Cannabis Effects on Human Performance & Behavior

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Outline

- Cannabinoid Pharmacology
- Cannabinoid Pharmacokinetics
- Interpretation of Forensic Cannabinoid Results
- Estimating Time of Drug Exposure
- Cannabis Effects on Driving Performance
Cannabis Pharmacology
Cannabis Mechanisms of Action

- THC binds to cannabinoid receptors & interferes with important endogenous cannabinoid neurotransmitter systems
  - CB-1 receptors primarily in CNS
  - CB-2 receptors in immune system
  - Non-CB1, non-CB2 receptors
  - Endogenous ligands include anandamide & other ethanolamides
  - Neurotransmitters released from cell membranes for rapid response
  - Reuptake mechanisms identified
Cannabis Mechanisms of Action

- Receptor distribution correlates with brain areas involved in physiological, psychomotor & cognitive effects
- High density in caudate nucleus & cerebellum: motor behavior
- Significant binding in striatum, cerebral cortex, & hippocampus: perception, cognition, memory, learning, endocrine function, food intake & regulation of body temperature
Cannabis Pharmacology

- **Acute Physiological Effects**
  - Tachycardia
  - Conjunctival injection
  - Dry mouth & throat
  - Increased appetite
  - Vasodilation
  - Bronchodilation
  - Decreased respiratory rate
Physiological Effects of Cannabis

Heart Rate

Δ BPM

Hours

Placebo
1.75% THC
3.55% THC
Cannabis Pharmacology

Acute Behavioral Effects

- Euphoria/Relaxation
- Altered time perception
- Lack of concentration
- Impairment of learning/memory
- Mood changes-panic reaction, paranoia
Subjective Effects of Cannabis

Feel Drug  N=6

Score

Placebo
1.75% THC
3.55% THC

Hrs

-1 0 1 2 3
Cannabinoid Pharmacokinetics
Absorption: Inhalation

- Rapid, peak occurs during smoking
- Systemic availability 18 - 50%
- Smoking dynamics important: # puffs, duration & volume of inhalation, hold time, time between puffs, smoking time, experience of smoker
- Highly efficient route of drug delivery to the brain, similar to iv route
Absorption: Oral

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

- Lipophilic, widely & rapidly distributed to tissues
- Clearance ≈ hepatic flow 0.8 L/min
- Highly protein bound in blood ≈ 97%
- Volume of distribution ≈ 10 L/kg
- Enterohepatic circulation
- Slow release of sequestered drug from tissues rate limiting step in elimination
Metabolism

- Rapid & extensive metabolism
- Phase 1: oxidation, primary metabolites 11-OH-THC, 8a & 8β-OH-THC, THCCOOH, little side chain oxidation
- Phase 2: glucuronidation, sulfation
- Cytochrome P450, CYP2C9 & 11, CYP3A no differences between sexes, frequent & infrequent users
- Liver, lung & intestine
Δ⁹-THC Metabolic Scheme

Δ⁹-THC → 11-Hydroxy-Δ⁹-THC → 11-Nor-9-Carboxy-Δ⁹-THC → Conjugation
Excretion

- Urine excretion $\approx 15\text{-}30\%$, fecal 27\text{-}65\%
- Calculated half-lives affected by sampling time, assay sensitivity & specificity, frequency of use
- Plasma THC $t_{1/2}$ estimates range 20 h to 12 d, best estimate $\approx 4.3$ d
- Urine THCCOOH $t_{1/2}$ best estimate $\approx 3.0$ days
THC, 11-OH-THC & THCCOOH
Plasma Concentrations

- THC
- 11-OH THC
- THCCOOH

Inhale
N = 6

THC ng/mL
Minutes
0 2 6 10 14 18 22
-2 0 30 60 90 120 150 180

THC
11-OH THC
THCCOOH
Inhale
N = 6
THC, 11-OH-THC, THCCOOH Plasma Levels

![Graph showing plasma levels of THC, 11-OH-THC, and THCCOOH over time.](image)

