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Changes in dependent patients with schizophrenia versus non-psychiatric controls during 28-days of cannabis abstinence

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ABSTRACT

Background: Tobacco and cannabis are highly co-morbid in the general population and in patients with schizophrenia. Given the putative causal mechanisms facilitating co-use, it is important to determine how cannabis cessation may influence concurrent tobacco use. Using a 28-day cannabis abstinence paradigm, we prospectively examined changes in tobacco consumption in patients with schizophrenia and controls with cannabis dependence and daily cigarette use.

Methods: Cannabis dependent patients with schizophrenia (n = 19) and controls (n = 20) completed the study with abstinence rates of 42% and 55%, respectively. Participants completed measures of substance use, withdrawal, and clinical symptoms weekly. Urine samples were collected twice weekly to biochemically verify abstinence.

Results: Patients reported a greater increase in cigarettes smoked per day (CPD) on Day 7 relative to baseline (2.97 cigarette increase for abstinent subgroup, $p < .01$) compared to controls (.06 cigarette increase for abstinent subgroup, $p = .95$). Initially, greater reductions in cannabis use related to greater increases in CPD relative to baseline in the patient subsample (simple slope = −2.31, $p = .05$), but by Day 28, CPD returned to baseline levels independent of cannabis use. CPD changes were unrelated to cannabis withdrawal. Results were similar for changes in caffeine consumption, but not for alcohol.

Conclusions: Findings suggest transient tobacco substitution for cannabis in patients with schizophrenia. This provides further support for a strong association between cannabis and tobacco in schizophrenia. Future studies should focus on targeting underlying mechanisms that promote co-use to better address potential changes in concurrent substance use during treatment interventions.

1. Introduction

Tobacco and cannabis are highly co-morbid (Agrawal et al., 2012). Current cannabis users are five to seven times more likely than non-users to smoke tobacco (Mohler-Kuo et al., 2003; Richter et al., 2004), and approximately 70% of cannabis users report tobacco use in the past month (Schauer et al., 2015). This combination of substances is concerning due to the multiplicative physical and mental health risks associated with their co-use (Ramo et al., 2012; Taylor et al., 2002). Given the putative neurobiological and behavioral mechanisms facilitating tobacco and cannabis co-use [See (Rabin and George, 2015) for review], it is critical to determine how cannabis cessation may influence concurrent tobacco use.

Cannabis and tobacco co-use is also highly relevant within the context of mental illness, especially among those with psychotic disorders such as schizophrenia (Margolese et al., 2004; Rabin et al., 2014). Both cigarette smoking and cannabis use occur at higher rates in schizophrenia compared to the general population (Kalman et al., 2005; Koskinen et al., 2010). Not only are these substance use disorders (SUD) more prevalent among patients, but also these individuals consume more heavily, have greater levels of dependence and are less likely to quit relative to non-psychiatric controls (Boggs et al., 2013; Tidey et al., 2005; Volkow, 2009).

While cannabis use and tobacco use are undoubtedly linked, the directionality of the relationship when one is ceased remains unclear. With respect to quitting cannabis, evidence suggests that compensatory

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increases in tobacco consumption may be expected. Copersino et al. (2006) examined changes in tobacco use during spontaneous cannabis quit attempts in non-treatment-seeking adult cannabis users (n = 104). The study reported that at least half of users reported increased tobacco use, suggesting that cigarette smoking may "substitute" for the reduction in cannabis consumption (Copersino et al., 2006).

In a subsequent study employing a 14-day cannabis abstinence period in non-treatment-seekers, similar increases in tobacco consumption were also observed (Allsop et al., 2014). On average, use escalated by about 2 cigarettes per day (CPD). Notably, those consuming the lowest levels of tobacco prior to quitting cannabis experienced the greatest increases in use. Interestingly, cigarette substitution was also more likely in those experiencing severe cannabis withdrawal, including symptoms of insomnia, restlessness and physical symptoms (Allsop et al., 2014). Thus, increased tobacco use may also be in response to attenuate cannabis withdrawal symptoms (Levin et al., 2010).

Notably, not all studies have found abstinence-induced increases in tobacco use. For example, Peters and Hughes (2010) found that non-treatment seeking participants who abstained from cannabis for a 2-week period demonstrated no concomitant increase in tobacco use. This finding has also been replicated in laboratory studies (Haney et al., 2004; Kouri and Pope, 2000) as well as in clinical trials (Hughes, 2008).

To date, there is limited research exploring how cannabis cessation might affect tobacco co-use in patients with schizophrenia. We previously explored cigarette smoking behaviors as a function of cannabis use patterns in schizophrenia (Rabin et al., 2014). In a comparison across current, former and never dependent users, our group found that tobacco consumption varied significantly. That is, current dependent patients smoked fewer cigarettes than former dependent and never dependent patients, and former dependent patients smoked fewer cigarettes than never dependent patients, suggestive of a dose-dependent relationship between cannabis and tobacco. In other words, as cannabis consumption decreases CPD increases, supporting a substitution effect. Another study that retrospectively examined quitting strategies among patients with schizophrenia suggested that increased tobacco use might be in response to withdrawal symptoms punctuated by reducing cannabis (Koola et al., 2013).

