Objectives

• Describe marijuana laws in the state of Oregon and the nation
• List evidence available for medicinal use of marijuana
• Describe risks associated with marijuana use, particularly in adolescents
• Explain how to communicate the risks and beneficial properties of marijuana to patients
Clinical Questions

• How does the law differ between medical marijuana and recreational marijuana?
• What does the evidence tell us about the effectiveness of marijuana for chronic pain?
• Is marijuana a “gateway drug”?
• If my patient asks for my opinion about marijuana use, what should I tell him or her?
Percentage of past month marijuana use among persons aged >12 years, by sex
National Survey on Drug Use and Health, US 2002-2014

-35% increase in past month use of marijuana since 2002
-92% increase in daily or almost daily use since 2002
-decreased perceived risk of marijuana use

* Past month marijuana use is defined as those who reported use of marijuana within 30 days preceding the date of interview.
† Percentage increase over time is statistically significant for males and females (logistic regression, p<0.001).

MMWR, 2016, #65
Hasin, 2015
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Oregon Marijuana Law

- **1935** – Uniform State Narcotic Drug Act made marijuana illegal
- **1973** – The Oregon Decriminalization Bill
  - Abolished criminal penalties for possession of a small amount of marijuana
- **1998** – Measure 67 - Oregon Medical Marijuana Act
  - Can have up to 1.5 pounds of marijuana at a time
- **2010** – Oregon Board of pharmacy reclassifies marijuana from Schedule I to Schedule II
  - Federal maintains that marijuana is Schedule I
- **2014** - Measure 91 - Recreational use of marijuana legalized
- **2015** - Senate Bill 844
  - Requires the Oregon Health Authority to establish a task force to study the medical and public health properties of cannabis
### Patients, Caregivers, Growers and Growsites

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Caregivers</th>
<th>Growers</th>
<th>Growsites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mailing Address in OR</td>
<td>65,217</td>
<td>29,350</td>
<td>38,650</td>
<td>26,943</td>
</tr>
<tr>
<td>Mailing Address Outside OR</td>
<td>1,941</td>
<td>584</td>
<td>360</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>67,158</strong></td>
<td><strong>29,934</strong></td>
<td><strong>39,010</strong></td>
<td><strong>26,943</strong></td>
</tr>
</tbody>
</table>

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### Patients by Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count of Reporting Patients</th>
<th>Percentage of Reporting Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Pain</td>
<td>60,584</td>
<td>89.6%</td>
</tr>
<tr>
<td>Spasms</td>
<td>19,588</td>
<td>29.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9,032</td>
<td>13.4%</td>
</tr>
<tr>
<td>Cancer</td>
<td>4,355</td>
<td>6.4%</td>
</tr>
<tr>
<td>Seizures</td>
<td>1,792</td>
<td>2.6%</td>
</tr>
<tr>
<td>Cachexia</td>
<td>1,016</td>
<td>1.5%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>649</td>
<td>1.0%</td>
</tr>
<tr>
<td>Glancoma</td>
<td>988</td>
<td>1.5%</td>
</tr>
<tr>
<td>PTSD</td>
<td>5,175</td>
<td>7.7%</td>
</tr>
<tr>
<td>Neurological</td>
<td>417</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

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2014 – Oregon Measure 91

• You can possess and use recreational marijuana if you are 21+. If you are younger, it is illegal.
• You can use recreational marijuana at home or on private property, including edibles.
• You can possess up to 8 oz of usable marijuana in your home
  – Medical Marijuana can possess 24 oz
• You can possess up to 1 oz of marijuana outside of your home
• You can grow up to 4 plants per residence, out of public view
• Approved medical dispensaries may sell small amounts of marijuana to recreational users
• You can’t take marijuana across state lines, including WA

www.WhatsLegalOregon.com
<table>
<thead>
<tr>
<th>Type of Marijuana Item</th>
<th>Medical Marijuana</th>
<th>Recreational Marijuana</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum Concentration or amount of THC per serving</td>
<td>Maximum Concentration or Amount of THC in container</td>
</tr>
<tr>
<td>Edible</td>
<td>N/A</td>
<td>100mg</td>
</tr>
<tr>
<td>Topical</td>
<td>N/A</td>
<td>6%</td>
</tr>
<tr>
<td>Tincture</td>
<td>N/A</td>
<td>4,000mg</td>
</tr>
<tr>
<td>Capsule</td>
<td>100mg</td>
<td>4,000mg</td>
</tr>
<tr>
<td>Concentrate or Extract</td>
<td>N/A</td>
<td>4,000mg</td>
</tr>
<tr>
<td>Other</td>
<td>N/A</td>
<td>4,000mg</td>
</tr>
</tbody>
</table>

Cannabis concentration and serving size limits based on indication.