- **ng/mL** on the y-axis.
- **Hours** on the x-axis.
- Three lines representing THC (green), 11-OH THC (cyan), and THCCOOH (red).
- The graph illustrates the peak levels of THC at around the 0-hour mark, followed by a gradual decrease in 11-OH THC and THCCOOH levels over time.
Cannabis Pharmacokinetics

- THC rapidly absorbed during smoking; absorption t 1/2  50.4 ± 11 sec
- Plasma THC after 1st puff mean 7.0 & 18.0 ng/mL after 1.75 or 3.55% THC cigarette
- THC distribution due to tissue uptake & metabolism
- Rapid onset of effects due to speed of drug delivery to the brain
- Smoking highly effective drug delivery system contributing to high abuse liability of smoked drugs
Blood/Plasma

- THC distributes poorly into RBCs
- Plasma THC ~ 2X blood THC
- If THC ~ 11-OH-THC could indicate oral use
- THC vs THC-glucuronide
- Stability & degradation
- Residual concentrations in chronic users
- Rapid THC decrease requires rapid sample collection & low LOQ
Interpretation of Forensic Cannabinoid Results

- Unknown dose
- Unknown time of usage
- Unknown administration route
- Unknown frequency of usage
- Residual drug concentrations?
Pharmacodynamics of Abused Drugs

- Non-linear relationships between concentration & effect
- Metabolism to active metabolites
- Lipophilicity affects drug disposition
- Initially high concentrations that decline rapidly due to distribution & metabolism
- Effects manifested as concentrations increase
Pharmacodynamics of Abused Drugs

- After equilibrium, may have linear concentration - effect curve
- Drug levels & effects out of phase: hysteresis effect
- Inter-individual variation in pharmacokinetics & pharmacodynamics
- Wide range of drug concentration with same level of impairment
Lack of Correlation

- Active metabolites
- Tachyphylaxis
- Tolerance
- Drug interactions
- Idiosyncratic reactions
- Inter-individual differences
Tachyphylaxis

- Rapidly developing tolerance following drug administration
- Nicotine (differences in arterial & venous concentrations?)
- Benzodiazepines
Nicotine Concentration-Effect Curves

[A] Heart Rate vs. Plasma Nicotine Concentration
[B] Plasma Nicotine Concentration vs. Heart Rate

Plasma Nicotine Concentration (ng/ml)

Heart Rate (Beat/min)
Types of Tolerance

**Pharmacokinetic:**
- Increased or decreased absorption, distribution, metabolism or excretion

**Pharmacodynamic:**
- Neuronal adaptation & cellular tolerance
Drug Interactions

- May alter intensity of pharmacological effects
- Due to pharmacokinetic or pharmacodynamic effects
- Affect interpretation of drug concentrations
Concentration-Effect Curves

- Non-linear, complex relationship between drug concentrations & physiological & behavioral effects
- Metabolism to active metabolites
- Drug concentrations may decline rapidly due to distribution & metabolism of drugs
- Development of tolerance
Hysteresis

- Acute cannabis effects have counter-clockwise hysteresis indicating prominent distribution phase
- Initially, lack of correlation between plasma concentrations & effects
- After blood/tissue equilibrium (~ 45 min), direct correlation of THC concentrations & effects, e.g., tracking up to 7 h
- Rarely is blood sampled in accident or DUID prior to equilibrium
Concentration Effect Curves

![Graph showing Concentration Effect Curves for VAS Feel Drug and Heart Rate](image)

- **VAS Feel Drug**
  - X-axis: THC ng/mL
  - Y-axis: VAS Feel Drug
  - Key time points: .07 h, .15 h, .38 h

- **Heart Rate**
  - X-axis: THC ng/mL
  - Y-axis: BPM
  - Key time points: .05 h, .10 h, .15 h, .25 h, .38 h, .79 h
Time of Drug Exposure?

