A Feasibility Test of the In Vivo Driving Impairment Research Method: Examining Cannabinoid Concentrations as Predictors of Risky Drinking

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ABSTRACT

We tested the feasibility of a new approach to examining drugged driving – the In Vivo Driving Impairment Research Method (IVDIRM). Heavy cannabis users with a history of driving after using were recruited. The volunteers agreed to have their cars instrumented with data loggers and drive normally for six to 10 days. Participants also agree to provide oral fluid samples, which later were assayed for cannabinoid concentrations, whenever they drove. We anticipated that participants, of their own volition, would produce multiple occurrences of drugged driving at different measured drug levels. Cannabinoid concentrations then would be used to predict driving behavior measured by the instrumentation, using a within-subjects design to accommodate individual differences in personality, driving style, risk-taking, etc. We tested the hypothesis that measuring and modeling cannabidiol (CBD) would improve prediction of driving impairment beyond simply looking at delta-9-tetrahydrocannabinol (THC). A sample of 30 participants provided 358 oral fluid samples that were linked to driving data, indicating indeed that the IVDIRM method was viable. Mixed-model analysis found that subjects' CBD levels were important for predicting risky driving; participants with high THC concentrations who also tested positive for CBD demonstrated a higher rate of elevated g-force events while driving than those who tested negative for CBD. When CBD was zero, the predicted proportion of elevated X-axis G-force events (from acceleration and braking) ranged from approximately 0.05 to 0.08 across the distribution of THC scores. When CBD was positive, the predicted proportion ranged from approximately zero to above 0.14. For elevated Y-axis G-force events (from turning and swerving), when CBD was zero the proportion was close to 0 and flat across THC scores. When CBD was positive, predicted elevated Y-axis events ranged from 0 to approximately 0.025.

Key words: cannabis use, menstrual cycle, stress, sex, females

This brief report has two objectives. The first is to introduce a new methodology for examining drugged driving, with a current focus on cannabis. Despite increased research on the topic, it remains unclear whether and to what extent cannabis contributes to crash involvement. Experimental cannabis dosing studies routinely find evidence of dose-specific impairment on cognitive and psychomotor driving-related skills, as well as on simulated driving (Capler et al., 2017; Hartman & Huestis, 2013). However, these studies tend to lack external and ecological

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validity. On the other hand, epidemiological drugged driving crash studies tend to lack internal validity (i.e., no experimental control) and have produced inconsistent findings. The two most recent major field crash studies produced contrasting results (Hels et al., 2011; Lacey et al., 2016), and in a recent meta-analysis (Gjerde et al., 2015) one in three studies examined found no association between cannabis use and crashes. Another meta-analysis (Rogeberg & Elvik, 2016) found that associations between cannabis use and crashes were weaker in higher quality studies. The new methodology described herein – the In Vivo Driving Impairment Research Method (IVDIRM) – is a naturalistic, hybrid method designed to bridge the gap between existing approaches. We present an initial feasibility study to test this methodology.

The second objective is to test the novel hypothesis that driving impairment is predicted not only by delta-9-tetrahydrocannabinol (THC) but also by cannabidiol (CBD), a compound that appears in only some strains of cannabis. Whereas THC is responsible for the euphoric high of cannabis (along with associated side effects of anxiety and paranoia) (Moore et al., 2007) some toxicological studies link cannabis high in CBD to mental and physical sedation (Crippa et al., 2004; Pearce et al., 2014; Zhornitsky & Potvin, 2012). Cannabis high in CBD mixed with THC is described as producing a sleepy, dreamlike experience and cannabis high in CBD alone as producing a lethargic "body-stoned" experience (Frank & Rosenthal, 1988; Martin, 2012). Because attention and vigilance are key factors to safe driving (Evans, 2004; Klauer et al., 2006), compounds that promote sedation might interfere with safe driving even if not intoxicating.