U.S.-grown marijuana, in its present form, is many time stronger than in the past.

http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/MedicalMarijuanaProgram/Pages/legal.aspx
Potency: Increased THC Content in Seized Marijuana, 1983-2009

Sources: The University of Mississippi Potency Monitoring Project
Cannabis “raw materials”

- marijuana (up to 20%+ THC)
- hashish (~2-20%)
- hash oil, marijuana concentrate (40-80%)
- marijuana concentrate (40-80%)
- “budder,” “butane honey oil”
- cannabidiol oil

Photo Source: www.dea.gov and cureepilepsy.org
“Marijuana is the beer of THC, as dabbing is to vodka.”
What’s *actually* in that marijuana you are buying?

<table>
<thead>
<tr>
<th>Δ⁹-tetrahydrocannabinol (THC)</th>
<th>Cannabidiol (CBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoria (reward pathway)</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Antianxiety</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>Antipsychotic effects</td>
</tr>
<tr>
<td>Appetite stimulant</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Analgesic</td>
<td>Anti-seizure</td>
</tr>
<tr>
<td>Impairs judgement</td>
<td>Anti-spasmodic</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Neuroprotective</td>
</tr>
<tr>
<td>Reduced coordination and balance</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
</tr>
</tbody>
</table>

Most marijuana labels are incorrect. Vandrey, JAMA, 2015 found 23% under-labeled, 60% over-labeled, 17% accurately labeled.
How *much* is too much?

- Standard marijuana “cigarette” or “joint” = 0.5g marijuana
- 1-2 joint/day = 0.5 to 1 oz of marijuana per month
- 24 oz of marijuana = 680 g of marijuana
  - 1360 marijuana joints
- 8 oz of marijuana = 227 g of marijuana
  - 454 marijuana joints
- 1 oz of marijuana = 28 g of marijuana
  - 14 marijuana joints

*Is marijuana policy ahead of the science?*

Clinical Questions

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• Is marijuana a “gateway drug”?
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Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisco, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidtkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

Medical Marijuana
Is the Cart Before the Horse?
Deepak Cyril D'Souza, MBBS, MD; Mohini Ranganathan, MD

Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems
A Clinical Review
Kevin P. Hil, MD, MHS


VA Evidence-based Synthesis Program, Kansagara, et al., 2016

What are the effects of cannabis on health outcomes and healthcare utilization for adults who have chronic pain?

• 2 Systematic Reviews, 5 RCTs, 3 Observational studies

• Summary:
  – Limited evidence with few rigorous trials and methodologic flaws
  – Low strength evidence that cannabis with precise THC:CBD content (1:1 to 2:1 ratio) has potential to improve pain, spasticity, and sleep in select population with multiple sclerosis
  – Most studies short term (<14 days), long-term benefits and harms unclear
  – 8 trials (N=1370) found non-significant trend toward 30% reduction in pain (OR = 1.41 (95% confidence interval [CI] = 0.99-2.00) compared to placebo and no difference in quality of life among groups
  – Insufficient evidence for medicinal use for cancer, RA, and MSK pain

*unpublished results. Results attributed to Kansagara, et al. VA Evidence-based synthesis program, 2016.
The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain

A Prospective Open-label Study

• Population: Adults with chronic pain and lack of analgesia with at least 2 analgesics from 2 different classes at full dose
  – MSK pain, neuropathic pain, radicular LBP
• Major exclusions: pts with drug abuse or dependence or at high risk for drug abuse or history of psychiatric comorbidity
• Primary outcome: Pain reduction after 6 months
• Dose of cannabis 20g/month (~3-4:1 THC:CBD)
  – 1g joint (6-14% THC; 0.2-3.8% CBD), baked cookies (11-19% THC; 0.5-5.5% CBC), or olive oil extract drops
  – Titrate dose for effect, up to TID
• ITT 206 patients, mean follow up 7 months


Avg use was 43.2 g/month

Primary Outcome:
Pain Symptom score improved from 83 to 75 (p<0.001)

Secondary Outcomes:
- family-social disability improved
- role-emotional disability improved
- satisfaction with outcome improved
- mixed results for functional improvements

5% discontinued due to side effects
Opioid Discontinuation Outcome

44-48% reduction from baseline (p<0.001)
MED changed 60mg to 45mg (p=0.19)

Practical Issues/Questions

• Half life 25-36 hrs, but analgesic effect only 3-4 hours
• How do you determine the dose?
• How do you ensure consistency in the product?
• What happens when you develop tolerance?
• What if your work will not allow it?
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Natural and Drug Reinforcers Increase Dopamine in NAc

Drugs of abuse increase DA in the Nucleus Accumbens, which is believed to trigger the neuroadaptations that result in addiction