- Unique metabolites
- Ratios of metabolites
- Detection times
- Ante or post-mortem specimen?
- Passive inhalation or external contamination?
Predictive Models for Estimating Time of Marijuana Use from Plasma Cannabinoid Concentrations
Mathematical Models for Prediction of Time of Drug Use

- Plasma concentrations after controlled administration of single smoked doses
- 95% Confidence Intervals calculated around estimated time of use
- Model I based on plasma THC
- Model II based on ratio of plasma THCCOOH to THC
Prediction of Time of Drug Use

- Validated models’ accuracy within 95% CI with THC & THCCOOH concentrations from other published oral & smoked clinical studies with frequent & infrequent cannabis users
  - Model I 90.0%
  - Model II 89.2%
- Proved accurate with later single & multiple controlled oral & smoking studies
- Models successfully employed in forensic investigations around the world, primarily in DUI & post-mortem cases
Predictive Models for Estimating Time of Marijuana Usage

Model I

\[ \log h = -0.698 \cdot \log \text{THC} + 0.687 \]

\( N = 168 \quad r = 0.949 \)

Model II

\[ \log h = 0.576 \cdot \log \frac{\text{THCCOOH}}{\text{THC}} - 0.176 \]

\( N = 168 \quad r = 0.919 \)
Confidence Intervals (95%) at Predicted Times of MJ Use

Predicted Elapsed Time (Hours)

Predicted Elapsed Time

Model II (upper)
Model I (lower)

Predicted Elapsed Time

Hours
Limitations

- Based on single acute drug exposures
- If whole blood, assume a 1:2 ratio for THC & THCCOOH in whole blood as compared to plasma
- THC concentrations $\geq 2$ ng/mL
- Model II tended to overestimate time of use in frequent users, most likely due to residual THCCOOH concentrations
Objective of Multiple Marijuana Cigarette Studies

To evaluate the models’ ability to accurately predict time of use following controlled administration of multiple marijuana cigarettes & with THC concentrations $\geq 0.5$ ng/mL
Experimental Methods

Healthy male marijuana users (N=38)
- Provided informed consent for double-blind, randomized, double-dummy, placebo-controlled, NIDA IRB approved protocol
- Phase I study conducted under IND & CRADA with Sanofi-Synthelabo, Inc.
- Resided on closed research unit 4 to 29 days

Dosing schedule
- 1 to 90 mg oral SR141716, a CB1-cannabinoid receptor antagonist
- 2 & 6 h later smoked a 2.64% THC cigarette
- 9 of 38 didn’t smoke 2nd cigarette due to medical disqualification or personal choice
Experimental Methods

- Smoked 8 puffs with 1 min puff interval
- Plasma collected immediately after & up to 6 h after marijuana smoking
- Plasma THC & THCCOOH (N=717) determined by SPE & NCI-GC/MS
- LOQ = 0.5 ng/mL THC & 2.5 ng/mL THCCOOH (Center Human Toxicology)
- Primary objective was to prove for 1st time that SR141716 blocked effects of smoked marijuana in humans through CB1 cannabinoid receptors
Data Analysis

- Actual times of last use compared to 95% CI predicted by the models

- Accuracy: 100 times number of correct predictions divided by total predictions

- % of over & underestimations & average error also calculated

- Evaluated accuracy of predictions after 2nd cigarette

- Included all data $\geq$ LOQ ($THC \geq 0.5$)
Multiple Cannabis Cigarettes: Model I (THC)

- 717 THC concentrations
- 90.7% accurate (650 of 717 cases predicted time of use within 95% CI)
- In 64 cases, overestimation of time of last use by <1 - 50 min (mean = 15 min)
- In 3 cases, underestimation of time of last use by 2 - 11 min (mean = 5 min)
Multiple Cannabis Cigarettes: Model II (THCCOOH/THC)

