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Biological correlates of self-reported new and continued abstinence in cannabis cessation treatment clinical trials

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ABSTRACT

Background: The agreement between self-reported cannabis abstinence with urine cannabinoid concentrations in a clinical trials setting is not well characterized. We assessed the agreement between various cannabinoid cutoffs and self-reported abstinence across three clinical trials, one including contingency management for abstinence.

Methods: Three cannabis cessation clinical trials where participants reported use and provided weekly urine samples for cannabis and creatinine concentration measurements were included. Bootstrapped data were assessed for agreement between self-reported 7+ day abstinence and urine cannabinoid tests using generalized linear mixed effects models for clustered binary outcomes. One study implemented contingency management for cannabis abstinence. Four hundred and seventy-three participants with 3787 valid urine specimens were included. Urine was analyzed for 11-nor-9-carboxy-Δ9-tetrahydrocannabinol and creatinine using immunoassay methods Biological cutoffs of 50, 100, and 200 ng/ml, as well as changes in CN normalized THCCOOH (25%/50% decrease), were assessed for agreement with self-reported abstinence during the three clinical trials.

Results: Agreement between measured THCCOOH and self-reported abstinence increases with increasing cutoff concentrations, while the agreement with self-reported non-abstinence decreases with increasing cutoff concentrations. Combining THCCOOH cutoffs with recent changes in CN-THCCOOH provides a better agreement in those self-reporting abstinence. Participants in the studies that received CM for abstinence had a lower agreement between self-reported abstinence and returned to use than those in studies that did not have a contingency management component.

Conclusion: Using combinations of biological measurements and self-reported abstinence, confirmation of study related abstinence may be verifiable earlier and with greater accuracy than relying on a single measurement.

1. Introduction

Cannabis is the most widely used illicit substance in many western countries and around the world (Vega et al., 2002). Cannabis use prevalence in the United States more than doubled from 4.1% to 9.5% between 2001/2 and 2012/13 (Hasin et al., 2015). In addition, approximately 12% of individuals who have used cannabis in the past year meet criteria for cannabis use disorder (CUD; Richter et al., 2017); however, measures of changes in cannabis use patterns over time are difficult to validate. Detection of positive cannabinoid concentrations in urine is subject to both physiological and pharmacological influences, including individual metabolism and hydration, as well as recency, frequency, concentration, and quantity of cannabis use. The primary psychoactive ingredient in cannabis, Δ^9-tetrahydrocannabinol (THC), is highly lipophilic and stored in the adipose tissues in the body, with increasing concentrations at increasing use frequencies. THC then metabolizes to the non-psychoactive 11-nor-9-carboxy- Δ^9-tetrahydrocannabinol (THCCOOH) and is excreted in the urine (Huestis and Smith, 2005).

Urine collection measures have a well-defined methodology and a well-characterized historic record of use in clinical trials. However, frequent cannabis users may submit positive urine samples for extended periods of time beyond initial abstinence. A pressing issue in cannabis cessation clinical trials is biological confirmation of new and continued abstinence during treatment. Pre-determined urinary THCCOOH cutoffs for biological confirmation of self-reported abstinence ignore the potentially lengthy detection times of urinary metabolites in frequent cannabis users (Dackis et al., 1982; Kelly and Jones, 1992). Upon

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abstinence, participants may have urine testing results that alternate between positive and negative over an extended period of time-based on a pre-determined cut-off. To accommodate this, some researchers have used higher THCCOOH cutoffs to determine biological evidence of abstinence (Levin et al., 2013), and Schwilke et al. (2011) developed a model to differentiate new cannabis use from residual THCCOOH excretion in a daily cannabis-using population using a cut-off derived from the previous urine measurement. Creatinine-normalized THCCOOH (CN-THCCOOH) values have also been used, as they have the advantage that two measures taken at separate visits are adjusted for differences that may occur due to hydration variability. The collection of cannabis use data through self-report during a clinical trial provides the added benefit of detailed use patterns as well as the ability to examine changes in frequency and intensity of use. However, the validity and accuracy of self-reported substance use amounts vary within a population and may be underreported in cases in which there is a reward for reduced use or abstinence (Carey, 1997; Del Boca and Noll, 2000; Williams and Nowatzki, 2005). In some cases, abstinence may be reported when the individual is in fact, not abstinent.

The primary goal of this analysis was to assess the biological correlates and their agreement with self-reported 7+ day abstinence in a cannabis cessation clinical trial setting with a population of participants with CUD. Specifically, we aimed to characterize the agreement between self-reported 7+ day abstinence with concurrent THCCOOH concentration cutoffs [widely used cut-off values (50 ng/ml (Substance Abuse and Mental Health Services Administration, 2004) and 100 ng/ml (Levin et al., 2013)) as well as higher values (200 ng/ml)] and recent changes in CN-THCCOOH. Additionally, we intend to examine the impact of contingency management implementation on the agreement between self-reported abstinence and biological measures.

