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Effects of cannabis use on body mass, fasting glucose and lipids during the first 12 months of treatment in schizophrenia spectrum disorders

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ABSTRACT

While acute cannabis use stimulates appetite, general population studies suggest that chronic use is associated with reduced risk of obesity and other cardiometabolic risk factors. In this study we investigated changes in body mass index (BMI), fasting blood glucose and lipids, and rates of metabolic syndrome risk factors in cannabis users vs. non-users in 109 minimally treated patients with first-episode schizophrenia, schizophreniform or schizo-affective disorder who were treated according to a standardized treatment regime with depot antipsychotic medication over 12 months. Participants underwent repeated urine toxicology tests for cannabis and those testing positive at any time during the study ($n = 40$), were compared with those who tested negative at all time points ($n = 69$). There was a significant group*time interaction effect ($p = 0.002$) with the cannabis negative group showing a greater increase in BMI than the cannabis positive group, after adjusting for age, sex, methamphetamine use and modal dose of antipsychotic. There were no group*time interaction effects for fasting blood glucose or lipids. Post hoc tests indicated significant increases in fasting blood glucose and triglycerides and a decrease in high-density lipoprotein cholesterol for the cannabis negative group, with no significant changes in the cannabis positive group. Rates of metabolic syndrome did not differ significantly between groups, although more cannabis negative patients had elevated waist-circumference at endpoint ($p = 0.003$). It may be that chronic cannabis use directly suppresses appetite, thereby preventing weight gain in users. However, other indirect effects such as dietary neglect and smoking may be contributory and could explain our findings.

1. Introduction

Acute cannabis use stimulates appetite and increases food intake (Kirkham, 2009), and as such has been proposed as a treatment for weight-loss in persons with cancer and HIV infection (Sansone and Sansone, 2014). On the other hand, there is emerging evidence that chronic cannabis use is associated with lower body mass and fewer cardiometabolic risk factors in general population samples, at least in adults (Penner et al., 2013;Le Strat and Le Foll, 2011;Hayatbakhsh et al., 2010;Smit and Crespo, 2001;Ngueta et al., 2015;Thompson and Hay, 2015;Vidot et al., 2016). The situation may be different in adolescents, where an association was reported between cannabis use and increased body mass index (BMI) in two studies (Huang et al., 2013;Ross et al., 2016), in younger girls only in another (Farhat et al., 2010), while no association was found in two other studies (Jin et al., 2017;Rodondi et al., 2006).

A link between cannabis use, body mass and cardiometabolic risk factors is of particular interest in individuals with schizophrenia, given both the high rates of cannabis use (Green et al., 2005) and the increased risk of cardiometabolic comorbidities (Correll et al., 2017) associated with this illness. Two known studies have addressed this possible link. In the first, the association between cannabis use and changes in metabolic syndrome risk factors over 9 to 24 months of treatment was investigated using data obtained from a treatment monitoring and outcome survey in a Dutch cohort with severe mental illness ($N = 3169$). Patients were chronically ill (mean illness duration 14.4 [10.7] yrs) and three-quarters were on antipsychotic medication prior to the study. Cannabis users (determined by patient interview) had lower BMI, smaller waist circumference, lower diastolic blood pressure, and more severe psychotic symptoms than non-users at baseline. Patients who stopped using cannabis after the first assessment had a greater increase in BMI, waist circumference, diastolic blood pressure and triglyceride concentrations than both the ongoing users and non-users. The

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authors concluded that extra attention should be paid to the monitoring and treatment of metabolic measures in patients who discontinue their cannabis use (Bruins et al., 2016). In the second study, an analysis of data derived from an Australian psychosis survey reported that, in adults with psychotic illness ($N = 1825$), frequent cannabis use was associated with reduced risk for individual metabolic syndrome criteria (increased waist circumference, elevated blood pressure, triglycerides and glucose and low HDL) (Waterreus et al., 2016).

In the present study, we compared longitudinal changes in BMI and metabolic measures in patients with schizophrenia spectrum disorder who tested positive versus those who tested negative for cannabis, during the first 12 months of treatment. By selecting patients who were previously never treated or minimally treated, and with a first-episode of illness, we were able to minimise the effects of previous treatment and disease chronicity. Furthermore, we treated the patients with a long-acting injectable antipsychotic, thereby removing a confounding effect of non-adherence and at the same time allowing accurate estimation of treatment dose and duration.

2. Methods

This was a single-site cohort study. We obtained approval from the Human Research Ethics Committee of Stellenbosch University Faculty of Medicine and Health Sciences. The study was conducted in accordance with the International Conference on Harmonization (1996) guidelines on good clinical practice (GCP) and was registered at the South African National Clinical Trials Register (DOH-27-0710-1957), URL: www.sanctr.gov.za/SAClinicalTrials/tabid/169/ Default.aspx.