Slide attributed to Nora Volkow, Director of NIDA, Marijuana’s effects on brain, body, and behavior
Long Term Effects of Marijuana

Addiction: About 9% of users may become dependent, 1 in 6 who start use in adolescence, 25-50% of daily users

Estimated Prevalence of Dependence Among Users

<table>
<thead>
<tr>
<th>Substance</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>32</td>
</tr>
<tr>
<td>Alcohol</td>
<td>15</td>
</tr>
<tr>
<td>Cannabis</td>
<td>9</td>
</tr>
<tr>
<td>Cocaine</td>
<td>17</td>
</tr>
<tr>
<td>Stimulant</td>
<td>11</td>
</tr>
<tr>
<td>Analgesics</td>
<td>8</td>
</tr>
<tr>
<td>Psychedelics</td>
<td>5</td>
</tr>
<tr>
<td>Heroin</td>
<td>23</td>
</tr>
</tbody>
</table>

*Nonmedical Use
Source: Anthony JC et al., 1994

Slide attributed to Nora Volkow, Director of NIDA, Marijuana’s effects on brain, body, and behavior
ADDITION IS A DEVELOPMENTAL DISEASE
it starts in adolescence and childhood

Percentage in each age group who develop first-time dependence

Age at tobacco, at alcohol and at cannabis use dependence as per DSM IV


Slide attributed to Nora Volkow, Director of NIDA, Marijuana’s effects on brain, body, and behavior
Cannabis use is associated with increased alcohol use disorder over time

• Among adults with no history of AUD, cannabis use was associated with increased incidence of an AUD three years later relative to no cannabis use (Odds Ratio (OR) = 5.43; 95% Confidence Interval (CI) = 4.54–6.49).

• Among adults with a history of AUD, cannabis use was associated with increased likelihood of AUD persistence three years later relative to no cannabis use (OR = 1.74; 95% CI = 1.56–1.95).

• These relationships remained significant after controlling for demographics, psychiatric disorders, and other substance use disorders.

Cannabis Withdrawal Syndrome

• Sudden discontinuation generally safe, no need to taper
• Withdrawal syndrome:
  - fatigue
  - low energy
  - depression, dysphoria
  - anxiety
  - insomnia
  - decreased appetite
  - nausea and vomiting
• No pharmacologic intervention needed (nor effective) for withdrawal
  – Do not use Dronabinol to help with marijuana replacement therapy
Addiction Treatment Options

• No medication-assisted treatment needed (nor effective) for cannabis use disorder in adults
  – N-Acetylcysteine 1,200mg BID + contingency management was effective in adolescents*

• Marijuana Use Disorder Treatment:
  – Cognitive Behavioral Therapy (CBT)
  – recovery groups (Marijuana Anonymous)

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Adverse Effects: Short-term

- anxiety, panic attacks
- psychosis
- increased heart rate and blood pressure
- decreased memory & learning
- difficulty thinking & problem solving
- decreased coordination
  - Increased risk of MVA if driving
- visuomotor skills deficit

*Effects transient, resolve without intervention.*
*Actual impairment persists past perceived impairment*
*Effects primarily associated with THC*
No one has died from a marijuana overdose, although some people have ingested way too much and wished they were dead or thought they were dying.
Adverse Effects: Long-term

“associated with”

• Altered brain development and neural connectivity
  – Reduced memory
  – Reduced learning
  – Reduced impulse control

• Worsen mental illness

• Immunosuppression

• Inhalation: increased risk cancer of head, neck, lungs, respiratory tract

• Increased risk testicular cancer

• Occlusion brain arteries, increased stroke

• Oculomotor control deficit

• Hyperemesis syndrome
Regular Marijuana Use Is Associated With Differences in Brain Gray Matter and Connectivity

Marijuana effects on Children and Adolescents*

- Impaired neural connectivity in specific brain regions
  - Particularly in areas of alertness, learning and memory
  - Declined IQ
  - Altered reward pathways
- Exacerbation of mental illness
- Increased risk of cannabis use disorder
  - 2-4 times more likely to develop CUD within 2 years of first use

- Prenatal exposure effects can also be long lasting (Hanan, Biological Psychiatry, 2016)

*through age 21

Key Points

• Useful in cachexia, MS spasticity, nausea and vomiting from chemotherapy
• Beware of the narrow therapeutic window
• Trial of high CBD content (low THC) marijuana for pain
  – Most appropriate in a patient with low risk
• Do not drive and use marijuana
• Uncertain effects of concomitant opioids and marijuana
  – Recommend choosing either opioids or marijuana for chronic non-cancer pain
• Marijuana can have permanent adverse effects on children and adolescents
• Avoid marijuana use in pregnancy and while breastfeeding until further research is done