2. Methods

2.1. Study designs

Data were taken from three recently completed medication trials of treatment-seeking cannabis-dependent participants [ACCENT (NCT01675661); buspirone (NCT00875836); and vilazodone (NCT01574183)] (Gray et al., 2017; McRae-Clark et al., 2009, 2016). The buspirone and ACCENT studies were 12-week, double-blind, placebo-controlled trials of 1) a flexible dose of buspirone (up to 60 mg/day) or 2) *N*-acetylcysteine (NAC: 1200 mg twice daily). The vilazodone study was an 8-week, double-blind, placebo-controlled trial of a flexible dose of vilazodone (up to 40 mg/day). The ACCENT study was conducted within the National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) and contained contingency management (CM) intervention intended to reinforce retention and abstinence. CM was not included in either the buspirone or vilazodone studies.

2.2. Study participants

Eligible study participants were between 18 and 65 years of age in the buspirone and vilazodone studies, and between 18 and 50 years for the ACCENT study; all participants met DSM-IV criteria for current cannabis dependence. Exclusion criteria included current dependence on any other substance (with the exception of caffeine and nicotine); history of psychotic, bipolar or eating disorder; current suicidal or homicidal risk; current major depression; current treatment with psychoactive medication (with the exception of stimulants and non-benzodiazepine sedative/hypnotics); major medical illness or disease; significant cognitive impairment; and pregnancy, lactation, or inadequate birth control. All potential participants received an evaluation for medical exclusions.

Those with hypersensitivity to buspirone or other product components, current consumption of substances that inhibit or induce Cytochrome P450 3A4 enzyme (CYP3A4) were excluded from the buspirone study; those with contraindications for NAC treatment, and/or recent synthetic cannabinoid use were excluded from the ACCENT study; and those taking CYP3A4 inhibitors were excluded from the vilazodone study. Participants were primarily recruited through media and internet advertisements. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and received approval from the University Institutional Review Board. All participants gave written, informed consent prior to study participation.

2.3. Measures and outcomes

Self-reported cannabis use for the 90 days prior to the study entry (ACCENT only 30 days prior to study entry), as well as at each weekly study visit, was estimated using the Timeline Follow-Back (TLFB) (Sobell and Sobell, 1992). Semi-quantitative urine cannabinoid tests (UCTs) were administered at screening and weekly throughout the studies as biological confirmation of abstinence. In the buspirone and vilazodone studies, UCT analyses were performed using the AXSYM® system from Abbott Laboratories; in the ACCENT study, all UCT analyses were conducted on the ARCHITECT c4000 system for immunoassay testing. This automated system provides inexpensive and easily implemented quantification of urine samples in a clinical trial setting as compared to mass spectrometry, which although likely more precise, can become cost prohibitive. Study participant TLFB data were assessed at each visit that had a concurrent viable UCT urine sample and participants were categorized into one of 4 groups: 1) new self-reported 7+ day abstinence from self-reported regular use at the prior visit, 2) self-reported continued abstinence from the prior self-reported 7+ day abstinent visit, 3) self-reported continued use from the prior non-abstinent visit, and 4) self-reported resumed use from a prior self-reported 7+ day abstinent visit.

A total of 4148 individual sample measurements from 494 participants had both cannabinoid and creatinine data available across the three studies. Prior to analysis, 139 (3.4%) individual urine measurements considered dilute due to significant water loading (urine creatinine < 10 mg/dl) and/or those with possibly inaccurate lab values (THCCOOH > 2000 ng/ml) were removed from the pool of samples. At each visit with a viable sample, 7+ day point prevalence abstinence was determined using the TLFB beginning at the time at which the UCT was conducted and moving backward in time 7+ complete days or until the nearest prior sample, whichever was temporally further. In addition, time since the last viable UCT sample, current raw and creatinine-adjusted cannabinoid concentrations, most recent prior available raw and creatinine-adjusted cannabinoid concentrations, and other clinical variables were tabulated at each visit. Since a primary impetus of this analysis was to determine agreement with patterns of changes of biological measures that may associate with recent and continued self-reported cannabis abstinence, measures without recent and valid UCT data within 21 days or with visit less than 4 days since the most recent visit were removed from the analysis pool (n = 222 samples, 5.4%). The final analytic data file contained 3787 individual samples from 473 participants (91.3% of the original sample pool).

At each study visit with a valid sample, indicators of UCT values below 50, 100, and 200 ng/ml were created. Additionally, indicators of CN-THCCOOH concentrations that decreased at least 25% and 50% since the last valid measure were created (ratio of urine2/urine1). CN-THCCOOH visit ratios values were also subjected to Schwilke and colleagues' (Schwilke et al., 2011) algorithm to detect resumption of cannabis use (rule 1 only). Although not specifically designed to detect new abstinence, the algorithm was included to test this application in a clinical trial setting. The algorithm developed by Schwilke and colleagues was designed to detect resumption of use from abstinence with two rules to account for differing patterns of urinary CN-THCCOOH concentrations dependent on the whether the initially measured urine was less than or greater than 800 ng/mg. Specifically, the second rule