In this research we examined both THC and CBD as predictors of driving impairment and hypothesized that high CBD would be associated with riskier driving. Few studies have examined CBD as a potentially impairing agent. Evaluations of a THC-CBD medical nasal spray found no effects on self-perceptions of impairment or psychomotor task performance (Celius & Vila, 2018; Rekand, 2014), nor did a laboratory study of pharmaceutical cannabinoids (Bird et al., 1980). However, a small pilot study on medicinal cannabinoids found trends suggesting impairment from CBD on vigilance tasks (Guy, Robson, Earnshaw & Flint, 2000). The IVDIRM feasibility study is the first to examine the relationship between THC and CBD on real-world driving and uses commercially available cannabis products to do so.

METHOD

The IVDIRM is an example of "controlled epidemiology". The method involves (1) recruiting heavy cannabis users with a history of driving after using; (2) equipping participants' vehicles with instrumentation and asking them to drive normally for six to 10 days; and (3) having them provide oral fluid samples during each driving trip. Oral fluid samples were assayed for THC and CBD concentrations (ng/ml) which were linked to driving behavior captured by the vehicle instrumentation. We anticipated that these heavy users, of their own volition, would produce multiple occasions of drugged driving and at varying drug levels. These cannabinoid concentrations would be used to predict risky driving.

Like other epidemiological drugged driving studies, analyses were based on drug levels measured in-the-system rather than on a comparison of strain potencies. Because we examined the same participants over time, we could control for individual differences in personality, driving style, risk-taking, etc., in relating drug results to driving. Success of the IVDIRM feasibility trial was predicated on participants providing oral fluid samples that could be linked to driving data, and the method producing analyzable data.

Participants

Participants were recruited via advertisements in cannabis dispensaries and through listservs of private cannabis clubs around Denver, Colorado. Eligible participants (a) used cannabis at least twice monthly; (b) drove several times per week; (c) were aged 21 and older; (d) were not pregnant; (e) had no more than two moving violations or one at-fault accident in the past 3 years; (f) had no driving while intoxicated (DWI) or driving under the influence (DUI) arrests on their driving record; (g) scored <12 on the Drug Abuse Screening Tool [21]; (h) had no use of illicit drugs other than cannabis; and (i) had

no indication of psychosis (Degenhardt, Hall, Korten & Jablensky, 2005).

Protocol

Instrumentation. Participants' vehicles were equipped with Aaronia GPS data loggers (http://www.aaronia.com/products/spectrum-analyzers/GPS-Logger) which recorded vehicle GPS information (e.g., coordinates, speed, heading, etc.) at one reading per second and acceleration data (g-forces on the X, Y and Z) at four readings per second.

Biological samples. Participants were instructed to provide an oral fluid sample using a Quantisal™ collection tube each time they went driving. For longer trips, subjects were asked to provide a second sample. Subjects stored tubes in a cooler provided by the study and samples were picked up every other day. Oral fluid samples were assayed for THC and CBD by Immunalysis Corporation (Pomona, California). Confirmation tests (to obtain quantitative concentrations) were performed using gas chromatography-mass spectrometry (GC/MS) or liquid chromatography-mass spectrometry (LC/MS/MS) technology. In addition to oral fluid collection, participants were given a calibrated breathalyzer that stored results internally and were instructed to provide a breath sample each time they provided a saliva sample.

Data Elements

Cannabinoid and alcohol concentrations. Assays of oral fluid samples produced quantitative concentrations (ng/ml) of THC and CBD. We determined *a priori* that drug concentrations would be valid for a 10-minute period and used to predict driving behavior within that period. If an oral fluid sample was collected at 1:05 p.m. those resultant drug concentrations would be used to predict only the driving data that occurred from 1:00 to 1:10 p.m. There were only two occurrences of mixing alcohol with cannabis, and both BACs were below .02 g/dl. Alcohol readings were not included in analyses.

GPS data. Time-stamped GPS readings provided a temporal framework for the dataset. A new driving trip was indicated by a 10-minute break in driving. GPS coordinate data were geocoded using ArcGIS software to reflect individual roads and formal road classifications (i.e., parking lot, interstate, expressway, arterial roadway, residential street, and ramps/exist).