- 704 THC & THCCOOH plasma pairs
- 95.2% accurate (670 of 704 cases predicted time of use within 95% CI)
- In 12 cases, overestimation of time of last use by <1 - 7 min (mean = 2 min)
- In 22 cases, underestimation of time of last use by <1 - 94 min (mean = 37 min, two cases > 1 h)
Results: After 2nd cigarette

- **Model I THC**
  - 290 THC & THCCOOH plasma pairs
  - 89.7% accurate (260 of 290 cases predicted time of use within 95% CI)
  - In 27 cases, overestimation of time of last use by <1 - 50 min (mean = 17 min)
  - In 3 cases, underestimation of time of last use by 2 - 11 min (mean = 5 min)
Results: After 2nd cigarette

- **Model II** THCCOOH/THC
- 290 THC & THCCOOH plasma pairs
- 97.6% accurate (283 of 290 cases predicted time of use within 95% CI)
- In 7 cases, overestimation of time of last use by <1 - 4 min (mean = 2 min)
- No cases where predicted time of use was underestimated based on 95% confidence intervals
Results: THC $\geq 0.5$ & $< 2$ ng/mL

- **Model I THC**
  - 76 THC cases $\geq 0.5$ & $< 2$ ng/mL
  - 80.3% accurate (61 of 76 cases predicted time of use within 95% CI)
  - In 15 cases, overestimation of time of last use by 3 - 50 min (mean = 31 min)
  - No cases where predicted time of use was underestimated based on 95% confidence intervals
Results: THC ≥ 0.5 & < 2 ng/mL

- Model II THC
  - 76 THC cases ≥ 0.5 & < 2 ng/mL
  - 76.3% accurate (58 of 76 cases predicted time of use within 95% CI)
  - No cases where predicted time of use was overestimated based on 95% confidence intervals
  - In 18 cases, underestimation of time of last use by <1 - 87 min (mean = 35 min)
95% CI of Models I & II

- 717 cases
- 98.5% accurate (706 of 717 cases predicted time of use within 95% CI)
- In 11 cases, overestimation of time of last use by <1 - 4 min (mean = 2 min)
- No cases where predicted time of use was underestimated based on 95% confidence intervals
95% CI of Models I & II

- After 2nd cigarette
  - 290 THC & THCCOOH plasma pairs
  - 98.3% accurate (285 of 290 cases predicted time of use within 95% CI)
  - In 5 cases, overestimation of time of last use by <1 - 4 min (mean = 3 min)
  - No cases where predicted time of use was underestimated based on 95% confidence intervals
95% CI of Models I & II

THC ≥ 0.5 & < 2 ng/mL

- 76 cases
- 100% accurate (76 of 76 cases predicted time of use within 95% CI)
Summary

- Models I & II > 90% accurate, model I overestimates & II underestimates time of use within 37 min
- After multiple smoked doses, model II 97.6% accurate with no underestimates
- When THC < 2 ng/mL, model I more accurate with no underestimates
Summary

- Combine CI for both models for conservative approach: overall 98.5% accuracy, 98.3% for multiple doses & 100% for THC < 2 ng/mL
Concentration-Effect Correlations

- Complex relationship between drug concentrations & physiological & behavioral impairment
- Few experimental data relating blood concentrations to driving impairment
- Interpretation of drug contribution to accident causation complicated by many factors including drug interactions, drug tolerance, driving experience, road & weather conditions, driver age & health
Effects on Driving Performance

- Epidemiological studies
- Experimental performance studies
- Simulator, open & closed driving courses
- DRE program
- Moeller 2000 cannabis & driving performance
Effects on Driving Performance

- Epidemiological studies
  - Comparison of incidence rates of drug in fatal & non-fatal motor vehicle accidents & in driving under the influence cases as compared to incident rates in normal drivers
  - If significantly higher %, drug may contribute
Methodological Problems

- Frequently are poorly controlled
  - Need cannabinoid concentrations in drivers on same road, same time without accidents
- Require blood rather than breath
- Selection bias in cases included in study, frequently only those where BAC < 0.1
Effects on Driving Performance

