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A method to achieve extended cannabis abstinence in cannabis dependent patients with schizophrenia and non-psychiatric controls

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

[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] Division of Brain and Therapeutics, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[d] Department of Psychology, University of Toronto Scarborough, Scarborough, Ontario, Canada
[e] Campbell Family Mental Health Research Institute, Toronto, Ontario, Canada
[f] Clinical Laboratory and Diagnostic Services, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[g] Department of Psychiatry, Geisel School of Medicine at Dartmouth, Lebanon, NH 03702, USA

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ABSTRACT

Background: Cannabis use disorders (CUD) are common in schizophrenia (~25%) compared to the general population (~3%). Tetrahydrocannabinol (THC), the principal psychoactive component in cannabis is fat-soluble, resulting in an extended period for cannabinoid elimination. While detection of cannabinoids in urine is indicative of prior cannabis exposure, time of last use is difficult to verify sustained abstinence for extended periods (e.g., 28-days) in chronic cannabis users. Therefore, we evaluated the utility of a sustained cannabis abstinence paradigm in patients with schizophrenia and non-psychiatric controls.
Methods: Cannabis dependent patients (n = 19) and controls (n = 20) underwent 28-days of monitored cannabis abstinence facilitated with contingency management. Urine samples were taken twice weekly. Abstinence was evaluated using 1) Self-report; 2) Qualitative biochemical confirmation using MEDTOX; and 3) in a subset of participants (schizophrenia, n = 13; controls, n = 13) gas chromatography-mass spectrometry (GC-MS) was performed to obtain quantitative creatinine-normalized carboxy-THC (THC-COOH) metabolite levels <20 ng/mL). Subjective assessments were used to assess behavioral correlates of cannabis abstinence and further supported time-dependent abstinence trajectories.
Results: Abstinence rates of 42.1% (8/19) in patients and 55% (11/19) in controls (p = 0.53) were observed. Increased cannabis withdrawal symptoms in both patients and controls supported abstinence.
Discussion: Our results suggest a feasible method for identification of short-term cannabis abstinence in individuals with schizophrenia at rates comparable to controls. Monitoring sustained abstinence may have implications for potential interventions for CUDs in schizophrenia.

1. Introduction

As more countries legalize cannabis, its use is becoming less stigmatized (Berg et al., 2015; Hall, 2015; SAMHSA, 2013). This may translate into more liberal use and increased rates of problematic cannabis use (Hasin et al., 2015; Johnston et al., 2012). While cannabis use disorders (CUD) in the general population are low (~3%) (UNODC, 2013), they are higher among psychiatric populations, including schizophrenia (~25%) (Koskinen et al., 2010).

There has been considerable work to better understand effects of cannabis in schizophrenia, with a strong emphasis on individuals with chronic use. Most studies attempting to characterize consequences of cannabis use have employed cross-sectional designs (Rabin et al., 2011), prohibiting firm conclusions regarding direct and causal effects of (non-acute) cannabis use. Thus a method using a longitudinal design may parse within-subject differences to determine changes in cannabis use over time. Accordingly, sustained abstinence among regular cannabis users may represent a robust magnitude of change in use and determine if effects of cannabis are permanent or reversible. However, a major limitation is failure to ensure that long-term effects of cannabis are not attributable to residual cannabinoids.

The primary psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (THC), which is largely responsible for psychoactive

* Corresponding author at: Department of Psychiatry, Icahn School of Medicine at Mt. Sinai, Hess Center for Science and Medicine, Floor 10-120, 1470 Madison Avenue, New York, NY 10029, USA.
E-mail address: rachel.rabin@mssm.edu (R.A. Rabin).

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effects of the plant. Unlike other drugs of abuse, cannabis can accumulate in lipophilic compartments, resulting in the presence of metabolites long after cessation of cannabis use (Goodwin et al., 2008). THC is slowly re-released into blood, metabolized to carboxy-THC (THC-COOH), an inactive metabolite, and then excreted in urine (Hunt and Jones, 1980). Chronic users require up to 28-days for complete cannabinoid elimination using a urinary THC-COOH cut-off of 20 ng/mL (Ellis et al., 1985; Goodwin et al., 2008; Smith-Kielland et al., 1999). Urinalysis is the most common method of drug testing for determining psychoactive substances. Urine immunoassay tests detect THC-COOH at concentrations ~50 ng/mL (Huestis et al., 1995). The long excretion half-life of THC-COOH makes it difficult to discern the timing of last drug exposure. Therefore, results from a single urine test may not confirm sustained abstinence in the initial period post-abstinence.

