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Incremental validity of estimated cannabis grams as a predictor of problems and cannabinoid biomarkers: Evidence from a clinical trial

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ABSTRACT

Background: Quantifying cannabis use is complex due to a lack of a standardized packaging system that contains specified amounts of constituents. A laboratory procedure has been developed for estimating physical quantity of cannabis use by utilizing a surrogate substance to represent cannabis, and weighing the amount of the surrogate to determine typical use in grams.

Method: This secondary analysis utilized data from a multi-site, randomized, controlled pharmacological trial for adult cannabis use disorder (N = 300), sponsored by the National Drug Abuse Treatment Clinical Trials Network, to test the incremental validity of this procedure. In conjunction with the Timeline Followback, this physical scale-based procedure was used to determine whether average grams per cannabis administration predicted urine cannabinoid levels (11-nor-9-carboxy-Δ9-tetrahydrocannabinol) and problems due to use, after accounting for self-reported number of days used (in the past 30 days) and number of administrations per day in a 12-week clinical trial for cannabis use disorder.

Results: Likelihood ratio tests suggest that model fit was significantly improved when grams per administration and relevant interactions were included in the model predicting urine cannabinoid level ($X^2 = 98.3$; $p < 0.05$) and in the model predicting problems due to cannabis use ($X^2 = 6.4$; $p < 0.05$), relative to a model that contained only simpler measures of quantity and frequency.

Conclusions: This study provides support for the use of a scale-based method for quantifying cannabis use in grams. This methodology may be useful when precise quantification is necessary (e.g., measuring reduction in use in a clinical trial).

1. Introduction

To advance our understanding of the precipitants and effects of cannabis use, define excessive or problematic use, and develop effective interventions for problematic use, we must first establish a reliable system for measuring quantity and frequency of cannabis use. The most commonly used quantification method is a calendar-based tool designed to enhance recall, known as the Timeline Followback (TLFB) method (Sobell and Sobell, 1992; Fals-Stewart et al., 2000). The TLFB probes individuals to report on substance use (yes/no), amount of the substance (e.g., in grams or joints), and in some instances, the number of times used per day in the designated assessment time frame (i.e., past 30 days, past 90 days). Asking individuals to report on their own quantity and frequency of cannabis use is perhaps the easiest and most cost-effective method; however, it is limited by an individual's ability to recall specifics about his/her use (e.g., Schwarz, 2007) and difficulty estimating the amount of cannabis physically used (Gray et al., 2009). While the TLFB uses memory aids to enhance retrospective recall, this does not circumvent quantity estimation errors. Researchers have developed standardization systems for estimating quantity of use for some substances. For example, cocaine and heroin quantity are often estimated by having participants report the amount of money spent on the substance per day (Ehrman and Robbins, 1994). Alcohol use is often reported with reference to a pre-defined "standard drink" based on the approximate ethanol content (Kalinowski and Humphreys, 2016).

Reliable quantification of cannabis use is particularly difficult because of multiple modes of preparations, variations in the amount used for each preparation, strength (i.e., amount of THC/psychoactive constituents, often referred to colloquially as "potency"), and the number of others sharing for a particular administration. Additionally, cannabis

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is not obtained in a standardized amount as are alcohol and cigarettes (Gray et al., 2009). To overcome this, Mariani et al. (2011) used a surrogate substance (oregano) in concert with a traditional 30-day TLFB to estimate how much cannabis individuals used during each episode of use. Individuals placed an amount of oregano that represented their typical quantity of use into a pipe or rolling paper/leaf cigar wrappers, depending on their typical methods of use. The oregano was then weighed on a scale to obtain typical quantity in grams. Given the added time and cost associated with this detailed quantification procedure, it is important to determine whether quantity (gram estimation) provides incremental predictive validity above and beyond frequency of cannabis use and simpler methods for assessing quantity of cannabis use.

Prior work has demonstrated that quantity of cannabis used significantly predicts cannabis problems and dependence, even after accounting for frequency of use (Norberg et al., 2012; Walden and Earleywine, 2008; Grant and Pickering, 1999; Zeisser et al., 2012); however, the detailed quantification procedure did not significantly add incremental validity to a single-item measure of quantity when predicting problems due to cannabis use ($\Delta R^2 = 0.05$; Norberg et al., 2012). To our knowledge, whether quantity (in grams) or Mariani et al. (2011) estimation procedure incrementally predicts quantitative urine cannabinoid levels has not been examined. If self-reported quantity of use reflects the degree of physiological exposure to cannabis use, it can be used to understand dose-specific effects on health and neurocognitive functioning. The association between self-reported cannabis use and biomarkers is limited due to variation in the bioavailability of cannabis. However, we can conclude that improvement in prediction of a cannabis biomarker (i.e., quantitative urine cannabinoid level) means that the added specificity in self-reported cannabis use results in a more accurate indicator of physiological exposure to cannabis. Thus, the goal of this study is to replicate and extend work by Norberg et al. (2012) and determine whether self-reported quantity (grams) of cannabis use, facilitated by use of the surrogate substance, predicts 1) quantitative urine cannabinoid levels, and 2) problems due to cannabis use, after accounting for self-reported frequency (number of days) of cannabis use and number of joints/blunts/other methods of administration per day. It is hypothesized that use of the surrogate substance to facilitate report of cannabis use quantity will provide incremental validity beyond number of days used and number of joints/blunts when predicting urine cannabinoid level, but not problems due to use, consistent with findings from Norberg et al. (2012).

