Marijuana and sleep disorders
Deirdre A. Conroy, Ph.D., D, ABSM, C. BSM
Clinical Director, Behavioral Sleep Medicine Program
Department of Psychiatry
## Conflict of Interest Disclosures for Speakers

1. I do not have any relationships with any entities **producing**, **marketing**, **reselling**, or **distributing** health care goods or services consumed by, or used on, patients, **OR**

2. I have the following relationships with entities **producing**, **marketing**, **reselling**, or **distributing** health care goods or services consumed by, or used on, patients.

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td></td>
</tr>
<tr>
<td>Speakers’ Bureaus</td>
<td></td>
</tr>
<tr>
<td>Financial support</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

3. The material presented in this lecture has **no** relationship with any of these potential conflicts, **OR**

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:
Outline

• Introduction and terminology
• Marijuana and specific sleep disorders
  – Insomnia
  – Sleep apnea
  – REM Behavior Disorder
• Summary and Future Directions
Changing attitudes- Monitoring the Future

Risk
% seeing "great risk" in using regularly

Marijuana use is increasing
## Michigan Laws & Penalties

### Conditional Release  Local Decriminalization  Drugged Driving  Hemp  Medical Marijuana

<table>
<thead>
<tr>
<th>Offense</th>
<th>Penalty</th>
<th>Incarceration</th>
<th>Max. Fine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Possession</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any amount</td>
<td>Misdemeanor</td>
<td>1 year</td>
<td>$ 2,000</td>
</tr>
<tr>
<td>In a park</td>
<td>Misdemeanor or Felony</td>
<td>2 years</td>
<td>$ 2,000</td>
</tr>
<tr>
<td>Use of marijuana</td>
<td>Misdemeanor</td>
<td>90 days</td>
<td>$ 100</td>
</tr>
<tr>
<td><strong>Sale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sale without remuneration</td>
<td>Misdemeanor</td>
<td>1 year</td>
<td>$ 1,000</td>
</tr>
<tr>
<td>Less than 5 kg</td>
<td>Felony</td>
<td>4 years</td>
<td>$ 20,000</td>
</tr>
<tr>
<td>5 - less than 45 kg</td>
<td>Felony</td>
<td>7 years</td>
<td>$ 500,000</td>
</tr>
<tr>
<td>45 kg or more</td>
<td>Felony</td>
<td>15 years</td>
<td>$ 10,000,000</td>
</tr>
<tr>
<td><strong>Cultivation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 20 plants</td>
<td>Felony</td>
<td>4 years</td>
<td>$ 20,000</td>
</tr>
<tr>
<td>20 - less than 200 plants</td>
<td>Felony</td>
<td>7 years</td>
<td>$ 500,000</td>
</tr>
<tr>
<td>200 plants or more</td>
<td>Felony</td>
<td>15 years</td>
<td>$ 10,000,000</td>
</tr>
<tr>
<td><strong>Hash &amp; Concentrates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penalties for hashish are the same as for marijuana. Please see the marijuana penalties section for further details.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paraphernalia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sale of paraphernalia</td>
<td>Misdemeanor</td>
<td>90 days</td>
<td>$ 5,000</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Ann Arbor</td>
<td>N/A</td>
<td>N/A</td>
<td>$ 100</td>
</tr>
</tbody>
</table>

Any conviction will result in a driver's license suspension for 6 months.
Medical marijuana (MMJ) in the state of Michigan
MMJ in Michigan

- Michigan Medical Marijuana Act passed in 2008 legalized the use of cannabis for the treatment of debilitating medical conditions.
- Joining 26 other states in the US
MCL § 333.26423: Definitions.

Sec. 3. Definitions. As used in this act:

(a) “Debilitating medical condition” means 1 or more of the following:
   (1) Cancer, glaucoma, positive status for human immunodeficiency virus, acquired immune deficiency syndrome, hepatitis C, amyotrophic lateral sclerosis, Crohn’s disease, agitation of Alzheimer’s disease, nail patella, or the treatment of these conditions.
   (2) A chronic or debilitating disease or medical condition or its treatment that produces 1 or more of the following: cachexia or wasting syndrome; severe and chronic pain; severe nausea; seizures, including but not limited to those characteristic of epilepsy; or severe and persistent muscle spasms, including but not limited to those characteristic of multiple sclerosis.
   (3) Any other medical condition or its treatment approved by the department, as provided for in section 5(a).
To qualify for the use of medical marijuana, the qualifying patient and his/her primary care giver should hold a registry identification card issued by the Michigan Department of Community Health.
MMJ in Michigan

- As of January 2016, 182,091 patients and 34,269 caregivers have been approved for medical cannabis registry identification cards in Michigan (Gaedeke, 2016)
Cannabis plant is comprised of 100 different active compounds called cannabinoids.

