Recent Self-Reported Cannabis Use Is Associated With the Biometrics of Delta-9-Tetrahydrocannabinol

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ABSTRACT. Objective: Research typically characterizes cannabis use by self-report of cannabis intake frequency. In an effort to better understand relationships between measures of cannabis use, we evaluated if Δ -9-tetrahydrocannabinol (THC) and metabolite concentrations (biometrics) were associated with a calibrated timeline followback (TLFB) assessment of cannabis use. **Method:** Participants were 35 young adult male cannabis users who completed a calibrated TLFB measure of cannabis use over the past 30 days, including time of last use. The calibration required participants handling four plastic bags of a cannabis substitute (0.25, 0.5, 1.0, and 3.5 grams) to quantify cannabis consumed. Participants provided blood and urine samples for analysis of THC and metabolites, at two independent laboratories. Participants abstained from cannabis use on the day of sample collection. We tested Pearson correlations between the calibrated TLFB measures and cannabis biometrics. **Results:** Strong correlations were seen between urine and

blood biometrics (all $r > .73$, all $p < .001$). TLFB measures of times of use and grams of cannabis consumed were significantly related to each biometric, including urine 11-nor-9-carboxy- Δ 9-tetrahydrocannabinol (THCCOOH) and blood THC, 11-hydroxy-THC (11-OH-THC), THCCOOH, THCCOOH-glucuronide (times of use: $r > .48$ –.61, all $p < .05$; grams: $r > .40$ –.49, all $p < .05$). **Conclusions:** This study extends prior work to show TLFB methods significantly relate to an extended array of cannabis biometrics. The calibration of cannabis intake in grams was associated with each biometric, although the simple TLFB measure of times of use produced the strongest relationships with all five biometrics. These findings suggest that combined self-report and biometric data together convey the complexity of cannabis use, but allow that either the use of calibrated TLFB measures or biometrics may be sufficient for assessment of cannabis use in research. (*J. Stud. Alcohol Drugs*, 79, 441–446, 2018)

MANY STUDIES INVESTIGATING CANNABIS consumption deploy the calendar-based Timeline Followback (TLFB) method to characterize cannabis use. The TLFB approach specifically measures how often (i.e., frequency: over past month, year, lifetime) a number of joints of cannabis are smoked (i.e., quantity) (Medina et al., 2009; Padula et al., 2007; Schweinsburg et al., 2008; Tapert et al., 2007). This method provides greater specificity of the quantity and frequency of cannabis consumed when compared with clinical interviews (Structured Clinical Interview for DSM-

IV [SCID]) or categorical self-reports of cannabis use (e.g., the adapted CAGE questionnaire); however, all self-report drug use measures have been fraught with accuracy challenges (Harrison & Hughes, 1997). This led one group to develop a calibrated TLFB approach (Norberg et al., 2012).

Norberg and colleagues (2012) modified the TLFB method by having participants view and feel a cannabis substitute to estimate the amount of cannabis (in grams) used to fill joints. They argued that this approach was a reliable and valid method to assess cannabis intake and that it appeared to have greater sensitivity to the amount of

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cannabis consumed. It is not without its own limitations, however, because self-report cannot assess objective levels of Δ -9-tetrahydrocannabinol (THC), which is the constituent principally responsible for the desired psychoactive cannabis effects. Biological measures or metrics (biometrics) of THC and its metabolites might fill this gap by quantifying actual THC intake within pharmacokinetic time windows (Huestis, 2007). All biometrics have limited detection windows given their kinetics of distribution and elimination; this suggests studies assessing long-term exposure to cannabis might benefit from a broader evaluation of the connection between self-report measures and biological measures of THC and metabolites, in line with calls for standardizing cannabis use metrics and quantification of biological samples (Lorenzetti et al., 2016; Solowij et al., 2016).

THC is one of 104 known phytocannabinoids, which are structurally related compounds unique to *Cannabis sativa* (ElSohly & Gul, 2014). THC is detectable in blood within minutes following smoking or inhalation use (ElSohly & Gul, 2014). Because of its high lipophilicity, THC bioaccumulates in various tissue reservoirs of the chronic frequent user. THC undergoes Phase I hydroxylation to form the psychoactive metabolite 11-hydroxy-THC (11-OH-THC), which is further oxidized to the inactive metabolite 11-nor-9-carboxy-THC (THCCOOH) (Mushoff & Madea, 2006). THCCOOH is further metabolized through a Phase II conjugation with glucuronic acid to form THCCOOH-glucuronide (Desrosiers et al., 2014; Drummer & Wong, 2013; Scheidweiler et al., 2016).