Gas chromatography-mass spectrometry (GC-MS) is a method for quantifying metabolite levels allowing for normalization of THC-COOH concentrations to urinary creatinine, controlling for hydration status (Lafolie et al., 1991). Furthermore, using ratios calculated from two sequential creatinine-normalized urine specimens (Urine2/Urine1) distinguishes whether new cannabis was introduced versus residual cannabinoids (Manno et al., 1984; Schwilke et al., 2011; Smith et al., 2009). Manno et al. (1984) proposed new cannabis use was indicated if the ratio of creatinine normalized THC-COOH concentration (ng/mg) of a later specimen to an earlier specimen was ≥1.5. Subsequently, Huestis et al. (1995) demonstrated more precise differentiation between new cannabis and residual cannabinoid excretion occurred if this ratio was >0.5. However, applying single ratios to data may yield either unrealistically low re-use rates, or unrealistically high re-use rates. As such, a recently published model predicts re-use of cannabis in chronic users more accurately by accounting for the time interval between urine specimens and initial cannabinoid concentrations (Schwilke et al., 2011). Extended cannabis abstinence does not imply a cannabis-free state; thus when evaluating long-term effects of cannabis on sensitive outcomes (e.g. cognitive function), investigators must ensure cannabinoids have been reduced to negligible levels (i.e. urinary THC-COOH <20 ng/mL).

While biochemical analysis is pertinent for determining abstinence, inclusion of self-reported and clinical data may be used in conjunction to support objective data as well. For example, cannabis withdrawal syndrome is a time-dependent, pharmacologically specific phenomenon associated with a constellation of clinically relevant symptoms (e.g. anxiety, depression, sleep and appetite disturbances) (Budney et al., 1999; Copeland et al., 2001; Kouri and Pope, 2000). Withdrawal symptoms appear ~24 h after abstinence initiation, peak within the first week and then gradually decrease over the following three weeks (Allsop et al., 2011; Budney et al., 2004).

Therefore, in the current study, we assessed a method to achieve sustained cannabis abstinence and metabolite elimination over a 28-day period in cannabis dependent patients with schizophrenia and non-psychiatric controls using contingency management (CM). CM is a well-established behavioral intervention for changing substance-using behaviors (Higgins et al., 1991) including cannabis (Schuster et al., 2016). We addressed the following questions:

(a) Is the proposed abstinence paradigm effective at producing sustained cannabis abstinence across 28-days?
(b) Is this paradigm able to distinguish individuals who are able to abstain from those who relapse?
(c) Is this paradigm feasible for patients with schizophrenia?

2. Materials and methods

2.1. Participants

Patients with schizophrenia were recruited through outpatient programs of the Centre for Addiction and Mental Health (CAMH) using flyers and through referrals made by outpatient staff. Non-psychiatric cannabis users were recruited from the community by posted advertisements. Study eligibility was assessed by telephone screening, followed by an in-person comprehensive interview. Recruitment occurred between April 2012 and December 2015.

Written informed consent was obtained from all participants seeking participation, as approved by the Research Ethics Board at CAMH. Male participants ages 18–55 were included. All participants met criteria for current cannabis dependence based on DSM-IV-TR (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). In addition, all participants had to achieve Full Scale Intelligent Quotient score ≥ 80 using the Weschsler Adult Reading Test (WTAR) (Wechsler, 2001). Psychiatric participants met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder and were psychiatrically stable with a total score < 70 on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1987), with no hospitalizations in 3 months prior to enrolment. Patients had to be maintained on a stable dose of antipsychotic medication with no changes to type of medication or 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. Potential participants were excluded if they were treatment-seeking for cannabis use. Additionally, individuals with a current substance use disorder (SUD) or past (remission <6 months) SUD (other than cannabis, nicotine, caffeine) or those testing positive on urine toxicology for illicit drugs other than cannabis were excluded. Head injury with loss of consciousness for >30 min or a neurological/medical condition altering cognitive function was also exclusionary.

2.2. Substance use measures

The SCID-IV was used to diagnose SUDs. Cumulative cannabis exposure was indexed as joint-years, where one joint-year is the equivalent of using on average one joint per day for one year (Rabin et al., 2013). The Timeline Follow-Back (TLFB) (Sobell et al., 1988) was collected for cannabis in grams (grams per day, GPD), tobacco cigarettes, alcoholic beverages and caffeine in the 7 days prior. Nicotine dependence was measured using the Fagerstrom Test of Nicotine Dependence (FTND) (Heatherton et al., 1991). The Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) assessed problematic drinking. Cannabis withdrawal was assessed using the Marijuana Withdrawal Checklist (MWC) (Budney et al., 2003).

2.3. Research procedures

Participants quit cannabis 12-h before the Day0 (baseline) visit. Participants then attended weekly clinical study visits to assess self-reported cannabis use and withdrawal symptoms of the previous week. Urine samples were collected at baseline, and twice weekly (separated by three to four days) and stored in a − 80 °C freezer for later GC-MS analysis at the CAMH clinical laboratory. By study endpoint, a total of 9 samples were collected from each participant.

Individual supportive therapy was given weekly (20–30 min) by trained clinical staff. Sessions included motivational interviewing, psychoeducation, and coping skills. CM was used as the primary reinforcer. As indicated by previous research, a one-time sizable financial incentive can be highly effective in promoting one-month of (smoking) abstinence (Gilbert et al., 1999). Therefore, we rewarded participants who successfully abstained from cannabis for the full 28-days with a $300 abstinence bonus.

2.4. Abstinence verification

Abstinence verification was confirmed using three criteria:

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