






Pharmacology of
Cannabinoids

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Disclosures



- Most of these data derive from my research at the National Institute on Drug Abuse for more than 23 years & have no conflict of interest disclosures
- Since 2016, I am a full-time consultant & work with pharmaceutical & diagnostic companies, some with interests in the cannabinoid field, including Hound Labs
- I also consult for drug policy companies & government agencies, including PinneyAssociates

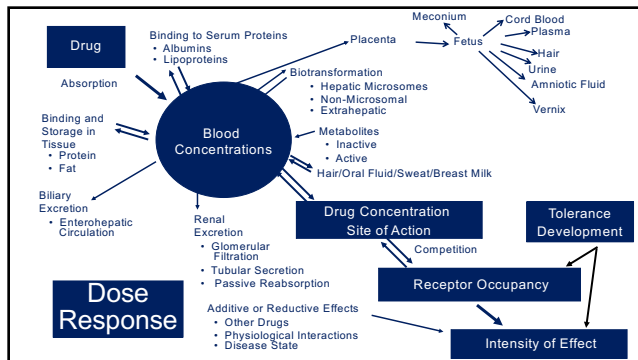
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Learning Objectives

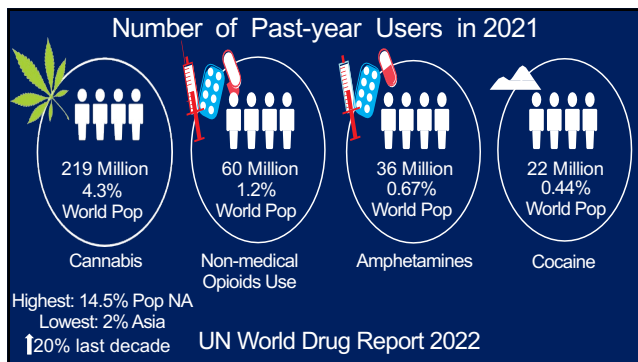


- After participating in this course, attendees will be able to describe:
 - The important functions of the endogenous cannabinoid system
 - Mechanisms of action of Δ^9 -tetrahydrocannabinol (THC) & cannabidiol (CBD)
 - The different types of available cannabinoid medications
 - The absorption, distribution, metabolism & elimination of THC
 - How counter-clockwise hysteresis complicates interpretation of blood THC concentrations
 - The differences between THC blood and plasma concentrations
 - The pharmacodynamic & pharmacokinetic differences between chronic frequent (daily) vs. occasional cannabis users
 - The pharmacodynamic & pharmacokinetic differences between smoked, vaped or oral cannabis administration

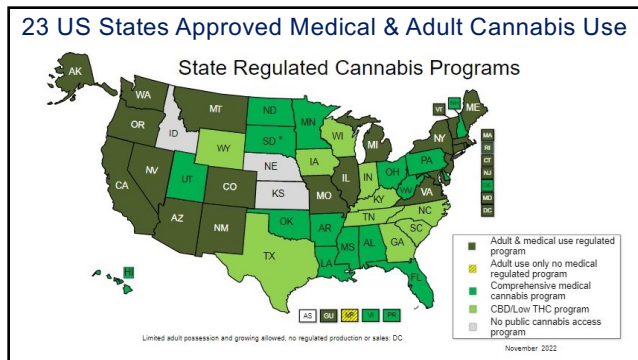
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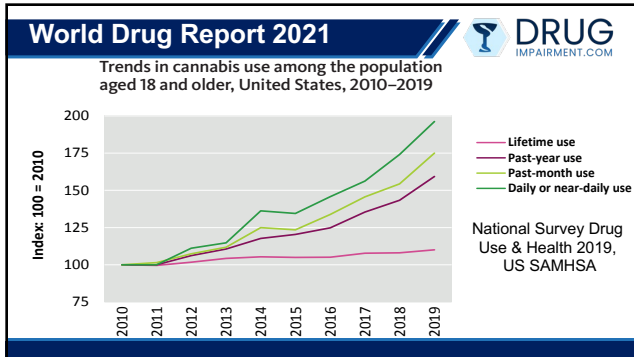
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Endogenous Cannabinoid System

- Man used the Cannabis plant medicinally & recreationally for millennia prior to understanding its important physiological, cognitive & psychomotor roles in humans
- CB1 cannabinoid receptor has highest density of any G protein coupled-receptor (GPCR) in brain & mediates most THC CNS actions

Eggen & Saffen, 2004

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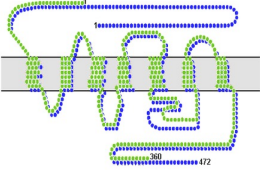
CB₁ & CB₂ Receptor Pharmacology

- G protein-coupled receptors (GCRs) bind the endogenous cannabinoids & phytocannabinoids (THC)
- Endocannabinoid system occurs in mammals, birds, fish, sea urchins, amphibians, leeches, mussels & most primitive animal with a nerve network, the Hydra
- CB1 one of highest density G-protein receptors in brain, localized on central & peripheral neuron
- Low density of CB1 receptors in astrocytes modulate synaptic transmission & plasticity

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Endogenous Cannabinoid System DRUG IMPAIRMENT.COM

- CB1 richly expressed in regions for cognition, emotion, perception & movement, with low levels in brainstem, except for emesis center
- Peripheral CB2 cannabinoid receptor reported in early 1990s, primarily in periphery, critically important for immune function

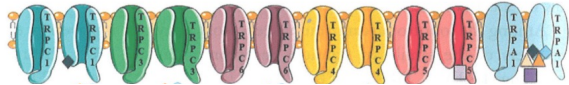


Struttura dei recettori CB1 e CB2

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Agonist-Biased Signaling & Functional Selectivity

- Cannabinoid ligands binding to cannabinoid receptors signal through different pathways including G proteins & β -arrestin, based upon the cell's function
- Endo- & phytocannabinoids also bind to other orphan G-protein receptors, transient receptor potential (TRP) ion channel, nuclear peroxisome proliferator-activated receptors (PPARs) & latest- hemopressin peptide receptors
- Biased agonism is the ability of ligands at same GPCR to elicit distinct cellular signaling profiles by stabilizing different active conformational states of the receptor



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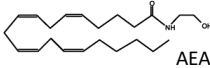
Cannabinoid Signaling DRUG IMPAIRMENT.COM