Accelerometer data. Accelerometer data were collected at 4 readings per second and were automatically linked with GPS data. Given the goal of the research, we only examined accelerometer data that fell within the 10-minute windows for which we had THC and CBD concentrations (see above). In other words, subjects provided one or two saliva samples per trip, and we only examined driving data collected in close proximity to the drug results.

Our analytic strategy involved leveraging the vast amount of accelerometer data collected to improve statistical power. However, raw accelerometer data is cumbersome and noisy and perhaps too refined for driving behavior. To simplify, we aggregated the raw data into 5-second blocks, which served as the unit of analysis for the study. Every five-second block, therefore, included 20 accelerometer readings (5 seconds x 4 readings per second) from which we computed the dependent measures. Every 10-minute window of valid THC/CBD concentrations contained 120 5-second blocks (120 x 5 seconds = 600 seconds).

Dependent measures. For this brief report we examined elevated G-force events as a measure of risky driving. Prior research found that "jerky driving"—for example, driving events (such as braking) exceeding 4.0 m/s^2 (.408 gs)—predicted crashes and near crashes (Bagdadi & Varhelyi, 2011; Simons-Morton et al., 2012). Therefore, in this study, for each 5-second block of driving data we used maximum absolute g-force readings from the accelerometer to compute whether or not there was an elevated g-force event. Separate X- and Y-axis elevated g-force variables were created, and these served as the dependent measures.

RESULTS

Sample

Out of 91 individuals who expressed interest, 30 were deemed eligible, recruited and consented. The majority (56.7%) was male and ages ranged from 22 to 57 (median = 37). Most of the sample was White, non-Hispanic (63.3%), with five Black, four Hispanic, one Asian, and one Native American driver. Most participants (60%) used cannabis several times per day, while the remainder used daily or almost daily. All

participants had a history of driving while under the influence of cannabis at least monthly. Most participants had not driven within 2 hours of drinking (86.7%) in the past six-months.

Data Summary

Participants produced 358 oral fluid samples from 258 distinct driving trips that were matched with driving data. We collected some driving data without oral fluid samples as well as samples without matched driving data (likely due to technical error or forgetful subjects). This is a discussed as a limitation. Only a small proportion of oral fluid samples (10.9%) tested negative for THC. The median THC concentration was 157 ng/ml, while the mean was 454 ng/ml (SD = 721.3). Most CBD concentrations (67.3%) were 0 ng/ml. The mean CBD value was 3.0 ng/ml (SD = 20.1) but the maximum was 290 ng/ml. THC and CBD concentrations were moderately correlated, $r(358) = .27$, $p < .01$.

Given that the distribution of THC scores was positively skewed, we subjected those values to a natural logarithm transformation (first adding .0001 to all cases to make it possible to solve when THC was 0). Because two-thirds of the oral fluid tests were negative for CBD and the positive scores were highly skewed, it was unclear whether any quantitative transformation was appropriate. Therefore, we dichotomized CBD (CBD = 0 ng/ml or CBD > 0 ng/ml) for the analyses.

Main Analyses

Multilevel logistic regression was conducted using generalized linear mixed modeling in SAS. We accommodated the multiply-nested data structure by modeling subject and trip-within-subject as random effects. The primary predictors were the natural log (ln) THC concentrations, CBD category (0 versus >0), and the ln THC x CBD category interaction. Driver sex, race (White versus non-White), age, frequency of cannabis use, and road type were included as covariates.

Elevated X-axis events involved observed occurrences of driving where acceleration or braking exceed .408 g-forces (4.0 m/s^2). A dichotomous outcome (no or yes) was created for each 5-second block and regressed onto the predictors (described above). Results are displayed in Table 1.

