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Effects of extended cannabis abstinence on clinical symptoms in cannabis dependent schizophrenia patients versus non-psychiatric controls

Rachel A. Rabin [a,b,*], Karolina Kozak [a,b], Konstantine K. Zakzanis [c], Gary Remington [a,b,d,e,f], Tony P. George [a,b,d,f]

[a] The Institute of Medical Sciences (IMS), University of Toronto, Toronto, Ontario, Canada
[b] Schizophrenia Division, Centre for Addiction and Mental Health (CAMH), Toronto, Ontario, Canada
[c] Department of Psychology, University of Toronto Scarborough, Scarborough, Ontario, Canada
[d] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[e] Campbell Family Mental Health Research Institute, Toronto, Ontario, Canada
[f] Division of Brain and Therapeutics, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT

Background: Rates of cannabis use among patients with schizophrenia are high, however little is understood about clinical effects of continued cannabis use and cessation after illness onset. Therefore, we investigated the effects of 28-days of cannabis abstinence on psychotic and depressive symptomatology in cannabis dependent patients with schizophrenia.
Method: Males with cannabis dependence and co-morbid schizophrenia (n = 19) and non-psychiatric controls (n = 20) underwent 28-days of monitored cannabis abstinence. Clinical symptoms were assessed at baseline and then weekly. Abstinence was encouraged using weekly therapy sessions and contingency reinforcement, confirmed by twice-weekly urine assays.
Results: Forty-two percent (8/19) of patients and 55% (11/20) of controls achieved 28-days of sustained cannabis abstinence. In patients, PANSS subscores did not change over time irrespective of abstinence status. In contrast, patient abstainers demonstrated a more pronounced reduction in depression scores compared to non-abstainers, however, the Abstinence Status x Time interaction was non-significant.
Discussion: Short-term (28-days) cannabis abstinence is not associated with improvement in psychotic symptoms, but may be associated with improvement in depressive symptomatology in patients with schizophrenia. Future studies employing larger samples as well as a continuous cannabis-using group may help to better characterize the causal effects of cannabis on symptom outcomes in this disorder.

1. Introduction

Cannabis use in adolescence has been linked to an increased risk of schizophrenia later in adulthood (Chadwick et al., 2013; Moore et al., 2007). Thus, it is not surprising that cannabis dependence is common in schizophrenia, especially among male patients (Koskinen et al., 2010). While evidence suggests that cannabis use can lead to the development of psychopathology, (D'Souza et al., 2005; Foti et al., 2010), the effect of cannabis on the course of the disorder after illness onset is less clear. Limited studies have examined this relationship using well-controlled longitudinal approaches, and doing so may elucidate the nature of this relationship.

Cross-sectional studies comparing the clinical phenotype of cannabis-using patients and non cannabis-using patients have yielded mixed results, prompting investigators to explore this relationship longitudinally (Zammit et al., 2008). Foti et al. (2010) examined the association between cannabis and course of illness in schizophrenia over the 10 years following first psychiatric hospitalization. The authors observed that cannabis users suffered more severe psychotic symptoms than non-users, and that this relationship was bidirectional (Foti et al., 2010). An earlier study spanning a 10-month period reported that cannabis use predicted a small yet statistically significant increase in psychotic symptoms (Degenhardt et al., 2007). Subsequent studies have shown that continued cannabis use in those with co-morbid psychotic disorders showed more positive symptoms compared to both discontinued cannabis users and non cannabis-users, over 1- (Stone et al., 2014) and 3-year (van der Meer et al., 2015) periods. Moreover, a large meta-analysis by Schoeler et al. (2016) found that at follow-up assessments continued cannabis-users experienced more severe positive psychotic symptoms, but not negative symptoms. This effect was not present in patients who discontinued cannabis (Schoeler et al., 2016). With respect to depression, a recent study showed that continued

* Corresponding author at: Icahn School of Medicine at Mount Sinai, 1470 Madison Avenue Floor 10-120, New York, NY 10029, United States.
E-mail address: Rachel.Rabin@mssm.edu (R.A. Rabin).

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cannabis abuse in first-episode patients was associated with higher subclinical depressive symptoms at 5-year follow-up (Gonzalez-Ortega et al., 2015).

While many studies have found a negative effect of cannabis on the course of schizophrenia, some longitudinal studies failed to find relationships between cannabis and clinical symptomatology (Degenhardt et al., 2007; Faber et al., 2012; Gonzalez-Pinto et al., 2011; Stirling et al., 2005). Barrowclough et al. (2013) reported no association between changes in cannabis dose and changes in positive symptom severity, even when patients became abstinent. The authors also found that greater cannabis consumption was associated with worse psychosocial functioning, but increased use however, did not correlate with worsening of psychotic symptoms severity. In addition, a prospective longitudinal study demonstrated that while cannabis-using patients were more frequently hospitalized than non-cannabis using patients, the two groups did not differ with respect to severity of psychopathology (van Dijk et al., 2012).