- Epidemiological studies
- Culpability analysis compares the responsibility ascribed to drivers in accidents in relation to positive drug tests
- If index significantly $>1$, suggestive that drug is contributing factor to accident/driving impairment
Methodological Problems

- Delays in specimen collection
- Lack sensitive, specific & quantitative cannabinoid data
- Measurement of inactive metabolites
- Small number of cannabis only cases
- Correlates of cannabis use similar to correlates of crash involvement (youth, male, socially deviant, poor school performance, rebellious)
Methodological Problems

- Potential bias in determining culpability
- No need for non-accident driver control if responsibility judged without knowledge of driver’s alcohol & drug status
- Lack of correlation between blood concentration & behavioral impairment
Cannabis: Driving Impairment

- Cannabis most common illicit drug world-wide in impaired drivers, motor vehicle injuries & fatalities
- >1/4 drivers over 16 reported occasional DUI of alcohol, marijuana or both (1996 NHS)
- Soderstrom 1988 1023 trauma cases
  - 34.7% > 2 ng/mL THC serum;
  - 33% ≥ 10 ng/mL
Cannabis: Driving Impairment

- In 1997, WHO reported that cannabis acutely impairs cognitive development & psychomotor performance, increasing the risk of motor vehicle accidents in the intoxicated driver.
- Renewed interest in cannabinoid therapeutics increases need for reliable means of determining drug impairment.
Culpability Analyses

Terhune 1982
- 52.9% THC only drivers judged culpable, as compared to 34% of drug-free drivers
- Drivers with BAC $\geq 0.10\%$ culpability 73.8%
- Ethanol & THC rate not significantly higher

Williams 1985
- No increased risk for THC alone
- Included fatalities up to 4 h after crash, time for THC to fall below detection limits & potentially bias results
- 2/3 of cannabis positive had THC in blood
Culpability Analyses

Terhune 1992 NHTSA 1882 fatalities US
- Increased risk alcohol & alcohol & drug cases
- THC alone, no increased risk

Hunter 1998 hospitalized AUS drivers
- Trend for higher odds ratios for accident if THC ≥ 2.1 ng/mL & THCCOOH ≥ 31 ng/mL

Drummer 1990-93 1,045 fatalities in AUS
- Lower odds ratios (0.6) in cannabis-positive
- Ethanol & THC significantly increased risk (5.6), but not higher than ethanol alone (6.0)
Culpability Analyses

- **Drummer 1998 National Road Safety**
  - If THC only, increased risk, but not significant

- **Longo 2000 2500 injured drivers AUS**
  - 2.8% positive for THC & THCCOOH
  - 8% THCCOOH only
  - Most involved alcohol also
  - THC only didn’t significantly increase risk
  - Alcohol & THC increased odds ratio, although not greater than alcohol alone
Culpability Analyses

- **Lowenstein 2001** 414 injured CO drivers
  - Admitted to ER within 1 h
  - Cannabis alone odds ratio 1.1
  - Cannabis & alcohol increased accident risk

- **Marowitz 1989**
  - Compared driving records of >100K CA drug arrestees to >40K general drivers
  - Drug arrestees significantly more traffic violations, accidents, & found responsible
  - Misdemeanor MJ arrestees twice 1-yr post-arrest accident rate as compared to controls
Drummer TIAFT 2002

- 13% fatally injured drivers in Australia had THC and/or THCCOOH
- THC in 70% of these, median blood 10ng/mL
- In 3,398 cases, if THC in blood, 2.8 times as likely to have crash as drug-free driver; similar to BAC 0.10-0.15 g%
- If THC $\geq$ 5 ng/mL, odds ratio = 6.8
- THC in 19% homicides; 15% drug deaths in similar concentrations
Experimental Lab Performance