2.1. Participants

We recruited patients from first-admissions to psychiatric hospitals and community clinics within the Cape Town region between April 2007 and March 2011. The patients and/or their legal guardians provided written, informed consent. Eligible participants were men and women, in- or out- patients, aged 16 to 45 years, meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (APA, 1994) diagnostic criteria for schizophreniform disorder, schizophrenia or schizo-affective disorder. Patients were excluded if they had, during their lifetime, been exposed to >4 weeks of antipsychotic medication, been treated with a long-acting injectable antipsychotic, had a serious or unstable medical condition, intellectual disability or if the psychotic episode was considered to be related to acute substance intoxication.

2.2. Assessments

A physical examination was conducted at the start and completion of the study. For the body mass and waist circumference measurements, patients removed all surplus clothing including shoes and socks. They were weighed on a regularly calibrated electronic scale. Waist circumference was measured between the lowest rib and the iliac crest with patients standing upright and breathing normally. BMI was calculated as the weight in kilograms divided by the square of height in meters. Metabolic assessments comprised fasting glucose, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and total cholesterol. Patients fasted for at least 8 h overnight and rested for 10 min prior to venepuncture. We recorded BMI and metabolic assessments at baseline and months 3, 6 and 12. Systolic and diastolic blood pressure were recorded at baseline and endpoint. Patients were categorised as meeting the metabolic syndrome criteria, adapted from the Adult Treatment Panel (ATP III-A) as proposed by the American Heart Association (Alberti et al., 2009). These criteria comprise elevated blood pressure (systolic >130 mmHg and/or diastolic >85 mmHg, or antihypertensive drug treatment), elevated triglycerides (≥1.7 mmol/l or drug treatment for elevated triglycerides), lowered HDL (≤1 mmol/l for men, ≤1.3 mmol/l for women or drug treatment for reduced HDL), elevated fasting glucose (≥5.5 mmol/l or drug treatment for elevated glucose), and central obesity as measured by waist circumference according to population-specific definitions. We made two adaptations to these criteria. First, we used a waist circumference cut-off for central obesity of ≥90 cm for men and ≥80 cm for women, as recommended by Matsha et al. (Matsha et al., 2013) based on a study conducted in a similar population, in our catchment area. Second, we used a threshold score of ≥6.1 mmol/l for defining impaired fasting glucose, as recommended by the World Health Organisation (World Health Organisation, 2006). Metabolic syndrome was defined as abnormal values for any three of the five criteria. We assessed psychosis symptom severity with the Positive and Negative Syndrome Scale (Kay et al., 1987). Alcohol use was assessed using a self-report questionnaire based on the CAGE criteria (Ewing, 1984). Urine toxicology screening for cannabis and methamphetamine was conducted at 9 time-points over the 12 months of treatment (screening, weeks 0 and 2 and months 1, 2, 3, 6, 9 and 12). Patients were grouped as cannabis positive if any of the post-screening tests were positive and as cannabis negative if all of the post-screening tests were negative.

2.3. Treatment

We treated the patients according to a fixed protocol, with a long-acting injectable antipsychotic, flupenthixol decanoate. Flupenthixol is a high potency thioxanthene, whose receptor binding profile of D1-5 dopamine, 5-HT2, H1 histamine and alpha-1 adrenergic-antagonism is not dissimilar to several second generation antipsychotics (de Wit, 2010). It has been associated with significant increases in BMI, waist circumference and triglycerides, and a decrease in HDL in patients with first-episode schizophrenia (Chiliza et al., 2015). Flupenthixol decanoate is widely available and remains a popular choice of psychiatrists for treating psychosis (Shen et al., 2012). There was a one week lead-in period with oral flupenthixol 1 to 3 mg/day followed by long acting flupenthixol decanoate injections every two weeks for the duration of the study. The starting dose was 10 mg 2-weekly. Additional oral flupenthixol was prescribed at the discretion of the investigator. Permitted concomitant treatment included lorazepam for sedation, orphenadrine or biperiden for extrapyramidal symptoms, propranolol for akathisia and medication for general medical conditions. Medications not permitted included other antipsychotics, mood stabilizers and psychostimulants.

2.4. Statistical analyses

All participants with a baseline and at least one post-baseline measure were included in the analyses. For baseline demographic and clinical group comparisons, we used independent samples *t*-tests for continuous variables and chi-square test for categorical variables. Linear mixed effect models for continuous repeated measures (MMRM) were constructed to assess the changes in BMI and metabolic measures over time. The model included fixed terms of age, sex, modal flupenthixol dose, methamphetamine positive test, group (cannabis users vs cannabis non-users), time, and the interaction terms "gender*time" and "group*time". Where data were not normally distributed, the data were log transformed. All tests were 2-tailed, with a significance level of 0.05. Within analyses Fisher's Least Significant Difference (LSD) tests were used for post-hoc multiple comparisons.

3. Results

Of 126 participants entered into the study, 109 had at least one post-baseline assessment and were included in the analysis. Forty (37%) tested positive for cannabis at least once after screening, and 69 (63%) tested negative for cannabis at all post-screening assessments. Table 1 provides the baseline demographic, clinical and laboratory details for

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