- Besides CB1 & CB2 receptors, there are other orphan GPCRs, e.g., GPCR 18, 55 & 119, transient receptor potential (TRP) channel subfamilies, nuclear peroxisome proliferator-activated receptor (PPAR) subfamilies & hemopressin peptide receptors that bind cannabinoids
- Multiple 2nd messenger systems with wide variety of responses

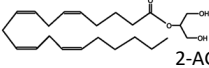
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Endogenous Cannabinoids (ECs) DRUG IMPAIRMENT.COM

- N-acyl-phosphatidylethanolamines (NAPEs) are biosynthetic precursors of AEA & other endogenous agonists at cannabinoid receptors, anandamide (AEA) & 2-arachidonyl glycerol (2-AG)



AEA



2-AG

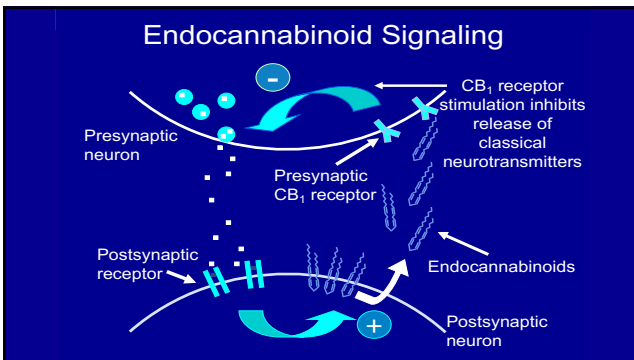
- Diacylglycerols (DAG) are the biosynthetic precursors of 2-AG & other acylglycerols

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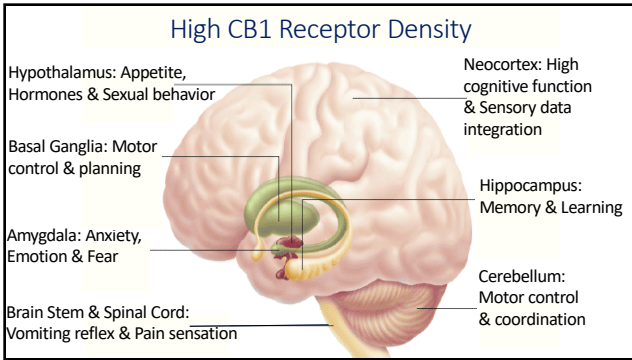
Endogenous Cannabinoid System DRUG IMPAIRMENT.COM

- EC ligands are core of lipid signaling system
- ECS plays important role in normal physiology, aberrant pathophysiology & offers hope for new pharmacotherapies for unmet clinical needs
- EC lipid congeners or lipoamines formed through conjugation fatty acids & amines connected through biosynthetic & metabolic pathways
- ECS is complex, with redundant synthetic pathways due to its critically important functions


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Drug Pharmacodynamics 


- Physiological effects
 - Heart rate, blood pressure, hormones, vision, hearing, touch, smell, respiration, consciousness, sedation, temperature control, hunger
- Cognitive effects
 - Executive function: attention, concentration, salience, memory, problem-solving, decision-making, impulsivity, inhibition, reaction time, risk taking, altered perception of time, visual search, disorientation
- Motor effects
 - Planning & implementation, reaction time, tracking, accuracy, tremors, lack of coordination/ataxia, speech difficulty, lack of coordination, weakness


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Drug Pharmacodynamics 

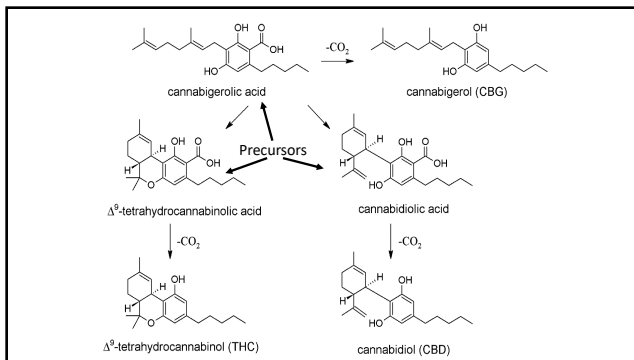
- Subjective effects
 - High, paranoia, psychosis/mania, negative affect, fear, euphoria, relaxation, mood changes, panic
- Onset, peak & duration of effects (window of drug impairment) may be unique for each effect
- Drug impairment occurs due to total performance decrement across effects
- Performance impairment changes with time after drug intake
- Behavior is the sum total of all effects occurring at a moment in time

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Cannabis 

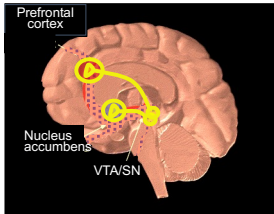
- Cannabis used medically & recreationally >4000 years
- Δ^9 -tetrahydrocannabinol (THC) is primary psychoactive compound in cannabis plant containing 21 carbons & no nitrogen 
- THC precursor Δ^9 -tetrahydrocannabinolic acid A, THCA-A present in plant that decarboxylates upon heating to produce highly lipophilic THC
- >500 chemicals (terpenes, flavonoids, polyaromatic hydrocarbons), >120 cannabinoids: cannabidiol (CBD, non-psychoactive), cannabinol (CBN, 10% as psychoactive as THC), cannabigerol (CBG) & Δ^9 tetrahydrocannabivarin (THCV)

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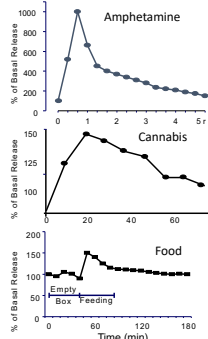


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Natural & Drug Reinforcers Increase Dopamine in NAC

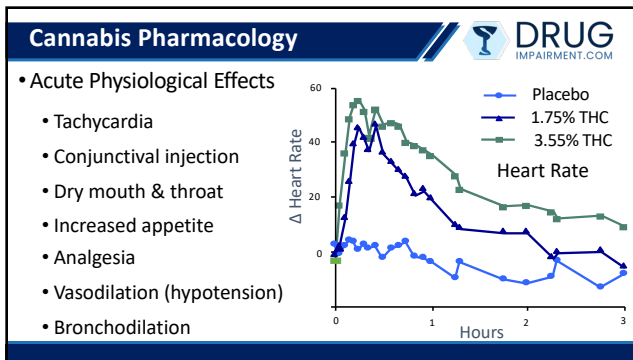


Drugs of Abuse Increase Dopamine in Nucleus Accumbens, Triggers Neuroadaptions Result in Addiction

