Marijuana as Medicine: Unintended Consequences and Concerns
Disclosures

• David Reagan, MD PhD, has disclosed no actual, potential, or perceived conflicts of interest.

• Michael Warren, MD MPH, has disclosed no actual, potential, or perceived conflicts of interest.
Objectives

• Describe the current policy landscape related to the use of marijuana as medicine.

• Identify the individual benefits associated with use of marijuana as medicine.

• Outline the population harms associated with use of marijuana as medicine.
Background
Marijuana: The Basics

• Produced from *Cannabis sativa*

• DEA Schedule I Drug
  – No currently accepted use of whole plant
    • (There are FDA-approved meds)
  – High potential for abuse

• Available (non-pharmaceutical grade) forms:
  – Cigarette/blunt/pipe/bong
  – Edibles
  – Tea/brew

Image sources:
Marijuana: The Basics

- Three main “types”
- Determined by enzyme concentration

**THC Type**
- 0.5-15% THC
- “Drug” type

**CBD Type**
- 0.05-0.7% THC
- Fiber / hemp / oil type

**Hybrid type**
- 0.5-5% THC

Marijuana: The Basics

• Delta-9-tetrahydrocannabinol (\(\Delta-9\)-THC)
  – Compound responsible for psychoactive effects
  – Time to onset of effect and duration of effect depends on method of ingestion

• Typical effects
  – Euphoria
  – Disinhibition, increased sociability
  – Enhanced sensory perception
  – Time distortion

• Adverse effects
  – Typical: Impaired judgment, reduced coordination, dry mouth, anxiety, fear, distrust, panic
  – Others: cyclic vomiting, stress cardiomyopathy
Marijuana: The Basics

- Even with approved medications, one person’s “desired effects” may be another person’s “adverse effects”

<table>
<thead>
<tr>
<th>Elation</th>
<th>Some patients experience “high”</th>
<th>Adverse event among 24% at anti-emetic dose and 8% at appetite stimulant dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laughing</td>
<td></td>
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<tr>
<td>Heightened</td>
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<td></td>
</tr>
<tr>
<td>Awareness</td>
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</tbody>
</table>

Source: US Food and Drug Administration. Available at: https://www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-emc0004-04.pdf
From opium poppy to oxycodone...
From mold to penicillin tablets and liquid…

From foxglove to digitalis...

Image sources:
2. Dioxin label: https://www.drugs.com/pro/digoxin-tablets.html
3. Digoxin tablets: https://www.drugs.com/digoxin.html
From marijuana to medicine...

- Current FDA-approved cannabinoid-based medications
  - Dronabinol (Marinol)—synthetic THC
    - Nausea/vomiting in chemotherapy patients
    - Appetite stimulation in AIDS patients
  - Nabilone (Cesamet)—synthetic THC
    - Multiple sclerosis
    - Adjunctive analgesic in cancer patients

- Pending approval
  - Epidiolex (>98% CBD)
  - Nabiximol (Sativex, 1:1 THC/CBD)

- FDA approval and pharmaceutical-grade manufacturing process assures safety, efficacy, quality, and consistency
Marijuana Intoxication & Use Disorder

Use/Intoxication

Substance Use Disorder

Mild: 2-3 Symptoms
Moderate: 4-5 symptoms
Severe: 6+ symptoms

Withdrawal can occur after heavy/prolonged use

Reversible

Self-Harm

A Common Pathway: Dopamine

Many Drugs Lead to Dopamine Release

- Amphetamines, Cocaine, Opioids, Nicotine, Sedatives, Marijuana, Ethanol

With increased dopamine:

- Dopamine receptors are decreased
  - Equilibrium is re-established
- When dopamine decreases, the number of receptors remains less
- Normal dopamine levels feel low
- Takes months or years to restore normal balance

MAO – Monoamine oxidase (inactivates DA)
VMAT2 – Vesicular monoamine transporter 2
DAT – Dopamine uptake transporter
D1 – D5 – Dopamine receptors
Your Brain After Drugs

Normal

Cocaine Abuser (10 DA)

