Medical Marijuana: Influence and implications on Primary Care

PRESENTERS:
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Objectives

1. Name the two major phytochemicals contained in “medical marijuana” (MM)?
2. List the physiological functions affected by cannabinoids
3. Understand that MM is not “one thing”
4. Recognize the potential toxicities of MM
5. Be aware of the limitations of medical evidence supporting the use of MM
6. Discuss the potential use of MM in treatment of pain
   – Contrast with the problems inherent in opioid treatment of pain
Why Medical Marijuana?

- **Cannabis plant:**
  - factory of biochemicals
- **Endocannabinoid system**
  - modulates numerous physiological processes
- **Anecdotal experiences**
  - Claims of success
\[
\text{\(\Delta-9\) THC}
\]
delta-9-tetrahydrocannabinol (THC)

\[
\text{CBD}
\]
cannabidiol
Endocannabinoid system

• Endogenous compounds
• Act at specific receptors in brain and body
  – CB1 (1\textsuperscript{st} in nervous system)
  – CB2 (1\textsuperscript{st} in periphery/immune system)
  – Others as well, less well understood
• Role in neuromodulation
• \textit{Widespread} effects in brain and body
  – Neurological-neuropsychological
  – Immune effects
Physiological actions/roles of endocannabinoids

1. Pain/sensory modulation
2. Cognitive/memory processing
3. Mood and behavior
4. Motor control/coordination
5. Endocrine functions
6. Vegetative functions
   a) Appetite
   b) Temperature control
   c) Heart rate regulation
   d) Nausea/vomiting
7. Intraocular pressure
8. Inflammation
9. Immune regulation/recognition

Cannabis: toxicities (general)

- Tachycardia
- Pulmonary toxicity (inhaled formulation)
- Pulmonary infection
  - Inhalation of associated microorganisms/fungi
- Immune suppression
  - Suppresses macrophages, T-lymphs
  - Increased interleukin I release
- Pesticides/byproducts
- Cyclic vomiting syndrome
- ICU admissions
Cannabis: Neuropsych toxicity

- Memory impairment
  - Short and long term
- Impaired executive functions:
  - ↓ concentration, judgment, attention span, motivation, problem solving, reaction time
- Impaired motor function
  - ↓ coordination
- Impairment of neural plasticity
- Neuropsychiatric:
  - Anxiety, panic attacks
  - Psychosis
    - ? With or without predisposition
  - Mania, manic episodes
    - ↑ cycling in bipolar
  - Depression
  - “Addiction”/dependence
    - “gateway drug”
“Medical marijuana”: not ONE thing

• “Artisanal” or “vernacular” products
  – All bioderived
  – Extensive variety of formulations
  – Minimal standardization
  – Content often poorly specified
  – No independent quality control

• Pharmaceutical products
  – Marketed
    • or in clinical trials
  – Synthetic vs. bioderived (plant product)
    • Highly purified
  – Objective standardization and regulation
Concept of “entourage effect”

• Proposed (beneficial) interactions between various phytochemicals
  – Do various cannabis constituents work synergistically or counterbalance each other to produce a desired effect?

• Could be “additive” or “inhibitory”

• Interaction of CBD and THC particularly relevant:
  – CBD may mitigate adverse effects of THC

• So... “medical marijuana” is not just one thing
What about toxicity?

• Numerous scientific studies
  – Observational cohort studies
  – Neuroimaging/neuropsychological studies

• Neurotoxicity (THC)
  – Increased risk of psychosis
  – Tremor, ataxia
  – Appetite changes
  – Neurocognitive effects
  – Particularly concerning in developing brain
Cognitive and memory impairment

• MS Cannabis smokers have > cognitive dysfunction than non-smokers
  – ↓ Working memory
  – ↓ Information processing speed
  – ↓ Executive functions

• Correlates with “different pattern” of cerebral activation seen with fMRI:
  – Less anatomically focused, more dispersed activation
  – This despite no structural differences

Tipping the balance?

- Few scientific studies confirm efficacy
- Numerous scientific studies confirm toxicity
- Medical marijuana not ONE thing!
- What about the developing brain?
Patient Joe

1. Chronic Back Pain
   1. Family history of substance abuse, really wants to avoid narcotics
   2. Severe kidney disease—NSAIDs not an option
   3. Failed PT, not getting relief
   4. Tried steroid injections, failed
   5. Surgery, still hurting
   6. Requesting help, “anything”, muscle relaxants not working
   7. Had questions about marijuana, reports he is scared because he tried increasing doses of THC and felt like he overmedicated. Didn’t discuss this until I asked if he had tried marijuana
Risks vs benefits
Figure 1. Marijuana use in the past month among people aged 12 or older, by substate region: percentages, annual averages based on combined 2012 to 2014 data

Note: For substate region definitions, see the "2012-2014 National Survey on Drug Use and Health Substate Region Definitions" at http://www.samhsa.gov/data/.