In blood, the presence of THCCOOH can be detected for up to 7 days in occasional cannabis users (Scheidweiler et al., 2013), and at least 30 days in chronic cannabis users during sustained abstinence with a low 0.25 $\mu\text{g/L}$ limit of quantification (Bergamaschi et al., 2013). Under more routine circumstances, THC in blood of occasional cannabis users decreases below most standard cutoffs (limits of quantification [LOQ] = 1–5 $\mu\text{g/L}$) between 3 and 4 hours after use and after several days in frequent users (Scheidweiler et al., 2013). In urine, the detection window for THCCOOH after hydrolysis is expected to be between 1 and 2 days following occasional use with a typical 50 $\mu\text{g/L}$ cutoff, and to be much longer in chronic cannabis users (U.S. Department of Health and Human Services, 2010), up to a month or more under extreme conditions (Mushoff & Madea, 2006). THC-glucuronide concentrations in urine are not an ideal candidate for monitoring as they are typically low and rapidly eliminated.

From our assessment of the literature, at least two studies evaluated the relationship between self-report measures of cannabis use and these blood and urine biometrics of cannabis exposure. One study did not use the TLFB methodology to assess quantity and frequency of cannabis use but used three self-reported measures of cannabis use, which were associated with THCCOOH concentrations in plasma and

hair THC (Meersseman et al., 2016). Another study did use TLFB, without the calibration of Norberg and colleagues (2012), and found a relationship with blood levels of THC and 11-OH-THC (Hjorthøj et al., 2012). In the present study, we evaluated how well a calibrated TLFB assessment of cannabis use, modified from that of Norberg and colleagues (2012), along with simple times-of-use TLFB measures, related to a broader array of blood and urine biometrics. We specifically assessed THCCOOH in the urine from one laboratory, and THC, 11-OH-THC, THCCOOH, and THCCOOH-glucuronide concentrations in blood from a second laboratory. Our working hypothesis was that all biometrics would correlate with calibrated TLFB measures, potentially more than TLFB times of use.

Method

Participants

Participants were 35 men ages 18–25 who consumed cannabis at least monthly (see Supplemental Table A for age; education level; race; and recent cannabis, alcohol, and nicotine use). (Supplemental material appears as an online-only addendum to the article on the journal's website.) Participants were recruited as part of a neuroimaging study of cannabis use, allowing us to evaluate our methods assessing quantity of cannabis consumed. We recruited individuals into bins of users representing light (<0.5 g per week), moderate (0.5–3.5 g per week), and heavy (>3.5 g per week) cannabis intake to optimize sample heterogeneity. This characterization was based on TLFB, but confirmed post hoc by biometrics (see Results in the supplemental material and Supplemental Table C). Participants were recruited (a) from the community with advertising posted within and near shops that sell smoking paraphernalia and (b) online via Craigslist and paid advertisements through Facebook. The Institutional Review Board at Northwestern University Feinberg School of Medicine approved the study protocol, and all subjects provided written informed consent. See the supplemental material for information on inclusion and exclusion criteria, as well as clinical measures.

All participants were studied over three visits (please see the supplemental material for general overview). The TLFB was completed on Visit 1, and cannabis biometrics were collected on Visit 3. To confirm cannabis use consistency over the three visits of our protocol with use preceding Visit 1 measured by TLFB, we completed a marijuana history questionnaire (supplemental material) independent of the TLFB to determine how much cannabis was consumed daily for each day between the first and third study visits (Visit 1–Visit 3). From this survey of use during the study, we found that 23 of 35 subjects used on the day before magnetic resonance imaging (MRI) scanning and biometric data acquisition (Supplemental Figure A).

To minimize the effects of cannabis intoxication on behavioral and cognitive assessments performed on the day of the MRI scan and urine/blood sampling, we required verbal agreement that participants had not used on that day (Visit 3). We visually assessed that no participant exhibited overt signs of intoxication, based on a four-item marijuana intoxication scale previously used by our laboratory (Gilman et al., 2014, 2016) to evaluate four signs of acute intoxication (Karschner et al., 2011): increased resting heart rate (>100 beats per minute), congestion of conjunctival blood vessels (red eyes), slowed speech response, and giddiness. All 35 subjects stated that they had not used on Visit 3 when biometric data were acquired, and no participants were excluded based on the criteria of Karschner and colleagues (2011).

Self-reported cannabis use measures

We modified a method developed by Norberg and colleagues (2012) to calibrate the quantity of cannabis consumed by an individual (see the supplemental material for detail). We presented each participant with four plastic bags of a cannabis-like substance in sizes of 0.25 g, 0.5 g, 1 g, and 3.5 g. Participants were instructed to handle the plastic bags to help estimate how many grams they used per average singular use, how many grams consumed over a week's time, and how many grams they purchased and how long it took them to finish that amount. We clarified how many grams they used across various methods of use. We used the calibration technique to estimate whether participants typically used more than 3.5 g of cannabis per week (heavy users), between 0.5 g and 3.5 g of cannabis per week (moderate users), or less than 0.5 g of cannabis per week (light users), allowing oversight of recruitment across a broad range of use. After determining the standardized amount of cannabis intake per method for each participant, we administered the TLFB calendar to quantify both the number of times of use and the grams of cannabis used over the month before the baseline visit (i.e., Visit 1, supplemental material).