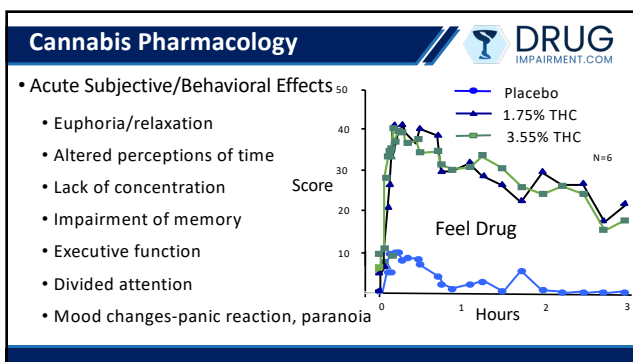


Time (min)	Amphetamine (% Basal Release)	Cannabis (% Basal Release)	Food (% Basal Release)
0	100	100	100
1	1000	120	100
2	400	140	100
5	200	130	100
10	150	120	150
20	120	150	100
30	110	130	100
40	100	120	100
60	100	110	100
180	100	100	100

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Cannabidiol (CBD)


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- Non-intoxicating cannabinoid that binds poorly to THC binding site on CB1 & CB2 receptors, but is an allosteric modulator of agonist activity at cannabinoid receptors
- CBD increases serotonergic & glutamatergic transmission through allosteric modulation of 5HT1A receptors leading to neuroprotection during acute hypoxic-ischemic conditions
- Higher CBD doses activate TRPV1 ion channel receptors promoting anxiolytic effects


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Cannabidiol Pharmacology 

- CBD metabolized in liver & intestine by CYP2C19 & CYP3A4 (phase 1) & UGT1A7, UGT1A9 & UGT2B7 (phase 2), producing hydroxylated & carboxylated metabolites
- Provides opportunity for multiple drug-drug interactions & adverse events
- CBD's inverse agonism at CB2 receptor & agonism at PPAR γ receptor may be responsible for its anti-inflammatory actions
- Also binds to adenosine receptors




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Potential Therapeutic Effects of CBD 

- Addiction disorders: Solowij 2018 in dependent cannabis users
- Antipsychotic: Leweke 2012 as effective as amisulpride, less AE
- Anxiolytic: Fusar-Poli 2009 activates limbic & paralimbic regions
- Antidepressant: Schiavon 2016 inverted U-shape dose response
- Cancer: Ivanov 2019 with γ -irradiation & chemotherapy, \uparrow cell death, \downarrow production of pro-inflammatory cytokines
- Chronic pain: National Academy of Sciences 2017
- Neuroprotection: Yücel 2016 protects against hippocampal pathology following chronic frequent THC intake
- Spasticity: Wade 2004 THC & CBD \downarrow in MS patients
- Transplantation: Soares 2021 pretreatment \downarrow organ rejection

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Current Neuropharmacology 2019;17(10):974-989.


Cannabidiol Adverse Effects and Toxicity

Marilyn A. Huestis¹, Renata Solimini², Simona Pichini², Roberta Pacifici², Jeremy Carlier³, Francesco Paolo Busardò^{4*}


¹Lambert Center for the Study of Medicinal Cannabis and Hemp, Institute of Emerging Health Professions, Thomas Jefferson University, Philadelphia, PA, USA;
²National Centre on Addiction and Doping, Istituto Superiore di Sanità, Rome, Italy. V.le Regina Elena 299, 00161, Rome, Italy;
³Unit of Forensic Toxicology (UoFT), Department of Anatomical, Histological, Forensic and Orthopedic Sciences, Sapienza University of Rome, Italy;
⁴Section of Legal Medicine, Università Politecnica delle Marche, Ancona, Italy



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Absorption: Inhalation 

- Highly efficient route of drug delivery to brain (similar to iv), with peak concentrations occurring prior to end of inhalation
- Rapid onset of effects due to speed of drug delivery to the brain
- Effective drug delivery contributes to high abuse liability of inhaled drugs (smoking, vaporizing, dabbing)
- Smoking dynamics important: # puffs, duration & volume of inhalation, hold time, time between puffs, smoking time & experience of smoker
- Individuals titrate their inhaled dose to their level of cardiovascular & subjective comfort



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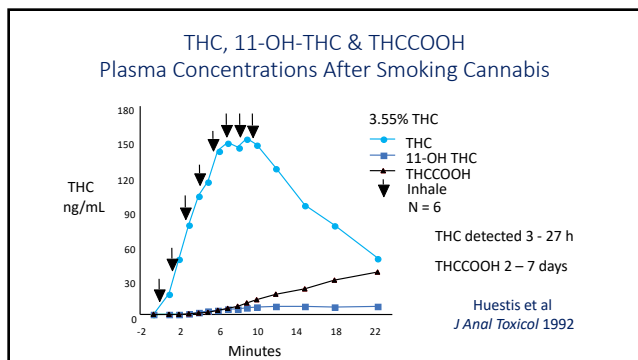
Acute Cannabinoid Pharmacokinetics in Occasional Cannabis Users

Journal of Analytical Toxicology, Vol. 16, September/October 1992

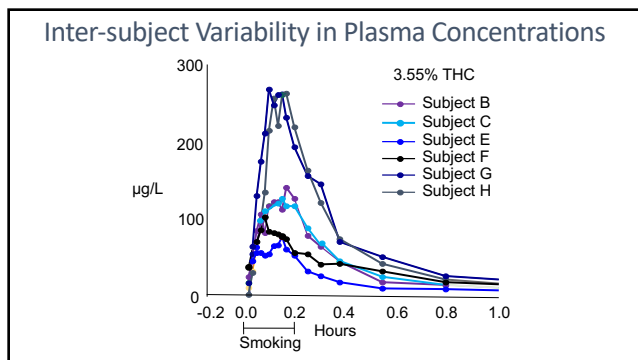
Blood Cannabinoids. I. Absorption of THC and Formation of 11-OH-THC and THCCOOH During and After Smoking Marijuana*