Cocaine Abuser (100 DA)
State Marijuana Laws: Current Landscape

Current TN Laws

- Tennessee Code Annotated § 39-17-402
  - Defines “marijuana”
  - Does not include industrial hemp
  - Allowances for cannabidiol products as approved by FDA or in case of intractable seizures
Medical Marijuana: Public Health Concerns

- The individual benefits of marijuana as medicine have been overstated.
- The population harms of marijuana as medicine have been understated.
- Medical marijuana is not a solution to the opioid crisis.
Individual Benefits of Marijuana as Medicine
Marijuana: Individual Benefits OVERstated

• Most comprehensive review to date by National Academy of Sciences in 2017
  – 22 conclusions re: therapeutic benefits, only 3 with “substantial or conclusive evidence” of benefit
    • Spasticity due to multiple sclerosis
    • Chemotherapy-induced nausea/vomiting
    • Chronic [neuropathic] pain
  – 4 conclusions with substantial evidence of harm:
    • Worsening respiratory symptoms and frequent chronic bronchitis
    • ↑ risk of motor vehicle crashes
    • Lower birth weight of offspring
    • Development of schizophrenia or other psychoses

Marijuana: Individual Benefits OVERstated

• Not a lack of information on this topic
  – What can be trusted?
  – Who benefits?

• Quality of available information varies widely
  – Study type
  – Publication source
  – Peer review status

Image source: Wake Forest School of Medicine. Available at: [http://libguides.wakehealth.edu/EBP/Study](http://libguides.wakehealth.edu/EBP/Study). Last accessed 02/08/2017
Marijuana: Individual Benefits OVERstated

ADDITION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients, Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

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Marijuana: Individual Benefits OVERstated

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial


- Study funded by pharmaceutical company
- “Open-label” → not blinded, large potential for placebo effect
- Patients had treatment-resistant epilepsy (e.g. Lennox-Gastaut and Dravet syndromes)
- 12% of patients had adverse events related to cannabidiol
- Conclusion: Need randomized controlled trial

reported in more than 10% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhoea (n=31 [19%]), fatigue (n=21 [13%]), and convulsion (n=18 [11%]). Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, including one death—a sudden unexpected death in epilepsy regarded as unrelated to study drug. 20 (12%) patients had severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]). The median monthly frequency of motor seizures was 30.0 (IQR 11.0–96.0) at baseline and 15.8 (5.6–57.6) over the 12 week treatment period. The median reduction in monthly motor seizures was 36.5% (IQR 0–64.7).

Population Harms of Marijuana as Medicine
Marijuana: Population Harms Understated

Average Delta-9-THC concentration of DEA Specimens by Year, 1995-2014

WA: Marijuana-related impaired driving

Percentage of Total Driving Cases Positive for Carboxy-THC and Delta-9-THC 2009-2015*

<table>
<thead>
<tr>
<th>Year</th>
<th>Carboxy-THC</th>
<th>Delta-9-THC</th>
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<tbody>
<tr>
<td>2009</td>
<td>26%</td>
<td>18%</td>
</tr>
<tr>
<td>2010</td>
<td>28%</td>
<td>19%</td>
</tr>
<tr>
<td>2011</td>
<td>28%</td>
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<td>2012</td>
<td>29%</td>
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<tr>
<td>2013</td>
<td>40%</td>
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<tr>
<td>2014</td>
<td>36%</td>
<td>28%</td>
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<tr>
<td>2015</td>
<td>39%</td>
<td>33%</td>
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SOURCE: Washington State Patrol Toxicology Laboratory and NWHiDTA
2015*: January through April 2015

Driver Comparison Groups

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<tr>
<td>Active-THC Only</td>
<td>Carboxy-THC Only</td>
<td>THC &amp; Alcohol 2.08</td>
<td>THC &amp; Drugs</td>
<td>THC &amp; Drugs &amp; Alcohol</td>
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</table>


Source:
CO: Marijuana-related impaired driving

Marijuana: Population Harms UNDERstated

Can you tell the difference?

Can you tell the difference?

Can you tell the difference?

Can you tell the difference?

Can you tell the difference?

