converted to psychosis.

Further analyses show that abuse/dependence of alcohol or cocaine was not associated with conversion to psychosis (amphetamine was not analyzed since only two subjects used it, and neither of those two converted). Nicotine use was found to be significantly associated with later conversion to psychosis (Fisher's Exact Test $P=0.005$). Eight of the 48 subjects smoked cigarettes. Seven of the eight cigarette smokers also used cannabis. Four of the six subjects who converted to psychosis smoked both cigarettes and cannabis.

4. Discussion

Individuals at high risk for psychosis, based on empirically derived criteria for the schizophrenia prodrome, were more likely to develop psychosis within 1 year if they had also abused cannabis and nicotine. In a similar sample of "ultra high risk" subjects, Yung et al. (2004) did not find this association between conversion to psychosis and cannabis abuse, but the fact that their sample had a relatively low base rate of cannabis use may explain the negative finding.

Research findings are mixed with regard to the role of nicotine and conversion to psychosis. Cannabis use is more common in cigarette smokers (Lewinsohn et al., 1999). In a historical-prospective cohort study of Israeli military recruits, Weiser et al. (2004) found that the risk for schizophrenia was higher in adolescents who smoked at least one cigarette a day. There was also a significant association between the number of cigarettes smoked and the risk of schizophrenia, with heavier smoking being associated with greater risk for schizophrenia. However, in their investigation of a cohort of Swedish conscripts, Zammit et al. (2003)

found a lower risk of schizophrenia in cigarette smokers. Due to our small sample size, it is not possible to know whether nicotine or cannabis use or some other variables like sex or age accounted for the conversion to psychosis.

The present findings are limited due to the small sample size and reliance on self-report measures of cannabis use. Future studies with larger sample sizes, specific information about age of first drug use and more frequent drug-testing may help to further elucidate the observed association between cannabis use and risk of psychosis. Additionally, a larger sample size will allow us to explore the association of other risk factors such as smoking to cannabis abuse and future psychosis.

Based on the current findings, however, we recommend vigorously screening and monitoring for potential cannabis use in at-risk subjects. Psychoeducation regarding the deleterious effects of cannabis use in vulnerable individuals could discourage use, and perhaps improve outcome.

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References

Andreasen, N.C., Endicott, J., Spitzer, R.L., Winokur, G., 1977. The family history method using diagnostic criteria: reliability and validity. Archives of General Psychiatry 34, 1229–1235.

Andreasson, S., Allebeck, P., Engstrom, A., Rydberg, U., 1987. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet 2, 1483–1486.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., Moffitt, T.E., 2002. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. British Medical Journal 325, 1212–1213.

Arseneault, L., Cannon, M., Witton, J., Murray, R.M., 2004. Causal association between cannabis and psychosis: examination of the evidence. British Journal of Psychiatry 184, 110–117.

Cantwell, R., Brewin, J., Glazebrook, C., Dalkin, T., Fox, R., Medley, I., Harrison, G., 1999. Prevalence of substance misuse in first-episode psychosis. British Journal of Psychiatry 174, 150–153.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders— Patient Edition (SCID-I/P, Version 2.0). Biometrics Research Department, New York State Psychiatric Institute, New York.

Hambrecht, M., Hafner, H., 1996. Substance abuse and the onset of schizophrenia. Biological Psychiatry 40, 1155–1163.

Haroun, N., Dunn, L., Haroun, A., Cadenhead, K.S., 2006. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. Schizophrenia Bulletin 32, 166–178.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Ryan, N., 1996. Kiddie-SADS-Present and Lifetime Version (K-SADS-PL, Version 1.0). University of Pittsburgh, School of Medicine, Pittsburgh.

Lewinsohn, P.M., Rohde, P., Brown, R.A., 1999. Level of current and past adolescent cigarette smoking as predictors of future substance use disorders in young adulthood. Addiction 94, 913–921.

Miller, T.J., McGlashan, T.H., Rosen, J.L., Cadenhead, K., Cannon, T., Ventura, J., McFarlane, W., Perkins, D.O., Pearlson, G.D., Woods, S.W., 2003. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophrenia Bulletin 29, 703–715.

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., Goodwin, F.K., 1990. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. Journal of the American Medical Association 264, 2511–2518.

Seeber, K., Cadenhead, K.S., 2005. How does studying schizotypal personality disorder inform us about the prodrome of schizophrenia? Current Psychiatry Reports 7, 41–50.

Semple, D.M., McIntosh, A.M., Lawrie, S.M., 2005. Cannabis as a risk factor for psychosis: systematic review. Journal of Psychopharmacology 19, 187–194.

Smit, F., Bolier, L., Cuijpers, P., 2004. Cannabis use and the risk of later schizophrenia: a review. Addiction 99, 425–430.

Weiser, M., Reichenberg, A., Grotto, I., Yasvitzky, R., Rabinowitz, J., Lubin, G., Nahon, D., Knobler, H.Y., Davidson, M., 2004. Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. American Journal of Psychiatry 161, 1219–1223.

Weiser, M., Davidson, M., Noy, S., 2005. Comments on risk for schizophrenia. Schizophrenia Research 79, 15–21.

Yung, A.R., Phillips, L.J., Yuen, H.P., McGorry, P.D., 2004. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophrenia Research 67, 131–142.

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., Lewis, G., 2002. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. British Medical Journal 325, 1199.

Zammit, S., Allebeck, P., Dalman, C., Lundberg, I., Hemmingsson, T., Lewis, G., 2003. Investigating the association between cigarette smoking and schizophrenia in a cohort study. American Journal of Psychiatry 160, 2216–2221.