Urine-based cannabis use measures

Urine specimens were analyzed at United States Drug Testing Laboratories (Des Plaines, IL) using a Diagnostics Reagents Inc. cannabinoid screening immunoassay (DRI; ThermoFisher, Sunnyvale, CA), a validated FDA-cleared (In-vitro Diagnostic) method (with a 20 $\mu\text{g/L}$ cutoff). Briefly, 1 ml urine was analyzed on an Olympus AU640 following the manufacturer's instructions on the package insert. Presumptive positive cannabinoid results were confirmed by a fully validated gas chromatography-mass spectrometry method (see Supplemental Table B for validation cutoffs). Imprecisions were 2.6% within runs and 5.9% between runs; biases within run were 88.2% target and between run was 111.3% target.

Blood-based cannabis use measures

Blood specimens were analyzed at the Chemistry and Drug Metabolism Section, IRP, National Institute on Drug Abuse (Baltimore, MD). Briefly, 0.2 ml whole blood was deproteinized with acetonitrile and cannabinoids were extracted from the supernatants by disposable pipette extraction WAX-S tips (DPX Labs, Columbia, SC). An aliquot of the resulting organic phase was diluted with aqueous mobile phase, centrifuged, and injected onto the LC-MS/MS. Linear ranges were 0.5–100 $\mu\text{g/L}$ for THC and THCCOOH, 0.5–50 $\mu\text{g/L}$ for 11-OH-THC, and 5–500 $\mu\text{g/L}$ for THC-COOH-glucuronide. Intra- and inter-day imprecisions were 2.4%–8.5%, and analytical recoveries were 88.9%–115% ($n = 25$) (Scheidweiler et al., 2016) (see Supplemental Table B for validation cutoffs). An advantage of this study is that we used lower LOQ (ranging from 0.5 to 5) than the standard cutoffs of 1–5 $\mu\text{g/L}$ (Scheidweiler et al., 2013), indicating sensitivity for detection at lower concentrations.

Data analysis

We evaluated the demographic and cannabis intake characteristics of our participants with *t*-tests, chi-square, and analyses of variance. We evaluated the relationship between the calibrated grams and times of use TLFB measures of cannabis intake and the THC biometrics with two-tailed Pearson correlations. Corrections for multiple comparisons for the correlations were handled using the false discovery rate of $p < .05$ (Benjamini et al., 2001).

Results

Relationships among cannabis biometrics

Given that the urine-based THCCOOH biometric was assessed at a laboratory independent from the one that assessed the four blood-based biometrics, we first checked the associations between urine-based THCCOOH and each of THC, 11-OH-THC, THCCOOH, and THCCOOH-glucuronide concentrations in blood. As shown in Table 1, these associations ranged from $r = .74$ to $r = .90$ (all $p < .001$, corrected) and are shown graphically in Figure 1, Panels A–D.

Relationships among Timeline Followback measures and cannabis biometrics

We next evaluated the association of TLFB measures in grams of cannabis used (over the past 30 days) to each of the five biometrics (Table 1), and found associations from $r = .40$ to $r = .49$ (all $p < .05$, corrected). The association of TLFB measures of times using cannabis (over the past 30 days) with each of the biometrics ranged from $r = .48$ to r

TABLE 1. Pearson correlations among cannabis TLFB measures and urine and blood concentrations of THC metabolites

Variable	Urine concentration (µg/L)						Blood concentrations (µg/L)								
	THCCOOH			THC			11-OH-THC			THCCOOH			THCCOOH-glucuronide		
	<i>r</i>	<i>p</i>	<i>n</i>	<i>r</i>	<i>p</i>	<i>n</i>	<i>r</i>	<i>p</i>	<i>n</i>	<i>r</i>	<i>p</i>	<i>n</i>	<i>r</i>	<i>p</i>	<i>n</i>
TLFB (grams, past 30 days)	.40	.018	35	.49	.004	33	.46	.008	33	.41	.018	33	.41	.019	33
TLFB (times used, past 30 days)	.48	.003	35	.61	.0002	33	.57	.0005	33	.55	.0008	33	.56	.0006	33
THCCOOH (urine, µg/L)	–	–	–	.74	<.00001	33	.87	<.00001	33	.85	<.00001	33	.90	<.00001	33

Notes: TLFB = Timeline Followback; THC = Δ -9-tetrahydrocannabinol; 11-OH-THC = 11-hydroxy-THC; THCCOOH = 11-nor-9-carboxy-THC.