Table 1. *Analysis of the Likelihood of Elevated X-Axis Events*

Effect	Test Statistics
Age	$F(1, 18418) = 1.5$, $p = .22$
Sex	$F(1, 18418) = 2.3$, $p = .13$
Race	$F(1, 18418) = .2$, $p = .63$
Cannabis Use	$F(1, 18418) = 0.1$, $p = .81$
Road Type	$F(3, 18418) = 17.9$, $p < .01$
ln THC	$F(1, 18418) = 21.5$, $p < .01$
CBD category	$F(1, 18418) = 5.5$, $p < .05$
ln THC x CBD	$F(1, 18418) = 8.3$, $p < .01$

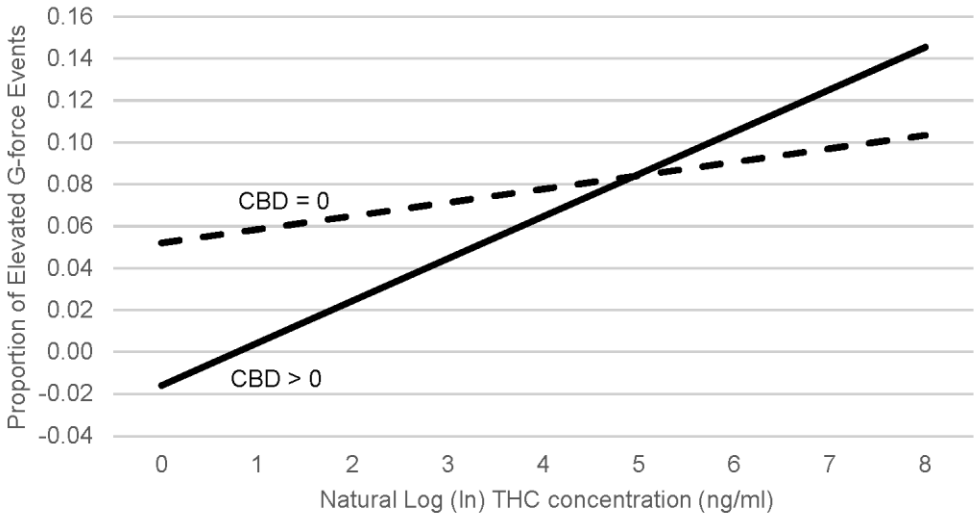

Figure 1. *Proportion of Elevated X-Axis G-Force Events as a Function of ln THC and CBD Category*

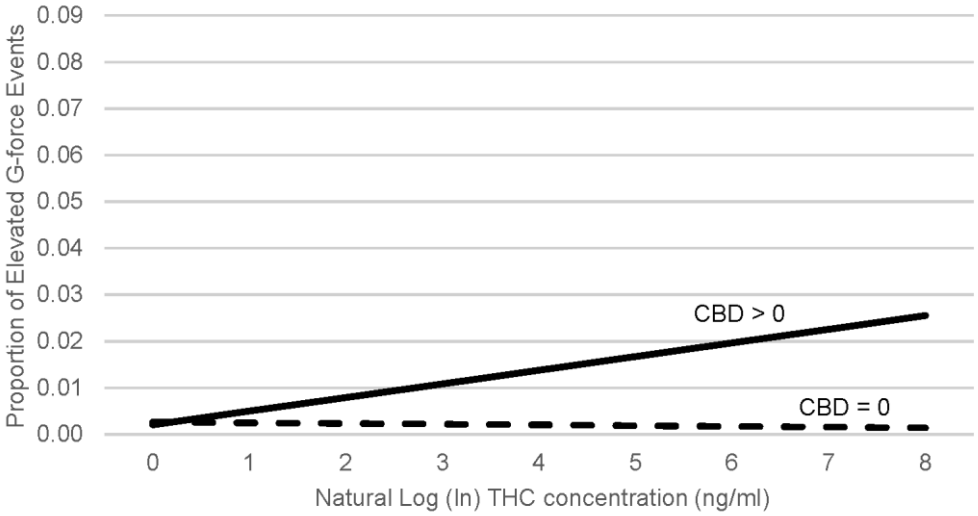

Figure 2. *Proportion of Elevated Y-Axis G-Force Events as a Function of ln THC and CBD Category*

Model-estimated likelihoods were computed across the range of THC scores, separately for samples with 0 CBD and those with CBD > 0 (Aiken & West, 1991). The results pattern is reflected in Figure 1. Elevated X-axis events were associated with increasing THC, but with a significantly steeper slope when CBD was positive. Being CBD positive predicted greater risk at higher THC levels but appeared protective at lower THC levels.

