Medical Cannabis: Current Landscape, Therapeutic Potential, and Risks

Disclosures
- Employee
  - Canopy Growth Corporation
- Former Employee
  - Zynerba Pharmaceuticals
- Former Consultant
  - Tilray
- Current Scientific Advisory Boards / Research Directorships
- Lambert Center for Medical Cannabis Education and Research (Thomas Jefferson University)
- Realm of Caring Foundation

What is Cannabis?
Cannabinoids

- 120+ cannabinoids in the plant
- Tetrahydrocannabinol (THC)
  - Majority of Research
  - Euphoric Effects
- Cannabidiol (CBD)
  - Research Catching Up
  - Still Don't Understand Mechanisms Fully
- Tetrahydrocannabinvarin (THCV)
- Cannabigerol (CBG)
- Cannabichromene (CBC)
State Laws

The Problem

- Decent Knowledge
  - THC and nausea & vomiting
  - THC and pain
  - THC/CBD and MS
  - CBD and pediatric epilepsy

- Little/No Knowledge
  - Cannabinoids and mental health
    - Anxiety (CBD?)
    - PTSD
    - Depression (CBD?)
    - Psychosis (CBD?)
  - Cannabinoids and...
    - ALS
    - Alzheimer’s
    - Autism (CBD?)
    - Cancer
    - Cerebral Palsy
    - Chronic Disease
    - Diabetes
    - Fibromyalgia (THC?)
    - Glaucoma
    - Hepatitis C
    - Lupus
    - Parkinson’s Disease
    - Sickle Cell
    - Tourette’s (THC?)

States where marijuana is legal

*Your condition is serious, Mr. Reynolds, but fortunately I recently scored some excellent weed that should alleviate your symptoms.*
Where's The Beef?

Types of Human Research
- Review
- Product/Regulatory
- Case Study
- Observational Study
- Experimental Study
- Clinical Trial

Review - Example
Product Study – Example
Case Study - Example

A little "dab" will do ya’: a case report of neuro-and cardiotoxicity following use of cannabis concentrates
Sharon S. Klieger, Charles J. Cee, Kurt Klahnich, and Steven Harmon
Division of Medical Toxicology, Department of Emergency Medicine, Arizona Emergency Health and Hospital System and University of Texas Southwestern Medical Center, Dallas, TX, USA. Southwestern Poison, Dallas, TX, USA

Abstract: The use of marijuana and cannabis concentrates is increasing, especially following decriminalization of cannabis in several states. Psychiatric and cardiotoxicity has been reported following cannabis use. We report a case of a patient who presented with severe neurologic and cardiotoxicity following the use of "dabs". The patient was a 19-year-old male in a coma with rapid, irregular heart rate, in the ICU with intubation, and hypotension. He was brought to the ER and found to be on 100% oxygen. His family was unable to provide any history of cannabis use. He was treated with methadone and tapering doses of lorazepam. He had complete recovery and was discharged to a rehabilitation facility.

Clinical Case Discussion
Cannabinoid Hypermucous Syndrome and the Consulting Psychiatrist: A Case Study of Diagnosis and Treatment
for an Emerging Disorder in Psychiatric Practice

This increasing prevalence of cannabis use in the United States requires awareness of cannabinoid disorders and familiarity with treatment options. We present a case of cannabinoid hypermucous syndrome that required psychiatric treatment and an extensive search for other causes of hypermucous disorders.
Observational Study – Example #1: Sample Description


Observational Study – Example #2: Epidemiological
Epidemiological Evidence: V.A.