2. Method

2.1. Participants

Adults ($N = 302$) ages 18–50 who were seeking treatment for cannabis use disorder (CUD) were recruited for a multisite clinical trial sponsored by the National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) using community/media advertisements (Clinicaltrials.gov: NCT01675661). Applicants were eligible if they provided a positive urine cannabinoid test at screening, endorsed criteria for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) cannabis dependence, were interested in treatment for CUD, and, if female, agreed to use birth control. Applicants were excluded if they met DSM-IV-TR substance dependence other than cannabis or tobacco, provided a urine drug screen positive for non-cannabinoid substances, recently used synthetic cannabinoids, were currently using or allergic to *N*-acetylcysteine (due to aims of the clinical trial), were in treatment for substance use, had asthma, were pregnant or breastfeeding, or had any uncontrolled medical or psychiatric illness. Two participants were excluded from analyses due to missing scale data (for computation of grams), resulting in an analytic sample of N = 300. The average age of participants was 30.3 (SD = 9.0) and the sample was 71.7% male, 58.7% White, 27.3% Black or African American, and 30.3% unemployed and looking for work. Additional characteristics of the full sample are provided in Gray et al. (2017).

2.2. Procedures and measures

Study procedures and results from the primary clinical trial have been described in detail elsewhere (McClure et al., 2014; Gray et al., 2017). The multi-site study was approved by Institutional Review Boards at each study site prior to data collection.

Briefly, participants were randomized to receive *N*-acetylcysteine (2400 mg/day) or matched placebo for 12 weeks. All participants received abstinence-based contingency management in addition to medication or placebo. At an initial screening visit, pre-treatment visit, weekly study visits, and at one month follow-up, participants provided urine samples for quantitative cannabinoid testing. Urine drug screens were collected twice per week, but quantitative testing was conducted only on the first sample obtained per week. They also reported on cannabis use in the past 30 days (at the screening visit) and in between study visits via the TLFB. Data from the initial screening visit, pre-treatment visit, and weekly study visits are included in the current analysis.

2.2.1. Self-report of cannabis use/gram estimation

At the initial screening visit, participants were asked to complete a *Timeline Follow-Back* (TLFB; Sobell and Sobell, 1992) to assess frequency and quantity of past 30 day cannabis use prior to study initiation. For each day, participants reported whether they had used cannabis (yes/no) and the number of joints, blunts, pipes, bowls, vaporizers, spliffs, edibles, or other methods used. If participants shared a joint/blunt/etc. or otherwise did not use a full joint/blunt/etc., partial numbers were reported. Participants were then provided with rolling papers and dried motherwort. For each method of cannabis use (e.g., joints, blunts) that the participant reported in the previous 30 days, they were asked to place an amount of motherwort (in place of the oregano used by Mariani et al., 2011) that represented their typical quantity of use into rolling papers or directly on the scale, depending on their typical methods of use. The motherwort was weighed on a scale to obtain typical quantity in grams.

At subsequent visits, the scale estimation procedure was only repeated if a participant reported a new mode of use (i.e., used blunts since last visit, but had not reported any blunt use at initial screening visit). Otherwise, participants reported only their daily cannabis use in between visits (yes/no) and the number of joints/blunts/etc. used. See Fig. 1 for an illustrative example of daily gram calculations for a hypothetical participant.

2.2.2. Quantitative urine cannabinoid level

Urine cannabinoid samples were collected at the screening visit, pre-treatment/randomization visit, and weekly during treatment. Urine cannabinoid (11-nor-9-carboxy-Δ9-tetrahydrocannabinol) was batch assayed in thawed frozen (-80C) samples using an enzyme immunoassay (Abbott Laboratories) on an Architect Autoanalyzer (Abbot Labs) in the Clinical Neurobiology Labs at the Medical University of South Carolina. The lowest quantifiable amount was 10 ng/mL and levels 20 ng/mL or above were reported, while values above 200 ng/mL were diluted to provide a quantifiable amount. The inter-assay coefficient of variability (CV) for two controls run with each assay were 11.2% (low) and 5.9% (high) respectively. Urine creatinine was also measured to provide an estimate of sample dilution, as previous research has shown that failure to account for sample dilution may lead to misinterpretation (Huestis and Cone, 1998; Lafolie et al., 1991). Because there is some deliberation regarding whether normalizing cannabinoid level through the use of a cannabinoid-creatinine ratio is the optimal way of accounting for dilution (Mikulich-Gilbertson, 2016), we instead used creatinine as a covariate in relevant models in which unadjusted cannabinoid level was the outcome variable. Creatinine-