Table 2. *Analysis of the Likelihood of Elevated Y-Axis Events*

Effect	Test Statistics
Age	$F(1, 18408) = 0.6$, $p = .44$
Sex	$F(1, 18408) = 3.0$, $p = .08$
Race	$F(1, 18408) = 3.2$, $p = .07$
Cannabis Use	$F(1, 18408) = 0.1$, $p = .75$
Road Type	$F(3, 18408) = 20.2$, $p < .01$
ln THC	$F(1, 18408) = 0.5$, $p = .46$
CBD category	$F(1, 18408) = 67.0$, $p < .01$

DISCUSSION

The feasibility of the IVDIRM was predicated (a) on heavy cannabis-using participants successfully collecting oral fluid samples without direct supervision, and (b) our ability to process the data to allow statistical examination. Both were accomplished in this trial. Thirty participants provided 358 oral fluid samples collected at the same time driving data were recorded via vehicle instrumentation. While this suggests strongly that the method is viable, the process was not perfect. For example, for some trips we had driving data but no oral fluid samples, and vice versa. Although we believe this to be random, rigor should and can be improved through more user-friendly instrumentation and enhanced case management of subjects.

The data were analyzed to test a novel hypothesis about CBD as a predictor of driving impairment. THC concentrations were associated with increased elevated X-axis events (i.e., "jerky" acceleration and braking), but the association was stronger when participants also tested positive for CBD. A similar pattern emerged for elevated Y-axis events ("jerky" turning and swerving), but stronger statistical evidence suggested that being CBD-positive was linked to greater risk regardless of THC concentrations. The results of this naturalistic IVDIRM study are taken as proof-of-principle evidence that measuring and modeling CBD, and not just THC, may inform our understanding and prediction of drug impaired driving.

The unique feature of the IVDIRM is that it objectively measures real-world driving and examines the same driver over time at different

drug levels; this allows us to control for individual differences in personality, driving style, risk-taking, etc. It is important to remember, however, that the IVDIRM is not experimental. We did not randomize subjects to drug conditions, but rather relied on naturalistic data collection, and it is not appropriate to make causal inferences from IVDIRM data. It also should be noted that throughout paper we discuss the sedating effects of high-CBD cannabis, but some argue (Russo, 2011; Piomelli & Russo, 2016) that the sedation is not even due to CBD but rather to the terpene *myrcene* which often co-occurs with CBD in natural cannabis. In this case, CBD serves as a predictive proxy, further underscoring that IVDIRM should not be used for causal statements.

We further do not know if subjects actually felt sedated while driving with CBD in their systems. Higher elevated g-force events could reflect corrections to lapses in control if sedated drivers "zoned out", but they also could reflect aggressiveness. We did not measure participants' subjective experiences and thus cannot address whether the sedation hypothesis is correct. All we have are data relating cannabinoid concentrations to vehicle behavior. However, analyses of additional driving measures and two additional supporting studies are available in preprint form at http://biorxiv.org/cgi/content/short/387936v1. Additional research on how cannabinoids other than THC relate to driving is needed.

We intend to apply future applications of the IVDIRM to confirming the results of the feasibility study but with a larger sample and closer attention to drug tolerance. The IVDIRM is not a perfect methodology, but it fills an important gap between extant experimental and epidemiological approaches and offsets some of the weaknesses characteristic of those designs. The results described herein suggest that the IVDIRM is a feasible approach to exploring drug-impaired driving and has potential to advance the field through as the result of its use. Suggestions from the community on improving this methodology are welcome and appreciated.

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