= .61 (all $p < .01$, corrected; Table 1) and are shown graphically in Figure 1, Panels E–I.

Discussion

This study produced three main findings. First, the urine biometric measured at one laboratory correlated significantly with the four blood-based biometrics measured at an independent laboratory, providing support for their validity and subsequent evaluation against self-report measures of cannabis use. Second, associations between the five biometrics and both TLFB measures (times used and grams of cannabis

used over the past 30 days) were significant after correcting for multiple comparisons. Third, contrary to expectations, TLFB measures of times using cannabis over the past 30 days produced stronger associations with all the biometrics than the TLFB measures of grams of cannabis use over the past 30 days.

This study directly supports and extends the work of Hjorthøj and colleagues (2012) and Meersseman and colleagues (2016) to argue that TLFB techniques strongly relate to the underlying biometrics reflecting cannabis use (Huestis, 2007). Our study extended the work of Meersseman et al. (2016) to use multiple blood-based biometrics with improved

FIGURE 1. Graphs of correlations between Timeline Followback (TLFB) and biometrics, and between urine and blood biometrics. Panels A–D show the correlation graphs and r values between urine biometrics (x-axis) and four blood-based biometrics (y-axis). As noted next to the r values, $^{**}p < .01$. Panels E–I show correlation graphs and r values between the calibrated TLFB measure of total times of cannabis use in 30 days (x-axis) and biometrics in urine (E) and blood (F–I) (y-axis). Correction for multiple comparisons followed a false discovery rate of $p < .05$, and $^{**}p < .01$ as noted by r values.

LOQ, and included a urine biometric. Although Meersseman et al. (2016) did not use the TLFB methodology to assess quantity and frequency of cannabis use, they observed that three self-reported measures of cannabis use were associated with THCCOOH in plasma. In contrast to the Hjorthøj et al. (2012) study, our work extended the panel of biomarkers from two blood-based biometrics to four with improved LOQ, and included a urine biometric. We also used a TLFB method modified from that of Norberg and colleagues (2012) to show that calibration of TLFB techniques correlates with biometrics, although the simple assessment of times of use with TLFB produced the strongest relationships with all five biometrics. Together, our work and their studies strongly argue for the validity of self-report methods of cannabis use. This being said, the observed self-reported measure of cannabis use did not correlate with the ground-truth of biometrics in the way that urine-based concentrations correlated with blood-based concentrations.

Based on the present study, we propose that an ideal approach to quantifying cannabis for future studies would be to use a combination of TLFB with biometrics to optimize assessment of cannabis use. Not all studies will have the resources to perform both, so in these cases either a calibrated TLFB in grams or in times of use might serve as an effective measure of cannabis use. A strength of our calibration method is that it is standardized and time efficient and requires fewer resources than the method of Norberg et al. (2012), which requires each participant to weigh and prepare a cannabis substitute. This may be important for other studies with time limitations and where multiple protocols are implemented. The current study showed that the calibration of grams of use was not as strongly related to biometrics as times of use, but this observation must be tempered by the fact that the times of use estimate was done through the lens of individuals calibrating their usage for the TLFB approach.

A limitation to using the calibrated method to assess the quantity of cannabis use is that the concentration of THC in cannabis sold on the street is not regulated and can be highly variable (ElSohly et al., 2000). Additional limitations include small sample sizes, and cross-sectional data, so we cannot infer causality regarding the relationship between the calibrated method of assessing cannabis quantity consumed and THC biometrics. There was also a nonstandardized time delay between assessing self-reported cannabis use on the TLFB and collection of biometrics. This time delay may introduce variance into the relationships between TLFB and biometric measures and reduce the statistical effect of their association; however, this may make our findings more generalizable to many time-restricted research and clinical scenarios. In addition, we did not account for individual differences in metabolism, which future studies may wish to include as a covariate. Last, the current study assessed young adult male users ages 18–25 years old, with more than 70%

beginning cannabis use before age 18. Thus, the findings of this study have limited generalizability among individuals who began using after age 18 and among individuals regularly using cannabis for less than 1 year.

In summary, a calibrated TLFB method of cannabis use (times and grams) over the past 30 days was significantly correlated with urine THCCOOH and multiple THC metabolites in blood, including THC, 11-OH-THC, THCCOOH, and THCCOOH-glucuronide. Although THC potency varies considerably in cannabis, the calibrated TLFB method provides an approach to assess the quantity of cannabis intake that correlates with five biometric measures. Future research might consider assessing cannabis use with THC biometrics along with calibrated TLFB to optimize characterization of the variation in cannabis consumed by study participants.

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