Marilyn A. Huestis, Jack E. Henningfield, and Edward J. Cone†
Addiction Research Center, National Institute on Drug Abuse, P.O. Box 5180, Baltimore, Maryland 21224

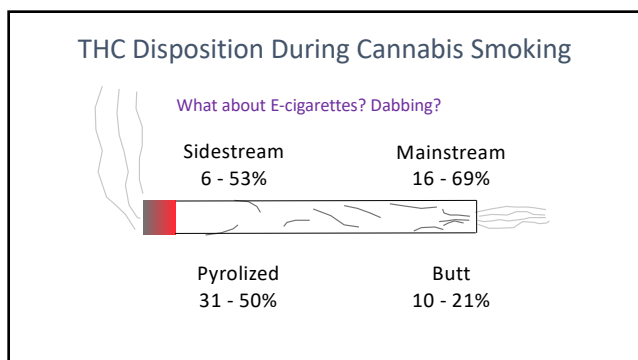
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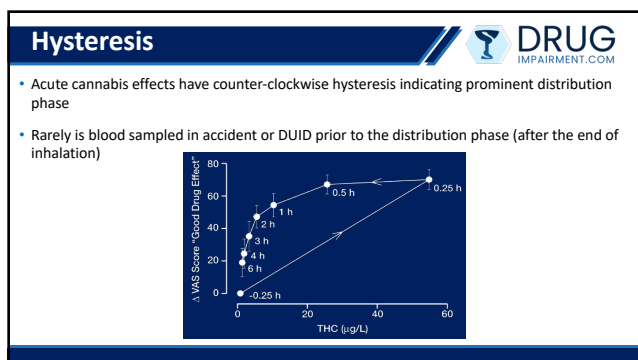
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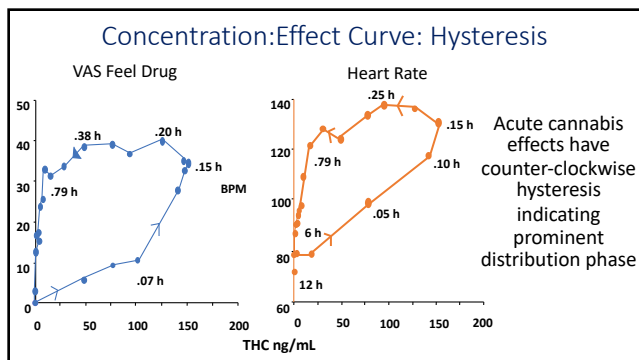
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Vaporized Cannabis




- During smoking or combustion produce toxic pyrolysis compounds
 - Carbon monoxide, polyaromatic hydrocarbons (PAHs)
 - Leads to bronchitis, coughing
- Vaporizer heats cannabis to temperature that volatilizes THC but minimizes PAHs, 210°C
- Captures vapor in balloon, minimizing sidestream loss & reducing THC degradation due to lower temperature
- Frequently used now medicinally & recreationally




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Occasional Cannabis Smokers Plasma & Oral Fluid Concentrations After Round the Clock Oral THC (Dronabinol)




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Absorption: Oral 


- Slow & erratic absorption
- Peak concentrations low, occur 1 - 5 h
- Systemic availability low 6 - 20%
- Vehicle important, degradation in gut, 1st pass effect in liver
- Effects appear later, last longer, greater effects at lower THC levels
- THC \approx 11-OH-THC




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Oral Synthetic THC/Marinol[®] 

- Synthetic THC in sesame oil
- FDA-approved medication for nausea & vomiting with cancer chemotherapy & HIV-wasting disease




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Around-the-Clock 20 mg Oral THC 

- Investigate THC & metabolite disposition in plasma during around-the-clock oral THC in chronic cannabis smokers
 - After smoked cannabis self-administration
 - Single-dose oral THC (dronabinol) pharmacokinetics
 - During continuous dosing
 - During monitored abstinence
- Evaluate tolerance development & model daily therapeutic & recreational THC intake

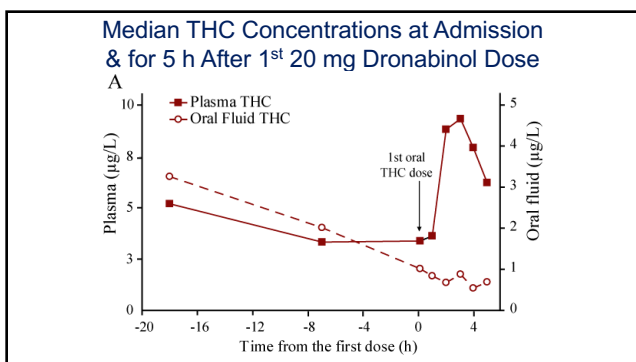
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Study Design



- Institutional Review Board-approved study & written informed consent
- Subjects 10
- Dosing 9 days 37 oral 20 mg THC doses Escalating 40-120 mg THC/day
- # Collections 36/subject
- Cannabis use 7.9 ± 8.0 (1 – 24 joints/day)
- Last cannabis use 0.7 ± 0.5 days (0 – 1)
- Lifetime use 10 ± 4.7 years (4 – 18)

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Cannabinoid Results in Plasma & OF

N = 360	Plasma			OF		
	THC µg/L	11-OH-THC µg/L	THCCOOH µg/L	THC µg/L	11-OH-THC µg/L	THCCOOH ng/L
% Positive	100	99.7	100	21.1	-	98.3
Range	1.2 - 67.6	0.6 - 38.9	13.3 - 498	0.5 - 399	-	7.5 - 1088
Median C _{max}	34.6	7.3	269	6.5	-	362
Median T _{max} (h)	104	150	161	-18.0	-	161

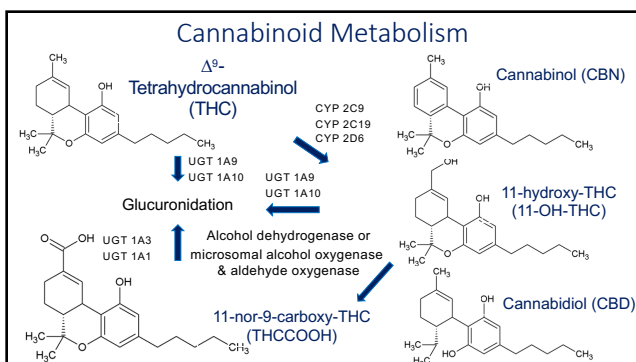
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Distribution