2 Primary cannabinoids are:
  - Δ9-Tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
Δ⁹-tetrahydrocannabinol (THC)

- Primary psychoactive/intoxicating component of cannabis plant
- Acts on endogenous CB1 receptors in the brain
- CB1 receptors are directly related to the regulation of the sleep-wake cycle
• The non-psychoactive/intoxicating constituent of the cannabis sativa plant.
• Acts on CB2 receptors in the brain
• Counters the effects of THC
• Many possible therapeutic effects
Cannabis characterization

- Plant Sub-Species
  - Indica
  - Sativa
  - Hybrid

- Cannabinoid Concentration
  - % THC
  - %CBD
Marijuana

- Psychoactive dried flower buds and leaves of the female hemp or cannabis plant (Cannabis sativa or Cannabis indica)
- Contains high levels of THC
- Smoked, vaped, or ingested (as in baked goods) especially for their intoxicating effect
What motivates medical cannabis users to use?

- Adults (N = 801, M age = 45) seeking medical cannabis certification or recertification in Michigan
- Completed a 36-item Comprehensive Marijuana Motives Questionnaire (CMMQ)

Bohnert KM, Bonar EE, Arnedt JT, Conroy DA, Walton MA, Ilgen, MA  Properties and utility of the comprehensive marijuana motives questionnaire among medical cannabis patients (Addictive Behaviors, revisions submitted)
Confirmatory factor analysis of the CMMQ

Motivations to use cannabis

• Sleep Problems Questionnaire
• 80% of participants used cannabis in the past 6 months to improve sleep.

<table>
<thead>
<tr>
<th>3. Past 6 Months Frequency of Cannabis Use to Help You Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never/Almost never</td>
</tr>
<tr>
<td>Rarely</td>
</tr>
<tr>
<td>Sometimes</td>
</tr>
<tr>
<td>Often</td>
</tr>
<tr>
<td>Always/Almost always</td>
</tr>
</tbody>
</table>

Cranford JA, Arnedt JT, Conroy DA, Bohnert KM, Bourque C, Blow FC, Ilgen MA, Prevalence and Correlates of Sleep-Related Problems in Adults Receiving Medical Cannabis *Drug and Alcohol Dependence* 2017 Nov 1;180:227-233
Outline

- Introduction and terminology
- Marijuana and specific sleep disorder
  - Insomnia
  - Sleep apnea
  - REM Behavior Disorder
- Summary and Future Directions
Insomnia
Marijuana and insomnia

- Early studies from the 1970s show THC
  - SOL
  - WASO
  - Increased SWS

- Chronic use of cannabis leads to withdrawal
  - Withdrawal can last up to 45 days (Budney et al 2003)
  - PSG changes: ↓ TST, SE%, %REM (Bolla et al 2008, 2010)
  - Zolpidem ER can help (Vandrey et al 2011)

- Recent research has focused on understanding the constituents of cannabis on sleep

Marijuana and insomnia

• Many studies focus on heavy, problematic, or treatment seeking substance use users
  – Poor sleep and insomnia is hallmark withdrawal symptom \((\text{Babson et al 2013b})\)
  – Insomnia increases risk for lapse/relapse to cannabis \((\text{Babson et al 2013a})\)

• The distinct effects of daily versus non-daily use on sleep remains unknown
## Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Daily users (n=49)</th>
<th>Non-daily users (n=29)</th>
<th>Non-users (n=20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>22.5 (3.1)</td>
<td>22.5 (3.5)</td>
<td>21.7 (2.4)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Female n (%)</strong></td>
<td>27 (55.1%)</td>
<td>15 (51.7%)</td>
<td>11 (55.0)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td>28 (57.1%)</td>
<td>15 (51.7)</td>
<td>11 (55.0%)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td>12 (24.5%)</td>
<td>6 (20.7%)</td>
<td>3 (15.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>9 (18.4%)</td>
<td>8 (27.6%)</td>
<td>6 (30.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Education n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 12</td>
<td>14 (14.3%)</td>
<td>8 (8.2%)</td>
<td>4 (4.1%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Unemployed (%)</td>
<td>61.2% (30/49)</td>
<td>51.5% (15/29)</td>
<td>50% (12/20)</td>
<td>0.70</td>
</tr>
<tr>
<td>cannabis dependence n(%)</td>
<td>20 (40.8%)</td>
<td>1 (3.4%)</td>
<td>0 (0%)</td>
<td>P&lt;.01</td>
</tr>
</tbody>
</table>
Definitions of use

