The Challenge of Cannabis-Related Driving Impairment

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22.2 million (8.3% of the population) Americans > 12 yo used cannabis in the past month (2015 National Survey on Drug Use and Health)

National Epidemiologic Survey on Alcohol and Related Conditions
Use in Past Year (Hasin et al., 2015)

Increases across all sex, race/ethnicities, educational levels, income levels, urbanicity, geographic regions
Distribution of CB1 Receptors in the Brain
Acute Effects
Cannabis and driving

- **Cognition:** Reduced learning, attention, processing speed, psychomotor abilities
- **Controlled on-road/simulator studies**
  - Delayed reactions (brake latency)
  - Poor lane tracking (standard deviation of lateral position)
  - Reduced judgment of speed and distances
  - Dose dependent
- **Epidemiology**
  - Modest increased crash risk (~ two-fold)
  - State experience unclear
- **Amplified by consumption of alcohol**
- **Cannabis users judge selves to be more impaired; more cautious (allow more headway; drive more slowly; avoid passing other cars)**
National Advanced Driving Simulator (NADS)
University of Iowa
Cannabis blood levels/Breath alcohol level and simulator swerving

Hartman et al., 2015

% Increase in Swerving Relative to Baseline

THC (ug/L) / Breath Alcohol Level

THC Only  Alcohol Only  Combined

Hartman et al., 2015
Cannabis blood levels/Breath alcohol level and simulator swerving

Hartman et al., 2015

THC Only  Alcohol Only  Combined

Hartman et al., 2015
Impact of Legalization in Colorado

- Marijuana-related traffic deaths (marijuana “mentioned”; includes other substances) increased 48% (2013-15) compared to 2010-2012; All traffic deaths only increased 11%.

National Fatalities (NHTSA, 2016)

Fatalities (thousands)

<table>
<thead>
<tr>
<th>Year</th>
<th>Fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>06</td>
<td>45</td>
</tr>
<tr>
<td>07</td>
<td>42</td>
</tr>
<tr>
<td>08</td>
<td>38</td>
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<td>09</td>
<td>35</td>
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<td>10</td>
<td>34</td>
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<td>33</td>
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<td>12</td>
<td>32</td>
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<td>13</td>
<td>31</td>
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<td>14</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>

Cannabinoid Screening (Colorado)

<table>
<thead>
<tr>
<th>Year</th>
<th>Cannabinoids (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>500</td>
</tr>
<tr>
<td>2010</td>
<td>400</td>
</tr>
<tr>
<td>2011</td>
<td>300</td>
</tr>
<tr>
<td>2012</td>
<td>400</td>
</tr>
<tr>
<td>2013</td>
<td>300</td>
</tr>
<tr>
<td>2014</td>
<td>400</td>
</tr>
</tbody>
</table>

RMHIDTA, 2015

Percent of All Traffic Deaths That Were Marijuana-Related*

<table>
<thead>
<tr>
<th>Year</th>
<th>Marijuana-Related (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>6.92%</td>
</tr>
<tr>
<td>2007</td>
<td>7.00%</td>
</tr>
<tr>
<td>2008</td>
<td>7.85%</td>
</tr>
<tr>
<td>2009</td>
<td>10.10%</td>
</tr>
<tr>
<td>2010</td>
<td>10.89%</td>
</tr>
<tr>
<td>2011</td>
<td>14.09%</td>
</tr>
<tr>
<td>2012</td>
<td>16.53%</td>
</tr>
<tr>
<td>2013</td>
<td>11.76%</td>
</tr>
<tr>
<td>2014</td>
<td>19.26%</td>
</tr>
<tr>
<td>2015</td>
<td>21.02%</td>
</tr>
</tbody>
</table>

* Commercialization and Legalization years are indicated.
Collision Claim Increases in Legal Recreational States (Highway Loss Data Institute, 2017)

- Colorado (first to legalize), Washington, Oregon
- Collision coverage/claims: Physical damage to driver’s vehicle (object or other vehicle); generally at fault
- Compared to nearby states
- Combined, 3% greater increase in claims than would be expected without legalization
Laboratory vs. Real World Findings

Why is there a disconnect between controlled studies vs. real-world findings?

» Epidemiologic findings based upon imperfect data
  • Incomplete reporting [e.g., toxicology], delayed blood collection

» Large numbers of THC+ unimpaired drivers may statistically mask the effects of impaired drivers

» Confounding by concurrent use of other substances

» Compensatory behaviors

» Magnitude of the effects seen in the laboratory may not be sufficient to substantially increase real world risks in all users
Limitations of the Fatality Analysis Reporting System (FARS)

- Inconsistent testing methods (who, which drugs, when, cutpoints, equipment, bodily fluid)
- Some test only: fatally injured drivers, all drivers in a fatal crash, no drivers
- Often no drug testing if alcohol present
- Inconsistency in performing screening, and confirmatory, tests
- Limit to reporting 3 drugs
- Presence ≠ impairment

“Currently, the data in FARS is insufficient to allow comparisons of drug use across years, or across States.”