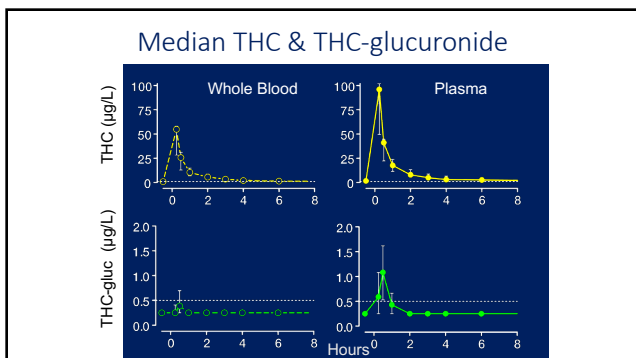
- Lipophilic, rapid distribution to highly perfused tissues, then fat
- Clearance \approx hepatic flow 0.8 L/min
- Highly protein bound in blood \approx 97%
- Volume of distribution \sim 3.4 L/kg
- Enterohepatic circulation
- Slow release of sequestered drug from tissues rate limiting step in elimination

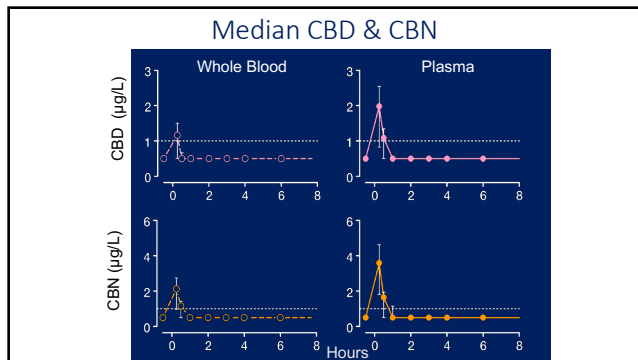
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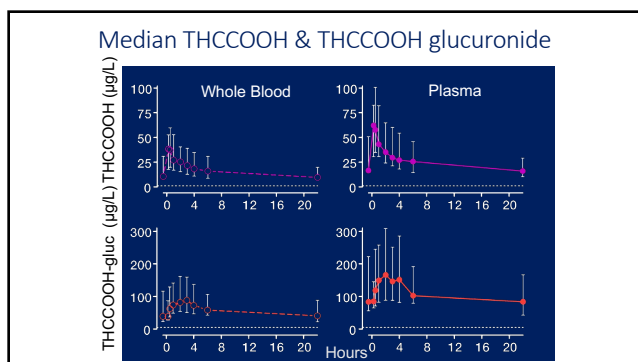
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Chronic Daily Cannabis Smokers 

- How Do You Study Pharmacokinetics of Chronic Daily Cannabis Smoking?
 - Controlled drug administration studies
 - For safety & ethical reasons, never dose participants with as much drug & for as long as they dose themselves
 - Monitor excretion of self-administered drug during abstinence
 - Requires long term residence on secure research unit to eliminate drug
 - Costly & difficult for daily cannabis smokers to abstain for 30 days due to cannabis withdrawal syndrome

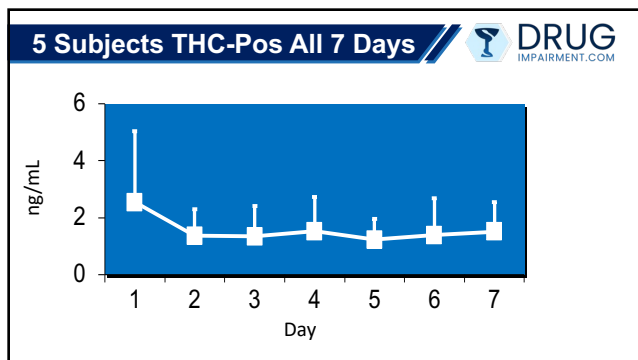
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Chronic Daily Cannabis Smokers 


- 28 subjects, 19 - 38 years
- 50% male, 82.1% AA
- Continuously resided on closed clinical unit
- Whole blood collected at admission & each 24 h for 7 days, urine for 30 days
- 12.8 ± 9.1 (2 - 40) joints or blunts/day



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Whole Blood THC 

Day	$\geq 0.25 \mu\text{g/L}$		$\geq 1 \mu\text{g/L}$	
	N	%	N	%
1	15	53.6	4	14.3
2	14	50.0	3	10.7
3	12	42.9	2	7.1
4	9	32.1	3	10.7
5	11	39.3	2	7.1
6	10	35.7	3	10.7
7	6	21.4	3	10.7

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Subjects Positive All 7 Days 

Subject	Self report J or B/day	Days used past 14 days	BMI	Gender
A	20	14	24.4	F
B	7	11	26.6	F
C	8	3	22.8	F
D	32	14	39.0	F
E	16	14	32.0	F

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Blood Cannabinoid Concentrations in Occasional & Chronic Frequent Cannabis Users After Smoked, Inhaled & Oral Cannabis

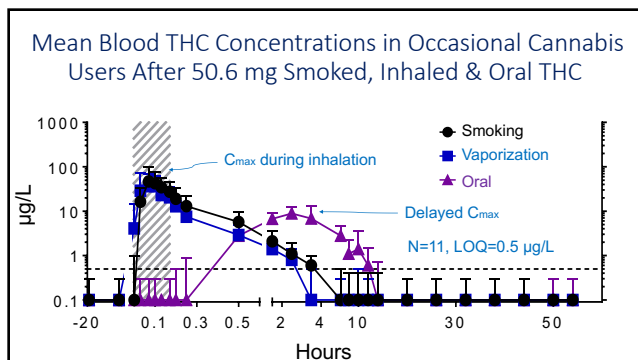


Clinical Chemistry 62:12 1579-1592 (2016) Drug Monitoring and Toxicology

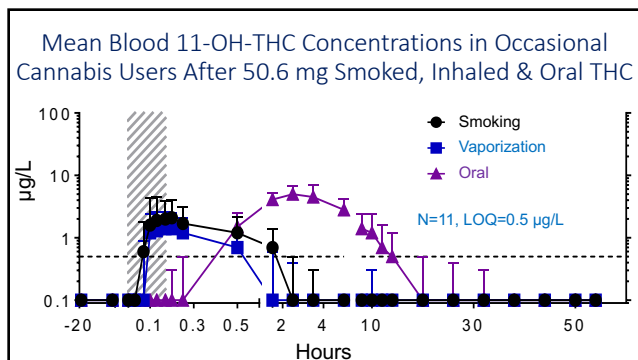
Free and Glucuronide Whole Blood Cannabinoids' Pharmacokinetics after Controlled Smoked, Vaporized, and Oral Cannabis Administration in Frequent and Occasional Cannabis Users: Identification of Recent Cannabis Intake