- VHA Trends in number of Veterans with PTSD and SUD diagnoses treated by VHA in the last year by drug diagnosis

Observational Study – Example #3: Group Comparison

Cannabis & Autism

<table>
<thead>
<tr>
<th>Baseline Patient Health Characteristics by Cannabinoid Use</th>
<th>Cannabinoid Therapy</th>
<th>Non-Cannabinoid Therapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Quality of Life (WHOQOL)</td>
<td>3.7 (1.2)</td>
<td>3.2 (1.3)</td>
<td>.06</td>
</tr>
<tr>
<td>Satisfaction with Health (WHOQOL)</td>
<td>3.1 (1.3)</td>
<td>2.4 (1.2)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>OHI Sleep (CSHQ)</td>
<td>29.5 (10.7)</td>
<td>37.9 (13.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Adult Sleep (PSQI)</td>
<td>9.9 (5.9)</td>
<td>11.0 (13.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Anxiety (HADS)</td>
<td>9.9 (6.1)</td>
<td>13.0 (5.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Depression (HADS)</td>
<td>3.9 (2.9)</td>
<td>5.3 (5.2)</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Observational Study – Example #4: Prospective Observational

Cannabis & PTSD

Is this really all we have?

- Yes
- But... the needed studies are a pain to complete
  - DEA Schedule 1
  - Applications
  - Inspections
  - Drug Product
  - NDA
  - Synthetic Manufacturing
  - Pharmaceutical Preparations
- So not many researchers are choosing to engage
Poll: Under what schedule in the CSA does THC fall?

- A: Schedule I
- B: Schedule II
- C: Schedule III
- D: All of the Above
- E: None of the Above

Poll: Under what schedule in the CSA does CBD fall?

- A: Schedule II
- B: Schedule III
- C: Schedule IV
- D: All of the Above
- E: None of the Above
The Bright Side

Experimental Study - Example

Blood THC + Drug Effect
25mg THC Dose

Vandrey et al., 2017
It's not all gumdrops and lollipops: Consequences
Short-term use

- Impaired short-term memory, making it difficult to learn and to retain information
- Impaired motor coordination, interfering with driving skills and increasing the risk of injuries
- Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases
- In high doses, paranoia and psychosis


Long-term use

- Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*
- Altered brain development*
- Poor educational outcome, with increased likelihood of dropping out of school*
- Cognitive impairment, with lower IQ among those who were frequent users during adolescence*
- Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*
- Symptoms of chronic bronchitis
- Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders


Medical Marijuana Dispensary

Ages 18+

Self-Report

Data on:
- Reasons for use
- Addiction
- Psychological symptoms
- Quit behavior
- Vulnerability factors
- Co-occurring substance use

Demographics

- 217 community-based adults (73.3% male) currently receiving medical cannabis for a physical or mental health condition at a cannabis dispensary
- Mean age of participants was 41.2 (SD = 14.9, Range 18 – 74 years)
- White/Caucasian (68.7%), followed by Hispanic (7.5%), Black/Non-Hispanic (7.0%), Black/Hispanic (3.3%), Asian (3.3%), and “Other” (10.3%).

Conditions

- Anxiety (61.8%)
- Chronic Pain (58.0%)
- Stress (48.6%)
- Insomnia (48.1%)
- Depression (44.8%)
- Appetite (29.7%)
- Headaches (28.4%)
- Nausea (22.4%)
- Muscle Spasms (20.3%)
- Posttraumatic Stress Disorder (18.9%)
Abuse & Dependence

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Cannabis</th>
<th>Cannabis-Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sample</td>
<td>49 (14)</td>
<td>26 (17)</td>
</tr>
<tr>
<td>Gender</td>
<td>22 (29)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Clinical Place</td>
<td>26 (13)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>23 (22)</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Depression</td>
<td>17 (21)</td>
<td>20 (23)</td>
</tr>
<tr>
<td>Age</td>
<td>31 (6)</td>
<td>33 (15)</td>
</tr>
<tr>
<td>Income</td>
<td>15 (13)</td>
<td>14 (13)</td>
</tr>
</tbody>
</table>