“... it is also not possible to make inferences about impairment, crash causation, or comparisons to alcohol from this limited data.”
Effects of Prolonged Presence of THC in Detecting Crash Risks (hypothetical example)

<table>
<thead>
<tr>
<th>Crash</th>
<th>No Crash</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC+</td>
<td>THC Impaired</td>
</tr>
<tr>
<td>8 vs 2</td>
<td>38 vs 32</td>
</tr>
<tr>
<td>OR = 4.3</td>
<td>OR = 1.27</td>
</tr>
</tbody>
</table>
SDLP ("swerving") Effect Sizes for Prescription Medications

- Low-Dose Cannabis (3h postdose)
- Antidepressants (mirtazapine 2 days)[1]
- Hypnotics (zolpidem; next am)[2]
- ETOH (BAC = .08)[3]
- Alprazolam (1h)[4]

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THC levels and *per se* Laws

18 States with zero tolerance on non-zero *per se* laws

Zero tolerance (THC/metabolite)
- AZ, DE, GA, IN, OK, RI, SD, UT

Zero tolerance (THC)
- IA, MI, WI

*Per se*
- 1 ng (PA), 2 ng (NV, OH), 5 ng (IL, MT, WA); non-zero metabolites (NV, OH, PA)

Reasonable inference
- 5 ng (CO)

*Governors Highway Safety Administration (GHSA) (2017)*
THC levels in blood and *per se* laws

- DREs determined driver was impaired due to cannabis
- 602 cases

**Figure 1:** THC concentration distribution in 602 Cases with DRE Evaluations

[Graph showing THC concentration distribution with various bars indicating percentage for different concentration ranges, including median, mean, SD, and range.]

- Median = 5.05
- Mean = 7.04
- SD = 6.10
- Range 1.0-47.0
- N=602
THC is Detectable in Blood in Frequent Users Days after Smoking

Chronic users (>5 days/week); ~30 participants

<table>
<thead>
<tr>
<th>Day</th>
<th>% detect</th>
<th>Median</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit</td>
<td>90%</td>
<td>1.4ng</td>
<td>6.3ng</td>
</tr>
<tr>
<td>1</td>
<td>68%</td>
<td>1.8</td>
<td>2.9</td>
</tr>
<tr>
<td>2</td>
<td>80%</td>
<td>1.2</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>79%</td>
<td>1.3</td>
<td>2.6</td>
</tr>
<tr>
<td>4</td>
<td>79%</td>
<td>1.1</td>
<td>2.3</td>
</tr>
<tr>
<td>5</td>
<td>77%</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>6</td>
<td>72%</td>
<td>1.0</td>
<td>2.2</td>
</tr>
<tr>
<td>7</td>
<td>79%</td>
<td>0.9</td>
<td>2.0</td>
</tr>
</tbody>
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Bergamaschi et al., 2013
Poor correlation of being “high” and blood concentrations of THC

Counter-clockwise Hysteresis (M. Huestis)
Oral fluid – Detection of THC

- Potential screening tool
- Easy to administer
- Minimally invasive
- Many studies suggest it may reflect recent drug use
- But some individuals may yield values > 5ng many hours after smoking

THC concentrations (median, IQR) in frequent and occasional users (after 6.8% cigarette)

Anizin et al, 2013
Questions to Ask Regarding Biological Assays

- Is the approach reliable?
  - Do you get the same values if you repeat the test under the same circumstances?
  - Do you get the same results under different circumstances (e.g., environmental)?

- Can the results be masked (e.g., by alcohol, other substances)?

- Do the assays work with different modes of ingestion (smoke, edible, dabs, etc.)?

- What do the results mean?
  - Time since use?
  - Impairment?
Drug Recognition Expert (DRE)

- Drug Evaluation and Classification (DEC) Program
  - Current Gold Standard; 152 hours training
  - Systematic, standardized 12-step evaluation of physical, mental, and medical components of substance use

- Hartman et al. (2016) – 302 THC-only and 302 un-impaired individuals
  - Best predictors: Finger-to-nose, Modified Romberg (eyelid tremors), One-leg stand (sway), Walk and turn; Requiring ≥ 2/4 (96.9% efficiency)

- Declues (2016; 2018) – 363 THC only/116 with DRE
  - WAT most sensitive (other studies show OLS); Modified Romberg (time) not sensitive
  - Multiple tests is best approach
SFST/DRE Evaluations