Matthew N. Newmeyer,^{1,2} Madeline J. Swartwood,¹ Allan J. Barnes,¹ Osama A. Abulseoud,¹ Karl B. Scheidweiler,^{1*} and Marilyn A. Huestis^{1,2}

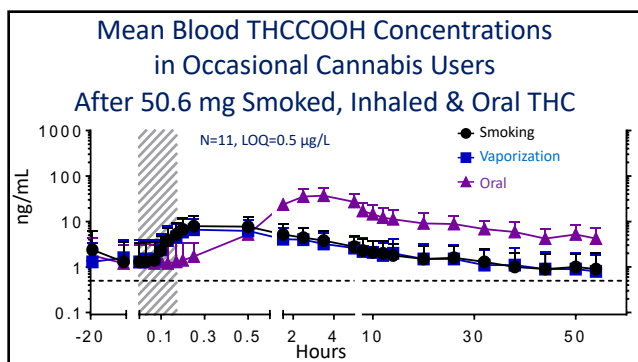
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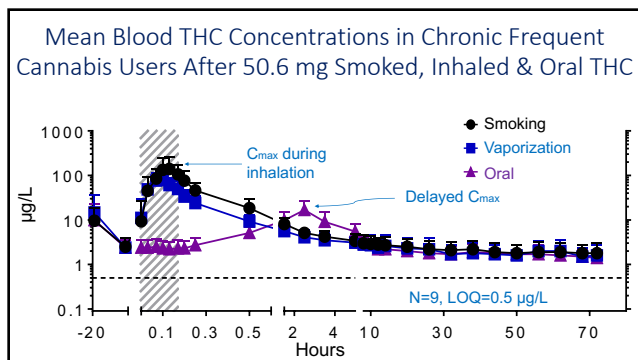
Blood THC, 11-OH-THC, THCCOOH, CBD, CBN, THC-glucuronide & THCCOOH-glucuronide After Smoking 6.8% THC Cigarette

Clinical Chemistry 57:10 1406-1414 (2011) Drug Monitoring and Toxicology

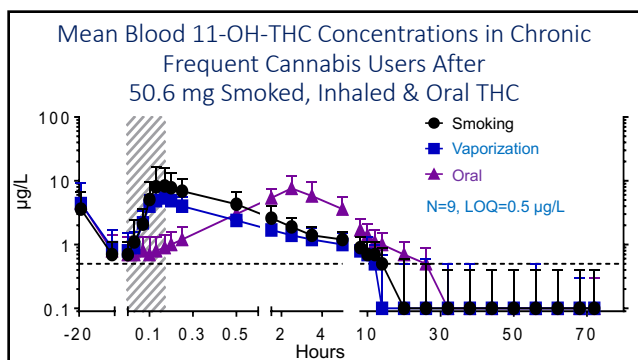
Identification of Recent Cannabis Use: Whole-Blood and Plasma Free and Glucuronidated Cannabinoid Pharmacokinetics following Controlled Smoked Cannabis Administration

David M. Schwabe,¹ Erin L. Karschner,² David A. Gorelick,¹ and Marilyn A. Huestis^{1*}

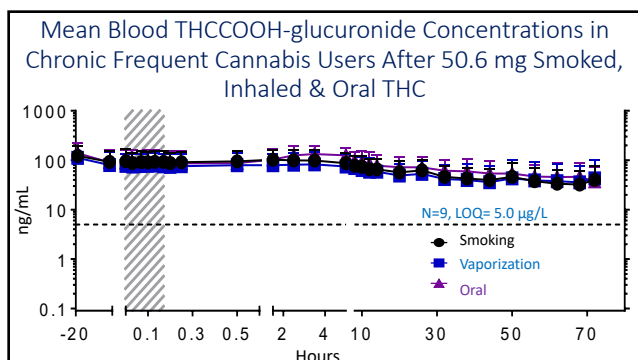
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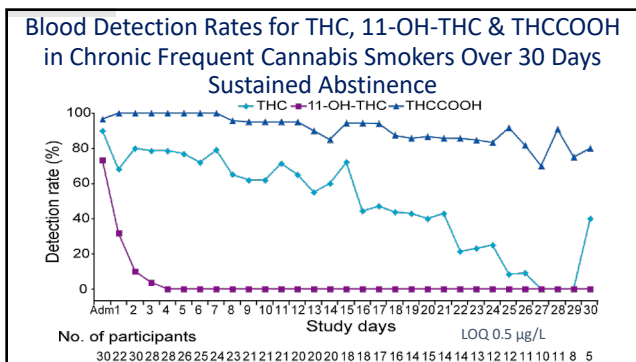
Residual Blood Cannabinoids Excretion in Chronic Frequent Cannabis Smokers Over 30 Days Sustained Abstinence

Clinical Chemistry 59:3 519-526 (2013) Drug Monitoring and Toxicology


Impact of Prolonged Cannabinoid Excretion in Chronic Daily Cannabis Smokers' Blood on Per Se Drugged Driving Laws

Mateus M. Bergamaschi,^{1,2} Erin L. Karschner,¹ Robert S. Goodwin,¹ Karl B. Scheidweiler,¹ Jussi Hirvonen,³ Regina H.C. Queiroz,² and Marilyn A. Huestis^{1*}

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Blood THC Over 30 Days Abstinence 

- 30 Chronic Daily Cannabis Smokers Blood THC Over 30 Days Abstinence
- Smoked mean 10.6 ± 6.3 cannabis joints/day (1 – 30) for 10.6 ± 5.8 (4 – 28) years
- All <5 µg/L within 19 h (but longer in cannabis users in Australia study)
- 10 of 11 positive day 26 (LOQ 0.25 µg/L)
- THC in 2 of 5 specimens on day 30 (0.3 µg/L)
- Consistent with time course of persisting neurocognitive impairment