Clinical Evidence

<table>
<thead>
<tr>
<th>Variable</th>
<th>CUD Mean (SD)</th>
<th>CUD-PTSD Mean (SD)</th>
<th>Unadjusted for Covariates</th>
<th>Adjusted for Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis Use Motives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Coping</td>
<td>12.04 (4.67)</td>
<td>15.87 (3.63)</td>
<td>17.73***</td>
<td>0.16</td>
</tr>
<tr>
<td>2) Enhancement</td>
<td>17.89 (5.35)</td>
<td>18.14 (4.04)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>3) Social</td>
<td>14.98 (5.77)</td>
<td>15.49 (5.58)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>4) Conformity</td>
<td>7.84 (4.07)</td>
<td>9.95 (5.21)</td>
<td>4.77*</td>
<td>0.05</td>
</tr>
<tr>
<td>5) Expansion</td>
<td>12.23 (5.54)</td>
<td>13.92 (6.47)</td>
<td>1.83</td>
<td></td>
</tr>
<tr>
<td>Cannabis Use Problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6) Compulsivity</td>
<td>6.84 (8.67)</td>
<td>11.86 (10.22)</td>
<td>6.53*</td>
<td>0.07</td>
</tr>
<tr>
<td>7) Withdrawal Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8) Quotiting</td>
<td>6.35 (7.06)</td>
<td>13.33 (10.09)</td>
<td>14.94***</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Success in Quitting

- Very difficult (on own or with professional treatment)
  - Relapse is common among those even in professional treatment programs
    - 63% of those receiving either MI or CBT relapsed within 4 months
    - 72% by 16 months
  - Among cannabis dependent outpatients
    - 26% lapsed within 1 month
    - 48% within 3 months
    - 71% within 6 months
    - 71% of lapsers experienced full relapse

Continuous Abstinence

Predictors of Relapse

- Low Levels of Physical Activity
  - Lapse within 4 days.
  - Greater use during 4 days.
- Poor Sleep
  - Lapse within 2 days.
  - Greater use across 6 months.
- Positive Expectancies (e.g., relaxation/tension reduction, perceptual/cognitive enhancement, social/sexual facilitation)
  - Lapse and Relapse across 4 months.
Clinical Evidence

PTSD  \rightarrow  CUD


Clinical Landscape & Implications

A study of physicians

- 352 physicians surveyed
- Associated attitudes, knowledge, and practices surrounding cannabis and anxiety/PTSD
- 35.4% Female
- Average age: 46.25 (SD = 13.36)
- Region
  - 32.3% Northeast
  - 28.2% South
  - 16.9% Midwest
  - 18.9% Western
  - 0.84% Outside U.S.
  - 0.57% U.S. Territories
- Prescriber Type
  - 68.5% Psychiatrist
  - 9.9% Physician, mental health
  - 7.4% Physician, non-mental health
  - 14.2% Other
- Hospital Facility
  - 20.3% Public City or State Hospital
  - 15.3% Private Hospital
  - 8.5% VA Hospital
  - 29% Other


Epidemiological Evidence: V.A.


Where do we go from here?
Recently Completed / Ongoing Research

- **Grant 1: Administration**
  - 76 Treatment-resistant Veterans with PTSD
  - Site: Scottsdale Research Institute – (+ Canadian Replication)
  - 4 Conditions (Crossover) – 6 month follow-up
  - High THC/High CBD
  - High THC/Low CBD
  - High CBD/Low THC
  - Placebo
  - Outcomes: PTSD, sleep, suicide, functioning, negative consequences

- **Grant 2: Observation**
  - 150 individuals with PTSD (50% weekly users, 50% non-users)
  - Site: VA Denver – Users: Medical & Recreational
  - Objective testing of cannabis
  - 5 time points over 12 months.
  - Outcomes: PTSD, sleep, suicide, functioning, negative consequences (trajectory, spontaneous initiation and cessation)

Upcoming Research

- **CBD as adjunct to PE (Loflin, PI)**
  - First VA-funded cannabinoid administration trial
  - 136 military Veterans with PTSD
  - PE + placebo vs. PE + 600 mg CBD (300 mg BID)
  - Primary Outcomes: CAPS-5 (Pre-Post)
  - Secondary Outcomes: PCL-5 (weekly)
  - Safety: UKU Side Effects Rating Scale (weekly)
  - Initiated Spring 2019

Questions?

“No, I don’t have any weed.”