• Daily users = using cannabis at least 6 days per week
• Non-daily users = use on at least 1 day in the past month and up to 5 days per week
• Non-users = not used cannabis in at least the last month
Cannabis use patterns

72.6 (20.7-78.0) minutes on use days
18.6 (5.0-18.3) minutes on use days

% use during the day
% use during day and night
% use at night

Daily users
Non-daily users
Sleep onset latency

<table>
<thead>
<tr>
<th></th>
<th>Sleep diary</th>
<th>Actigraphy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-User</td>
<td>14.13</td>
<td>11.8</td>
</tr>
<tr>
<td>Non-Daily</td>
<td>13.06</td>
<td>12.01</td>
</tr>
<tr>
<td>Daily</td>
<td>16.74</td>
<td>14.32</td>
</tr>
</tbody>
</table>

* Significant difference
Wake after sleep onset

![Bar graph showing minutes spent awake after sleep onset for different user statuses.](image)

- **Non-User**: 11.23 minutes
- **Non-Daily**: 33.16 minutes
- **Daily**: 61.48 minutes

Legend:
- Sleep diary
- Actigraphy
Sleep disturbance by use group

**Insomnia Severity Index >10**
- Daily Use: 20
- Non-Daily Use: 10.3
- Non-User: 38.8

**Pittsburgh Sleep Quality Index >5**
- Daily Use: 45
- Non-Daily Use: 34.5
- Non-User: 55.1
Cannabis “species” and concentration preference in MMJ users with insomnia
### Species preferences in MMJ users for sleep

- **Medical cannabis dispensary in San Francisco**

<table>
<thead>
<tr>
<th></th>
<th>M or N</th>
<th>SD or (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.4 years</td>
<td>14.3 years</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>119</td>
<td>73%</td>
</tr>
<tr>
<td>Amount of time using</td>
<td>10.8 years</td>
<td>10.4 years</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>110</td>
<td>67.1%</td>
</tr>
<tr>
<td>Black/Non-Hispanic</td>
<td>12</td>
<td>7.5%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11</td>
<td>6.8%</td>
</tr>
<tr>
<td>Black/Hispanic</td>
<td>6</td>
<td>3.7%</td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
<td>3.1%</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>11.8%</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed high school</td>
<td>158</td>
<td>97%</td>
</tr>
<tr>
<td>Completed college</td>
<td>64</td>
<td>39%</td>
</tr>
<tr>
<td>Advanced degree</td>
<td>24</td>
<td>15%</td>
</tr>
</tbody>
</table>
Species preferences in MMJ users for sleep

Specific reason for use
- 85% Insomnia
- 15% Nightmares

CUD Diagnosis
- 53% CUD
- 47% No CUD

Strain Preference
- 38% Sativa/Primary
- 34% Sativa Hybrid
- 28% Indica/Primary
- Other

Specific reason for use:
- 85% Insomnia
- 15% Nightmares

CUD Diagnosis:
- 53% CUD
- 47% No CUD

Strain Preference:
- 38% Sativa/Primary
- 34% Sativa Hybrid
- 28% Indica/Primary
- Other

Slide courtesy of Kim Babson, PhD

Insomnia and greater sleep latency more likely to report using higher concentrations of CBD.