- **Limitations**
  - Controls not well matched to cases
  - Tested under different conditions
  - Often report only "true positives" (cases correctly identified as THC only)
    - Inform which of the components most strongly predicted the overall conclusion; no external standard
    - Miss (1) false positives (those who didn’t do well, and did not have THC), (2) false negatives (those with THC, but passed the tests)
AB266

Assessing Cannabis-Related Driving Impairment

Program of Research
Aims
Assessing Cannabis-Related Driving Impairment

1. Effect of dose of THC on driving performance
2. Time course of driving impairment (hours since use)
3. Utility of saliva or exhaled air (breath) to inform regarding time since use, or impairment
4. Determine whether standardized, tablet-based measures can augment the standard field sobriety test
Study Design

- Parallel design with healthy participants (each person sees one treatment)
  - Minimize practice effects
  - Maximize retention in study

- Smoke
  - 0% THC (n = 60)
  - 5.9% THC (n = 60)
  - 13.4% THC (n = 60)

- Assess throughout the day
  - Driving Performance – simulations
  - Standardized Field Sobriety Test/DRE assessment
  - Tablet-based (iPad) cognitive/motor performance
  - Fluids (cannabinoids, metabolites) – Blood, Saliva, Breath
**Study Schedule**

0: 30 min

1: 1h 45 m

2: 4 hours

3: 5 hours

1. 30 min Driving Simulation 200 DRE
2. 60 iPad 230 Driving Simulation
3. 75 DRE 260 iPad
4. 105 Driving Simulation 275 DRE
5. 135 iPad 300 Driving Simulation
6. 150 DRE 330 iPad
Driving simulator
Driving Simulation Scenarios – Distracted Driving/Multi-tasking

- Identify circle that is different than others
- Two levels of difficulty
- Response time and accuracy
- Driving performance prior to/during task
  - Standard deviation of lateral position (SDLP) – swerving
  - Speed deviation
Simulator performance predicts on-road driving

Healthy Adults

HIV+ and HIV- Adults
Performance-based field sobriety tests
*Approximately 2 minutes each*

- **Divided attention**: Ability to track a moving target object while simultaneously attending to another
  - Divided attention, executive functioning (shifting), psychomotor coordination, staying on task

- **Lane tracking**: Ability to keep object between two lines as the lines shift (psychomotor coordination, sustained attention)
Performance-based field sobriety tests
Approximately 2 minutes each

- **Time Estimation:** Ability to estimate passage of time (must simultaneous perform other simple task in order to minimize subvocal counting)

- **Learning/Memory:** Memorize abstract figures and locations

- **Balance:** Lightweight Bluetooth device syncs with iPad; uses data from accelerometer, magnetoscope, and gyroscope to determine movement and sway
DRE Evaluations for the Current Project

- California DRE Instructors (Sgt. Glen Glaser, State Coordinator)
- Double-blind, placebo controlled; randomized assignment
- All participants examined under the same circumstances
- DRE Evaluations
  - Finger to Nose (FTN)
  - Modified Romberg Balance (MRB)
  - One Leg Stand (OLS)
  - Walk and Turn (WAT)
  - Lack of Convergence (LOC)
Edibles

- THC-infused food (baked goods [cookies, brownies], chocolates, gummies)
- After passing through the liver (first-pass metabolism), THC is transformed to **11-hydroxy-THC** (readily crosses the blood-brain barrier; more potent than THC)
- Hour to 1.5 hours to feel full effect
- Often absorbed better with food
Plasma THC Levels – Smoked vs. Oral

Mean plasma concentrations of Δ9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) following administration smoked cannabis vs. oral dronabinol.

Cannabis and Driving

- Identifying individuals whose driving is impaired due to cannabis remains a challenge
- *Per se* laws are most effective when there is a robust correlation between fluid levels and impairment; not yet true for THC/driving
- Impact of other administration methods: Vape pens, dabbing, edibles, transdermal, salves, topicals, lip balm, sublingual, suppository
- Impact of concentrates (up to 90% THC; Wax, shatter, budder, dabs) on driving
- Do regular cannabis users develop tolerance to the driver impairing aspects of cannabis?
- What are the effects of cannabis combined with alcohol, other drugs, including prescription medications?
- *Synthetic THC*: Spice, K2, etc.
- Impact in older users
## Research Team

### UCSD
- Igor Grant, MD – CMCR Director
- Thomas Marcotte, PhD
- Barth Wilsey, MD
- Robert Fitzgerald, PhD
- David Grelotti, MD
- Emily Sones
- Sandy Sanford
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- Jennifer Faccio, PharmD
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- Deborah Cookson, MPH
- Philip Sobelsky, PhD

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- Jayson Siller
- Travis Easter
- Richard Horrocks
- Ryan Orloff
- Gary Martens
- Kerry Comphel
- Kevin Craig
- Billy Phu
- Eric Stayer
- Bryan Duncan
- Helena Williams
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