- Help understand effects & predict impairment in complicated tasks
- Provide basis for simulator studies; closed & open driving courses
- Earliest evidence of a drug’s hazard potential
- Provides much better control of experimental conditions
In 1993, Foltin & Evans reviewed cannabis performance effects & found consistent decrements in tracking, DSST, list recall, arithmetic, memory recall, vigilance, divided attention, circular lights, paired associates, digit span, list learning, stroop & list recognition tasks. Inconsistent results for choice & other reaction time tasks.
Methodological Issues

- Face validity of task?
- Inability to give doses as large as those that are self-administered
- Ability to translate to impairment of complex behavior; task difficulty
- Limited numbers of subjects due to cost
- Cannabis’ effects more neurological, less psychomotor than after ethanol
- Is standard DUID examination sensitive to driving impairment following cannabis?
Experimental Lab Performance

- THC has significant effects on cognitive & psychomotor tasks associated with driving
- Critical skills for safe operation of motor vehicles including measures of coordination, tracking, & vigilance, memory, learning, attention, information processing, decision-making, & perception following cannabis use
Debate continues on whether or not these effects increase accident risk.

Most effects return to baseline within 3 to 4 h, although some complex, divided attention tasks have decrements in performance up to 24 h.
Simulator, Open & Closed Driving Courses

- Resembles actual driving, but lacks emergencies, distractions, & unexpected events
- Inability to give doses as large as those that are self-administered
- The more difficult & unpredictable the task, the more likely THC will impair performance
Simulator, Open & Closed Driving Courses

- THC increases variability of longitudinal (speed & headway) & lateral control (lane position)
- THC impairs monotonous & prolonged driving
- Decision times increase for evaluation of situations & for determining appropriate responses
THC moderately impairs driving

Dose dependent increase in standard deviation of lateral position (SDLP) up to 2 h after 100, 200, 300 µg/kg smoked THC; ~ 0.03-.07% BAC

In city traffic, 100 µg/kg ~ 0.04% BAC

Impairment of controlled information processing is most important psychomotor effect
Robbe 1994 & 1998 NHTSA

- THC effects mood, memory & attention
- Individuals attempt to compensate with increased effort & risk avoidance
- Willingness to drive decreased with increasing doses of cannabis
- No relationship between effect & plasma concentration of THC or THCCOOH
Robbe 1994 & 1998 NHTSA

- Real driving involves multi-tasking & unexpected presentation of hazardous conditions
- Situations put high demands on driver’s information processing capabilities
- Responses to external stimuli may be impaired while DUI of THC
- THC & EtOH greatly increase risks
Moeller DUI Germany

- **Modified DRE-type exam at scene of accident or traffic stop**
- **Determines impairment & need for blood test**
- **Evaluating on-site drug tests**
- **Administrative & criminal limits for drug concentrations in serum**
Moeller DUI Germany

- Limits based on capabilities of all labs in program, extensive proficiency testing, limits reduced over time with better lab performance
- THC in serum
- No relationship between THC concentration & signs of impairment
Cannabis: Driving Impairment

- **ROSITA project, EMCDDA, European Commission Transport RTD Programme**
- Impairs attention & short term memory
- Impairs vigilance, signal detection & balance
- Automatic nature of well-practiced test insensitive to THC effects - results in impaired attention to unexpected events
- Produces moderate driving impairment in drug prioritization classification of drugs & medicines for roadside impairment testing
**Issues**

- *Do we continue to require demonstrated driving impairment via eyewitness testimony or through DRE evaluation plus toxicological evidence?*

- *OR administratively set a quantitative cutoff in blood, plasma or serum, as was done in Germany & Belgium (or for instance with workplace urine drug testing program) based on public safety concerns*

- *Consider estimates of recency of use, ie. prediction models?*
Issues

- Plasma or serum THC of 2 ng/mL (1 ng/mL whole blood) easiest to support due to residual drug concentrations in frequent cannabis users
- Need additional data on drug excretion in frequent cannabis smokers
- Need sensitive, specific & accurate methods for THC & THCCOOH in blood, plasma or serum for all DUID & ME labs
- Need rapid collection of specimens