## K49 Can Oral Fluid Cannabinoid Testing Differentiate Cannabis Smoking From Intake of Oral THC and Oromucosal Sativex® Administration?

*Dayong Lee, MS*, National Institute on Drug Abuse, 251 Bayview Blvd, Ste 200, Baltimore, MD 21224; Erin Karschner, BA, NIDA Intramural Research Program, Chemistry & Drug Metabolism Section, 5500 Nathan Shock D, Baltimore, Maryland 21224; Allan J. Barnes, BS, NIDA Intramural Research Program, 5500 Nathan Shock Dr, Rm 373, Baltimore, MD 21224; Garry Milman, PhD, National Institute on Drug Abuse, 251 Bayview Blvd, Ste 05A.505.16, Baltimore, MD 21224; Robert S. Goodwin, DO, PhD, NIDA Intramural Research Program, Chemistry & Drug Metabolism Section, 5500 Nathan Shock Dr, Baltimore, MD 21224; and Marilyn A. Huestis, PhD, Chemistry & Drug Metabolism, Intramural Research, NIDA, NIH, 251 Bayview Blvd, Rm 05A721, Baltimore, MD 21224*

After attending this presentation, attendees will be informed about cannabinoid disposition in Oral Fluid (OF) after a single oral $\Delta^9$-tetrahydrocannabinol (THC) or Sativex® oral mucosal administration. Dronabinol, synthetic THC, is approved in the U.S. for treating anorexia caused by AIDS and chemotherapy-associated nausea/vomiting. Sativex®, a cannabis oromucosal spray containing approximately 1:1 THC and cannabidiol (CBD), is in phase III trials for cancer pain in the U.S. and approved for multiple sclerosis symptoms in several European countries, Canada, and New Zealand. While several studies investigated OF cannabinoid pharmacokinetics following cannabis smoking, there is only one with multiple oral THC doses and none with Sativex®. This presentation characterizes OF cannabinoid time-course profiles, windows of detection, and cannabinoid ratios after the oral and sublingual drug delivery routes. Differences from cannabis smoking were evaluated for possible approaches to identifying relapse and compliance with cannabinoid pharmacotherapy.

This presentation will impact the forensic science community by providing the first data defining cannabinoid disposition in oral fluid after single-dose medicinal cannabinoid products. These data will improve interpretation of oral fluid cannabinoid testing and aid in formulating policy and legislation for oral fluid testing and in effectively managing patients undergoing cannabinoid pharmacotherapy.

**Methods**: Fourteen cannabis smokers (aged 19 – 43 yrs, 79% male, 64% African American) provided written informed consent for this double-blind, double-dummy, within-subject, Institutional Review Board-approved study. The participants resided on a closed research unit at least 10h prior to each drug administration. Five or 15mg synthetic oral THC; two (low dose, 5.4mg THC, and 5.0mg CBD) or six (high dose, 16.2mg THC, and 15.0mg CBD) actuations of Sativex®; or placebo oral THC and six placebo Sativex® actuations were administered in random order. Dosing sessions were separated by at least five days. OF specimens were collected with the Quantisal™ collection device, 0.5 hr before and 0.25, 1, 4.5, 7.5, and 10.5 hr after dosing initiation. THC, CBD, cannabinol (CBN), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) were quantified by 2D Gas Chromatography/Mass Spectrometry (GC/MS). If analyte concentrations exceeded the upper limit of linearity, participants' OF specimens were diluted with drug-free OF-Quantisal™ buffer mixture. Limits of quantification were 0.5ng/mL for THC, CBD, and 11-OH-THC, 1ng/mL for CBN, and 7.5pg/mL for THCCOOH.

**Results**: After oral THC, OF THC decreased over time from baseline concentrations ≤20.5ng/mL; concentrations were not significantly different from those after placebo, reflecting residual THC excretion from previously self-administered smoked cannabis. CBD and CBN were only detected in three specimens with concentrations ≤1.1ng/mL. After Sativex®, THC, CBD and CBN increased greatly with peak concentrations of 266 – 11,424, 196 – 12,120, and 9.5 – 560ng/mL (low dose, respectively); 1,323 – 18,216, 1,552 – 18636, and 74 – 22,32ng/mL (high dose, respectively) occurring at 0.25 – 1 hr, except one CBD at 4.5 hr. After low- and high-dose Sativex®, all specimens were positive for THC and CBD until 10.5 hr post-dose with concentrations 1.0 – 92.0 and 0.5 – 131ng/mL, respectively. After low- and high-dose Sativex®, 43% and 79% of specimens, respectively, were CBN-positive for 10.5 hr with concentrations ≤6.9ng/mL. Median (range) CBD/THC and CBN/THC ratios were 0.82 – 1.34 (0.27-2.26) and 0.04 – 0.06 (0.01-0.52), respectively, over 0.25 – 10.5 hr. In comparison, median (range) CBD/THC and CBN/THC ratios after smoking a single 6.8% THC cigarette were 0.04 – 0.05 (0.03-0.09) and 0.07 – 0.08 (0.04 –0.15), respectively, within 0.25 – 6 hr post dose. OF THCCOOH concentration changes over time were less evident and significantly masked by baseline concentrations in all dosing sessions. THCCOOH/THC ratios were <4pg/ng for 4.5 and 1 hr post Sativex® and smoked cannabis, respectively, while ratios were never below 4pg/ng after oral THC and placebo. THCCOOH/THC ratios increased over time in each dosing session.

**Conclusions**: Oral THC and Sativex™ administered in low and high dosages produced OF cannabinoid disposition different from those after smoked cannabis; THC, CBD, and CBN were rarely detected after oral THC while Sativex® generated high CBD/THC ratios. Low THCCOOH/THC ratios suggest recent Sativex® and smoked cannabis exposure. Study results indicate that relapse to smoked cannabis during oral THC pharmacotherapy for cannabis dependence should be evident with OF cannabinoid monitoring. In contrast, compliance with Sativex® pharmacotherapy should be clearly apparent by the high OF CBD/THC ratio as compared to that following cannabis smoking; however, additional research is needed to determine if relapse to cannabis smoking can be identified during Sativex® pharmacotherapy, as the high OF CBD/THC ratio after Sativex® may not be altered

 ** Presenting Author*

sufficiently to identify single smoked cannabis episodes. Interpretation of OF cannabinoid tests will be improved by these data, the first defining OF cannabinoid disposition after single-dose medicinal cannabinoid products. These data also are valuable for formulating policy and legislation for OF testing, and for effectively managing patients undergoing cannabinoid pharmacotherapy.

**Oral Fluid, Cannabinoids, Cannabis**

 ** Presenting Author*