Image sources: https://www.childrenscolorado.org/conditions-and-advice/marijuana-what-parents-need-to-know/resources/
Marijuana: Population Harms UNDERstated

Annual children’s hospital visits and regional poison center cases for unintentional marijuana exposures in children 9 years or younger in Colorado between 2009 and 2015. Children’s hospital visits include emergency department visits, urgent care visits, and inpatient hospital admissions.

Marijuana: Population Harms UNDERstated

Last-month use of marijuana, ages 12-17 (as of 2015)


…death of a man aged 19 years after consuming an edible marijuana product… initially the decedent ate only a single piece of his cookie, as directed by the sales clerk. Approximately 30–60 minutes later, not feeling any effects, he consumed the remainder of the cookie. During the next 2 hours, he reportedly exhibited erratic speech and hostile behaviors. Approximately 3.5 hours after initial ingestion, and 2.5 hours after consuming the remainder of the cookie, he jumped off a fourth floor balcony and died from trauma. The autopsy, performed 29 hours after time of death, found marijuana intoxication as a chief contributing factor….only confirmed findings were cannabinoids (7.2 ng/mL delta-9 tetrahydrocannabinol [THC] and 49 ng/mL delta-9 carboxy-THC, an inactive marijuana metabolite). The legal whole blood limit of delta-9 THC for driving a vehicle in Colorado is 5.0 ng/mL.
Marijuana: Not Solution to Opioid Crisis

- Population-level studies have looked at opioid prescribing and overdose deaths in states with medical marijuana
  - Did not look at patient-level
  - "Ecological fallacy"—cannot make conclusions about individuals based on group data

Sources:
1. Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare Part D. Health Affairs. 35(7); 2016: 1230-1236.
Marijuana: Not Solution to Opioid Crisis

• Be careful when replacing one addictive substance with another

• Argument is for “harm reduction”

• But will reduction actually occur?

“For nervous prostration, brain exhaustion, depression of spirits, mental and physical debility, neurasthenia, sick headache, neuralgia, cases of the opium, tobacco, alcohol or chloral habit, weak status of the voice…..”

The following medical organizations have voiced concern and advised against using marijuana for medicine outside of the FDA approval process or a similar rigorous process:

- American Academy of Neurology
- American Psychiatric Association
- American Society of Addiction Medicine
- American Academy of Pediatrics
- American Medical Association
The AAN does not advocate for the legalization of marijuana-based products for use in neurologic disorders at this time, as further research is needed to determine the benefits and safety of such products. This is of paramount importance when marijuana-based products are used in patients with underlying neurologic disorders, or in children whose developing brains may be more vulnerable to the toxic effects of marijuana.

The AAP opposes “medical marijuana” outside the regulatory process of the US Food and Drug Administration. Notwithstanding this opposition to use, the AAP recognizes that marijuana may currently be an option for cannabinoid administration for children with life-limiting or severely debilitating conditions and for whom current therapies are inadequate…The AAP opposes legalization of marijuana because of the potential harms to children and adolescents.
Our AMA calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease…Our AMA urges that marijuana's status as a federal schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines, and alternate delivery methods. This should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product.
There is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Adolescents are particularly vulnerable to harm, given the effects of cannabis on neurological development.

The National Council on Alcoholism and Drug Dependence, Inc. (NCADD) is opposed to the broad availability of smoked marijuana. Marijuana grown and provided for legal medical use should be scheduled and monitored under FDA oversight, and should be held to the same FDA standards imposed on other dangerous prescription drugs including those regarding warnings, labeling, and the ordering and filling of prescriptions.
ASAM does not support the legalization of marijuana and recommends that jurisdictions that have not acted to legalize marijuana be most cautious and not adopt a policy of legalization until more can be learned from the “natural experiments” now underway in jurisdictions that have legalized marijuana. ASAM supports the use of cannabinoids and cannabis for medicinal purposes only when governed by appropriate safety and monitoring regulations, such as those established by the FDA research and post-marketing surveillance processes.
Summary

• From a public health standpoint, there are three main concerns:
  – Individual benefits of medical marijuana have been overstated
  – Population harms of medical marijuana have been understated
  – Medical marijuana is not a solution to our opioid crisis

• The Tennessee Department of Health supports ongoing, quality research and a science-informed approach to this topic (legitimate scientific experiments with informed consent and IRB approval).