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Contents lists available at ScienceDirect
Forensic Science International
 journal homepage: www.elsevier.com/locate/forensicint

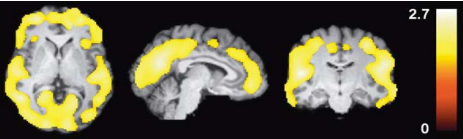
Fitness to drive and cannabis: Validation of two blood THCCOOH thresholds to distinguish occasional users from heavy smokers 

Marie Fabritius^{a,b}, Marc Augsburg^{a,c}, Haithem Chtioui^a, Bernard Favrat^{a,d,e}, Christian Giroud^{a,b}

- Proposed blood THCCOOH thresholds to distinguish occasional & frequent cannabis smokers
 - Occasional smokers (<3 ng/mL), smoking up to 1 joint/week
 - Heavy, regular smokers (>40 ng/mL), smoking >10 joints/month
- 146 case specimens from traffic offenses with self-reported cannabis use frequency
- Could not interpret concentrations between 3 & 40 ng/mL

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[¹⁸F]FMPEP-d₂ Labels CB₁ Cannabinoid Receptors in Brain of Chronic Daily Cannabis Smokers




Molecular Psychiatry (2012) 17, 642–649
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 www.nature.com/mp

ORIGINAL ARTICLE

Reversible and regionally selective downregulation of brain cannabinoid CB₁ receptors in chronic daily cannabis smokers

J Hirvonen¹, RS Goodwin², C-T Li¹, GE Terry¹, SS Zoghbi¹, C Morse¹, VW Pike¹, ND Volkow³, MA Huestis^{2,4} and RB Innis^{1,4}

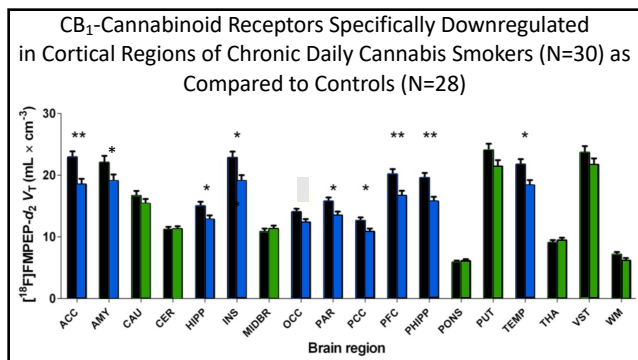
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Study Design & Participants 

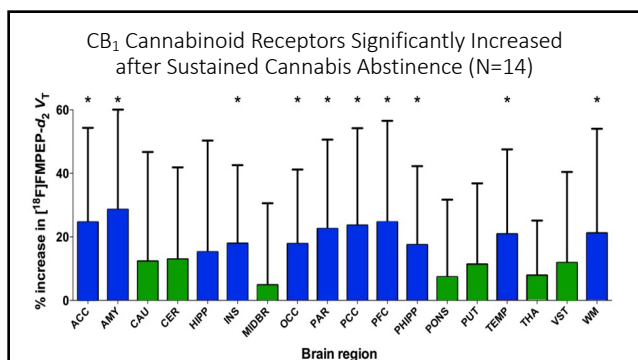
- [¹⁸F]FMPEP-d₂ PET in cannabis users & healthy male subjects
- Repeat [¹⁸F]FMPEP-d₂ PET in cannabis users after 30 day monitored abstinence

	Healthy Subjects	Cannabis Smokers
N	26	26
Age (years)	22 ± 10	29 ± 8
BMI (kg/m ²)	27 ± 5	24 ± 4
Cannabis use	<10X life	12 ± 8 years; 10 ± 7 joints/d

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Residual Psychomotor Impairment in Chronic Frequent Cannabis Smokers During Sustained Abstinence

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Psychomotor Function in Chronic Daily Cannabis Smokers during Sustained Abstinence

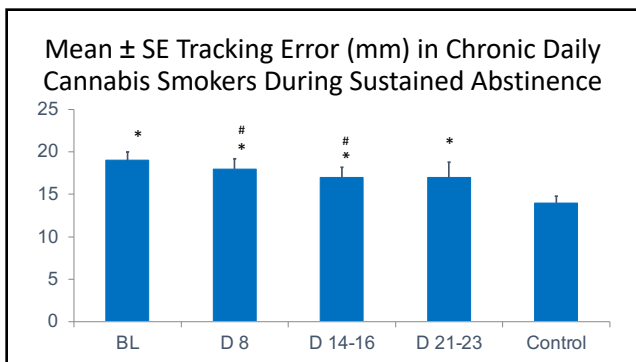
Wendy M. Bosker¹, Erin L. Karschner², Dayong Lee², Robert S. Goodwin², Jussi Hirvonen³, Robert B. Innis³, Eef L. Theunissen¹, Kim P. C. Kuypers¹, Marilyn A. Huestis^{2,3}, Johannes G. Ramaekers^{1,3,9}

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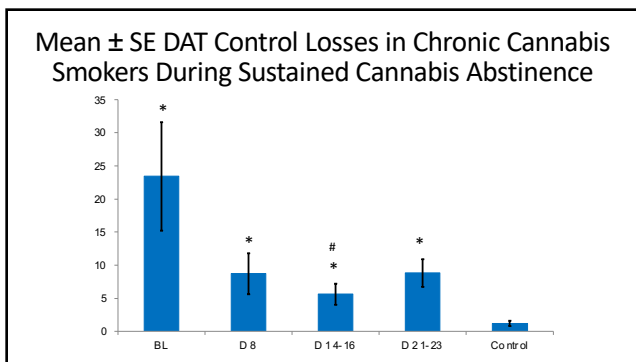
Psychomotor Impairment 

- What is duration of psychomotor impairment in chronic daily cannabis smokers?
- Compared psychomotor performance on tasks validated by Jan Ramaekers at University of Maastricht to predict impaired on the road driving
- Compared performance of chronic frequent smokers to occasional cannabis & ecstasy users over 22 days

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What About Tolerance to THC with Chronic Frequent Cannabis Intake?