Belendiuk et al 2015

*Slide courtesy of Kim Babson, PhD*
Outline

• Introduction and terminology
• Marijuana and specific sleep disorder
  – Insomnia
  – Sleep apnea
  – REM Behavior Disorder
• Summary
Sleep apnea
Dronabinol (Marinol) is a nonselective CB1 and CB2 receptor agonist /pure isomer of THC

Decreased apneas during sleep in rats (Calik and Carley 2017)

Cannabis and OSA

- Phase II multisite study N=75 with mod or severe OSA
- Randomized placebo controlled trial
  - Placebo, 2.5 mg or 10 mg dronabinol daily 1 hour before BT for 6 weeks
- Primary outcomes:
  - Apnea Hypopnea Index (AHI)
  - Epworth Sleepiness Scale (ESS)
  - Maintenance of Wakefulness Test (MWT)
### Change from baseline in AHI after 6 weeks of treatment

**Change in AHI**
- 2.5 mg by 10.7 +/- 4.4
- 10 mg by 12.9 +/- 4.3

Baseline AHI = 25.9 +/- 11.3 events/hour

**Change in ESS**
- 2.5 mg by -3.8 +/- 0.8
- 10 mg by -2.3 +/- 1.2

Baseline ESS = 11.5 +/- 3.8

**Change in MWT**
- Unchanged

Baseline MWT = 19.2 +/- 11.8 min
Position statement: Avoid using medical marijuana to treat sleep apnea

It is the position of the AASM:
- That medical cannabis and/or its synthetic extracts should not be used for the treatment of OSA due to unreliable delivery methods and insufficient evidence of treatment effectiveness, tolerability, and safety, and OSA should be excluded from the list of chronic medical conditions for state medical cannabis programs.
- That patients with OSA should be advised to discuss their treatment options with a licensed medical provider at an accredited sleep facility.

"Until we have further evidence on the efficacy of medical cannabis for the treatment of sleep apnea, and until its safety profile is established, patients should discuss proven treatment options with a licensed medical provider at an accredited sleep facility," said lead author Dr. Kannan Ramar, professor of medicine in the division of pulmonary and critical care medicine at Mayo Clinic in Rochester, Minnesota.

The position statement is published in the April 15 issue of the Journal of Clinical Sleep Medicine.
Outline

• Introduction and terminology
• Marijuana and specific sleep disorder
  – Insomnia
  – Sleep apnea
  – REM Behavior Disorder
• Summary
REM Behavior Disorder
CBD on sleep in patients with Parkinson’s and RBD

- 4 patients with PD and complex sleep behaviors
- Three patients had CBD 75 mg/day
- One patient had CBD 300 mg
- 6 week treatment

Chagas et al 2014 J. Clin Pharmacy and Therapeutics
Small case study of RBD in PD patients (n=4)

Four patients treated with CBD had prompt and substantial reduction in the frequency of RBD-related events without side effect.

Table 1. Description of patients with PD and symptoms compatible with RBD

<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms</th>
<th>Polysomnography</th>
<th>Cannabidiol dose</th>
<th>Frequency of symptoms before treatment</th>
<th>Frequency of symptoms after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Swearing, talking, yelling, pushing, kicking, punching and gesturing</td>
<td>Compatible PLMI = 0</td>
<td>75 mg</td>
<td>2–4× week</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Yelling, talking, laughing, gesturing, pushing and kicking</td>
<td>Patient did not enter REM sleep during examination PLMI = 0</td>
<td>75 mg</td>
<td>2–4× week</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Talking, yelling, singing, pushing, punching and kicking</td>
<td>Patient refused to undergo examination</td>
<td>75 mg</td>
<td>7× week</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Laughing, kicking, pushing and punching</td>
<td>Compatible PLMI = 84.9</td>
<td>300 mg</td>
<td>2–4× week</td>
<td>1× week</td>
</tr>
</tbody>
</table>

PLMI (events/h), Periodic Leg Movement Index; RBD, REM sleep behaviour disorder; PD, Parkinson’s disease.

© 2014 John Wiley & Sons Ltd

Journal of Clinical Pharmacy and Therapeutics, 2014, 39, 564–566
Outline

• Introduction and terminology
• Marijuana and specific sleep disorder
  – Insomnia
  – Sleep apnea
  – REM Behavior Disorder
• Summary
• Cannabinoids affect endogenous receptors in the brain, which are involved in sleep regulation
• MMJ is legal in MI but specific sleep disorders not yet listed as debilitating condition
• There is a bidirectional relationship between poor sleep and heavy cannabis use
• Studies show preference for and possible improvements with CBD
Future Directions

- Larger sample sizes and longer follow up periods
- How specific cannabinoids affect sleep disorders e.g. ratios, dose, timing, route of administration, and safety
- How treatment of sleep disturbance (CBTi) might impact cannabis use; NIH project underway