Taken together, it remains unclear whether cannabis cessation similarly affects co-morbid tobacco use in patients with schizophrenia and non-psychiatric controls. Therefore, we sought to better characterize the substitution effects between cannabis and tobacco using a prospective longitudinal design. Using a 28-day cannabis abstinence paradigm (Rabin et al., 2017b), we examined changes in tobacco consumption among daily smokers with CUD who were also either patients with schizophrenia or non-psychiatric controls. We hypothesized that reductions in cannabis use would correspond with increased cigarette smoking, particularly among patients with schizophrenia. The role of cannabis withdrawal in predicting changes in cigarette use was also evaluated and, in light of prior research, a positive relationship was expected. Lastly, we investigated whether changes in use would extend to alcohol and caffeine consumption. However, given that not all participants were daily users of these substances, such outcomes were considered exploratory.

2. Material and methods

2.1. Participants

Patients with schizophrenia were recruited through the Centre for Addiction and Mental Health (CAMH) using flyers posted around the hospital and through referrals made by outpatient clinicians. Non-psychiatric cannabis users were recruited from the community by posted ads.

Male participants between the ages of 18 and 55 were recruited for the study. All participants met criteria for current cannabis dependence based on DSM-IV-TR (American Psychiatric Association, 2000). A positive urine test for THC-COOH (MEDTOX®; Wilmington, NC) was required to confirm current cannabis use. To control for the effects of tobacco on cognition, all participants were daily cigarette smokers (≥5 CPD). Moreover, all participants had to achieve Full Scale Intelligent Quotient (FSIQ) scores ≥80, using the Wechsler Adult Reading Test (Wechsler, 2001). Psychiatric participants met DSM-IV-TR criteria for schizophrenia. Patients were psychiatrically stable at the time of the interview, indicated by a total score < 70 on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1987) and had no hospitalizations within the 3 months prior to enrollment. Additionally, patients had to be maintained on a stable dose of antipsychotic medication with no changes for at least one month.

Non-psychiatric controls were excluded if they met criteria for a current or past Axis I diagnosis (except for major depression in remission > 1 year) or if they were taking psychotropic medications. Individuals with a current or past (remission < 6months) SUD (other than cannabis, nicotine, caffeine) or those testing positive on urine toxicology for illicit drugs other than cannabis (i.e., cocaine, opiates, amphetamine, phencyclidine, barbiturates) were not eligible for study participation.

Additionally, participants were excluded if they were actively seeking treatment for cannabis. Head injury with loss of consciousness for > 30 min requiring hospitalization, or evidence of neurological/medical conditions affecting cognition was also exclusionary. Written informed consent was obtained from all participants, as approved by the Research Ethics Board at CAMH.

2.2. Substance use measures

The Timeline Follow-Back (Sobell et al., 1988) (TLFB) was completed weekly and involved asking participants to retrospectively report their substance use 7 days prior. Information was collected for cannabis in grams, tobacco cigarettes, alcoholic beverages, and caffeine, as well as for any other illicit substances. Units of both caffeine and alcohol were standardized with type of beverage consumed and amount (e.g., # of ounces). For caffeine, one unit was the equivalent of one 8-ounce cup of coffee. For alcohol, one unit was the equivalent to one beer (12 ounces), one glass of wine (5 ounces), or liquor or mixed drink containing 1.5 ounces.

Cumulative cannabis exposure was indexed by joint-years, where one joint-year is the equivalent of using one joint per day for one year (Rabin et al., 2013). Level of nicotine dependence was measured using the Fagerström Test of Nicotine Dependence (FTND) (Heatherton et al., 1991) and the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) assessed problematic drinking. Lastly, cannabis withdrawal was assessed using the Marijuana Withdrawal Checklist (MWC) (Budney et al., 2003).

2.3. Laboratory procedures

Study participants were instructed to abstain from cannabis for 28 days. Participants were able to consume other drugs ad libitum, as per their usual pattern. Participants attended weekly study visits for 4 weeks. Clinical measures assessing psychiatric, depressive and withdrawal symptoms were assessed weekly. Urine was collected twice weekly and then stored in a −80 °C freezer for future gas chromatography mass spectrometry (GC–MS) analysis. To encourage cannabis abstinence, individual supportive therapy was given weekly (20–30 min) by trained clinical staff in the Schizophrenia Division at CAMH. Contingency management was used as the primary reinforcer: participants who successfully abstained from cannabis for the full 28 days were rewarded with a $300 bonus.

2.4. Abstinence verification

Abstinence verification was based on weekly self-report and twice-