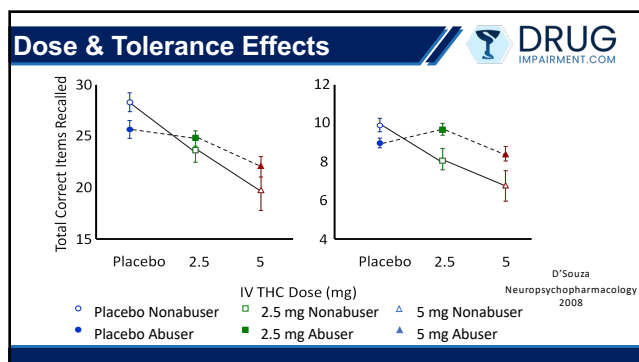


Journal of Analytical Toxicology Advance Access published March 4, 2015
Journal of Analytical Toxicology, 2015, 38, 1-11
 doi:10.1093/jat/tkv012 Article

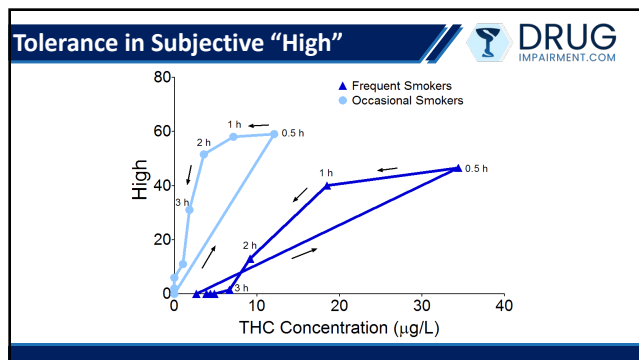
Smoked Cannabis' Psychomotor and Neurocognitive Effects in Occasional and Frequent Smokers

Nathalie A. Desrosiers^{1,2}, Johannes G. Ramackers³, Emeline Chaudard⁴, David A. Gorelick^{5,6} and Marilyn A. Huestis^{1*}
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Clinical Chemistry 62:2
367-377 (2016) Drug Monitoring and Toxicology

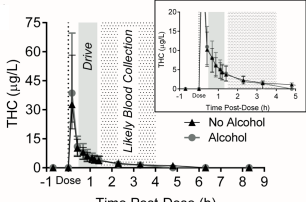
Effect of Blood Collection Time on Measured Δ^9 -Tetrahydrocannabinol Concentrations: Implications for Driving Interpretation and Drug Policy

Rebecca L. Hartman,¹ Timothy L. Brown,² Gary Milavetz,³ Andrew Spurgin,³ David A. Gorelick,^{1,4} Gary R. Gaffney,⁵ and Marilyn A. Huestis^{1*}

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Effect of Collection Time on Blood THC Concentrations



- Hartman et al *Clinical Chemistry* 2016
- THC decreased median of 73.5% without alcohol & 75.1% with alcohol in 1st 30 min
- THC decreased median of 90.3% & 91.3% 1.4 h post-dose
- If delayed blood collection, THC may be lower than *per se* cutoffs despite greatly exceeding them during driving
- Concentrations during driving cannot be back-extrapolated due to unknown time after intake & inter-subject variability in rates of decrease



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Is There A THC Blood Concentration That Indicates Driving Impairment? 1, 2 or 5 µg/L?

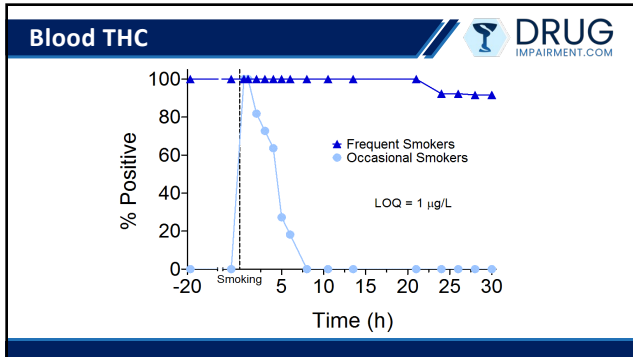
Clinical Chemistry 60:4
631-643 (2014) Drug Monitoring and Toxicology

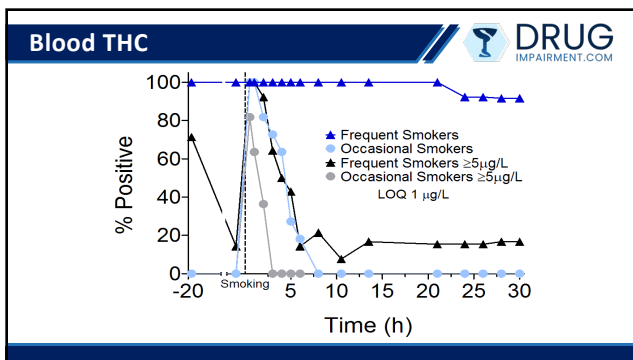
Phase I and II Cannabinoid Disposition in Blood and Plasma of Occasional and Frequent Smokers Following Controlled Smoked Cannabis

Nathalie A. Desrosiers,^{1,2} Sarah K. Himes,^{1,2} Karl B. Scheidweiler,¹ Marta Concheiro-Guisan,¹ David A. Gorelick,³ and Marilyn A. Huestis^{1*}

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Identifying Recent Cannabis Use

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- Hubbard et al *J Anal Tox* 2021
- Defining per se cutoffs for THC in blood is difficult because concentrations vary by route of administration, smoking topography, frequency of use & potency
- Is there a biomarker (evaluated up to 10 cannabinoids) in each fluid (blood, OF or breath) that indicates cannabis use within 3 h?
- 191 participants receive placebo (0.02%), or 5.9% or 13.4% THC
- 10 ng/mL THC in OF highest performance for biomarker of use within 3 h post-smoking, 23.2% of participants had THC ≥10 ng/mL 5 h after smoking

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Cognitive & Motor Performance Monitoring 

- Blood THC concentrations do not correlate well with impaired driving performance
- Blood THC concentrations decrease rapidly after use & THC stored in the body & brain extensively after chronic frequent use
- Objective measures of cognitive &/or motor impairment on mobile devices performed at the roadside would be highly useful
 - Functional near infrared spectroscopy (fNIRS) measures of PFC activation (Gilman et al 2019)
 - EEG monitoring with portable ABM head sensors (Brown et al 2020)
 - Handheld tablets (Vincent et al 2019 Automated Neuropsychological Assessment Metrics (ANAM Mobile), Marcotte et al UCSD future)

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