Taken together, research to date on the effects of cannabis and clinical outcomes in schizophrenia presents an inconsistent picture (Zammit et al., 2008). Reasons for the heterogeneous findings may be due to methodological variations between studies and failure to control for a host of confounding variables (e.g., sex, sociodemographic factors, other substance use, medication adherence). In addition, most studies did not examine heavy, chronic cannabis consumption, but rather light or variable use, and did not include biochemical verification of cannabis use (or lack of use for non-users). Moreover, attrition in cohort studies tends to be greater for individuals who have more severe mental health problems and substance use disorders (SUDs), therefore results from longitudinal data may be an underestimation of cannabis' true impact (Zammit et al., 2008). To help clarify such relationships, well-controlled clinical studies are warranted. Therefore, we conducted the first prospective study of 28-days of cannabis abstinence to assess the clinical effects of chronic cannabis use on schizophrenia psychopathology in male outpatients with co-morbid cannabis dependence. We predicted that after sustained cannabis abstinence, patients would demonstrate a reduction in symptoms, specifically in PANSS positive scores and depressive symptomatology.

2. Materials and methods

2.1. Participants

Written informed consent was obtained from all participants, approved by the CAMH Research Ethics Board and in accordance with the ethical standards of the 1964 Declaration of Helsinki. Patients with schizophrenia were recruited through flyers posted around the Centre for Addiction and Mental Health (CAMH) and through referrals made by outpatient clinic psychiatrists. Non-psychiatric control cannabis-users were recruited from the community by posted ads. Study eligibility was assessed with an initial telephone screening, followed by an in-person interview. Recruitment began in April 2012 and ended in December 2015.

Non-treatment seeking male participants between the ages of 18 and 55 were recruited for the study. Only males were recruited this study as previous research has found that patients with schizophrenia and co-morbid cannabis dependence are predominately male (Kavanagh et al., 2004; Koskinen et al., 2010). All participants were administered the Structured Clinical Interview for DSM-IV-TR (SCID) and met criteria for current cannabis dependence (APA, 2000). A positive urine test for THC-COOH (MEDTOX®; Wilmington, NC) was required to confirm current cannabis use. All participants were daily cigarette smokers (≥5 cigarettes per day, CPD). All participants had to achieve Full Scale Intelligent Quotient (FSIQ) scores ≥80, using the Weschsler Adult Reading Test (WTAR) (Wechsler, 2001). Patients met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder and were psychiatric stable, determined with a PANSS total score <70 (Kay et al., 1987) and no hospitalizations in the 3 months prior to enrolment. Additionally, patients were maintained on a stable dose of antipsychotic medication with no changes in dose for at least one month. Non-psychiatric controls were excluded if they met criteria for a current or past DSM-IV Axis I diagnosis (except for major depression in remission >1 year) or if they were taking psychotropic medications. Individuals were not eligible for study participation if they met criteria for a current or past (remission <6 months) SUD (other than cannabis, nicotine, caffeine), or testing positive on urine toxicology for illicit drugs other than cannabis (e.g., cocaine, opiates, amphetamine, phencyclidine, barbiturates). Head injury with loss of consciousness for >30 min or a neurological/medical condition affecting cognition was also exclusionary.

2.2. Measures

2.2.1. Baseline substance use measures

Current cannabis dependence, past alcohol and other SUDs were diagnosed at the screening visit using the SCID for DSM-IV-TR. Cumulative cannabis exposure was indexed as joint-years, where one joint-year is the equivalent of using one joint per day for one year (Rabin et al., 2013). Nicotine dependence was measured using the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). The Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) assessed problematic drinking behaviors.

2.2.2. Weekly substance use measures

The Timeline Follow-Back (TLFB) (Sobell et al., 1988) is a self-report of substance use frequency and was collected for cannabis, tobacco cigarettes, alcoholic beverages and caffeine in the previous 7 days. This measure was completed at the screening, baseline and weekly visits. Cannabis use was expressed in grams. Participants were asked to estimate the number of grams of cannabis they consumed per day in the previous week; on average participants reported that one joint was equal to one gram of cannabis. Cannabis withdrawal was assessed using the Marijuana Withdrawal Checklist (MWC) (Budney et al., 2003) at screening, baseline and weekly visits.

2.2.3. Clinical measures

In schizophrenia, positive and negative symptoms were assessed using the PANSS (Kay et al., 1989). The Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) assessed depression exclusively in patients and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1967) assessed mood symptoms in both patients and controls. All clinical measures (including the SCID) were conducted by RAR, a doctoral student, who had extensive training and experience administering these psychiatric assessments.

2.3. Laboratory procedures

Participants were instructed to quit cannabis 12-h prior to the baseline visit to minimize the possibility of cannabis intoxication and withdrawal (Budney et al., 2003). Clinical measures assessing psychotic, depressive and withdrawal symptoms were assessed at baseline, and weekly. Cognition was evaluated biweekly, on Days 0, 14 and 28 (data presented elsewhere). Twice-weekly urine samples were collected and then stored in a −80 °C freezer for future gas chromatography mass spectrometry (GC–MS) analysis (Goodwin et al., 2008). Contingent payments at Day 28 were used as the primary reinforcer of abstinence: participants who successfully abstained from cannabis for the full 28-days (MEDTOX; THC-COOH <50 ng/ml) were rewarded with a $300 (CAD) bonus. To further encourage cannabis abstinence, individual supportive therapy was given weekly (20–30 min) by trained clinical staff in the Schizophrenia Division at CAMH. Sessions included a combination of motivational interviewing, psycho-education, and coping skills. See Fig. 1 for Study Timeline.

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