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Surveys on Drug Use and Health (NSDUHs), 2012 to 2014.
Figure 2. Perceived great risk of harm from smoking marijuana once a month among people aged 12 or older, by substate region: percentages, annual averages based on combined 2012 to 2014 data

Note: For substate region definitions, see the "2012-2014 National Survey on Drug Use and Health Substate Region Definitions" at [http://www.samhsa.gov/data/](http://www.samhsa.gov/data/).

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Surveys on Drug Use and Health (NSDUHs), 2012 to 2014.
Number and age-adjusted rates of drug overdose deaths by state, US 2013

2013 Age-adjusted rate

- 2.8 to 11.0
- 11.1 to 13.5
- 13.6 to 16.0
- 16.1 to 18.5
- 18.6 to 21.0
- 21.0 to 35.5

Source: CDC
Opioid use disorder

• Strong desire for opioids
• Inability to control or reduce use
• Continued use despite interference with major obligations
• Using larger amounts over time
• Development of tolerance
• Spending a great deal of time obtaining opioid
• Withdrawal symptoms after stopping or reducing
• Reference: SAMHSA
“Drug seeker”

- Fear
At least HALF of all opioid overdose deaths involve a prescription opioid.
Recent Research

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, 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
Meta-Analysis

Figure 2. Improvement in Pain

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Cannabinoid Events</th>
<th>Placebo Events</th>
<th>Odds Ratio (95% CI)</th>
<th>ForCES</th>
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<tbody>
<tr>
<td>Abrams et al., 2007</td>
<td>13</td>
<td>25</td>
<td>625</td>
<td>3.43 (1.03-11.48)</td>
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<tr>
<td>Nabiximols</td>
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<tr>
<td>GW Pharmaceuticals, 2005</td>
<td>54</td>
<td>149</td>
<td>59</td>
<td>148</td>
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<td>Johnson et al., 2010</td>
<td>23</td>
<td>53</td>
<td>12</td>
<td>56</td>
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<tr>
<td>Langford et al., 2013</td>
<td>84</td>
<td>167</td>
<td>77</td>
<td>172</td>
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<tr>
<td>Newicklos et al., 2007</td>
<td>16</td>
<td>63</td>
<td>9</td>
<td>62</td>
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<td>Penney et al., 2012</td>
<td>32</td>
<td>90</td>
<td>24</td>
<td>91</td>
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<td>Seharajah et al., 2010</td>
<td>8</td>
<td>15</td>
<td>9</td>
<td>14</td>
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<tr>
<td>Speroli et al., 2014</td>
<td>34</td>
<td>123</td>
<td>19</td>
<td>137</td>
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<tr>
<td>Overall</td>
<td>254</td>
<td>685</td>
<td>215</td>
<td>685</td>
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</tbody>
</table>

Odds indicate 30% or greater improvement in pain with cannabis compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall (OR and 95% CI). The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).

Last corrected on April 12, 2016.
Figure 4. Odds of Having Any Adverse Event With Cannabinoids Compared With Placebo, Stratified According to Cannabinoid

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>More Adverse Events With Cannabinoid</th>
<th>More Adverse Events With Placebo</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight</th>
<th>Odds Ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Tetrahydrocannabinol capsules</td>
<td>Tourette</td>
<td>Müller-Vahl et al.,160 2003</td>
<td>5</td>
<td>9</td>
<td>3</td>
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<td></td>
<td>Müller-Vahl et al.,162 2001</td>
<td>5</td>
<td>12</td>
<td>2</td>
<td>12</td>
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<td></td>
<td>Ungerleider et al.,146 1982</td>
<td>136</td>
<td>172</td>
<td>99</td>
<td>181</td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td>170</td>
<td>204</td>
<td>104</td>
<td>204</td>
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<tr>
<td></td>
<td>Nabilone</td>
<td>Nausea and vomiting</td>
<td>Chan et al.,28 1987</td>
<td>32</td>
<td>36</td>
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<td></td>
<td></td>
<td>George et al.,35 1983</td>
<td>17</td>
<td>20</td>
<td>11</td>
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<td></td>
<td></td>
<td>Johansson et al.,36 1982</td>
<td>14</td>
<td>26</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
<td>Subtotal</td>
<td>79</td>
<td>101</td>
<td>49</td>
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<tr>
<td></td>
<td>Levonantradol</td>
<td>Nausea and vomiting</td>
<td>4.59</td>
<td>1.17</td>
<td>2.27</td>
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<td>Heim et al.,33 1984</td>
<td>32</td>
<td>45</td>
<td>13</td>
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<td></td>
<td></td>
<td>Hutchison et al.,34 1983</td>
<td>23</td>
<td>26</td>
<td>20</td>
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<td></td>
<td></td>
<td>Subtotal</td>
<td>55</td>
<td>71</td>
<td>33</td>
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<tr>
<td></td>
<td></td>
<td>Ajulemic acid (CT3)</td>
<td>Pain</td>
<td>1.00</td>
<td>10.24</td>
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<td></td>
<td></td>
<td>Karst et al.,63 2003</td>
<td>12</td>
<td>19</td>
<td>5</td>
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<tr>
<td></td>
<td>Pain</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Multiple sclerosis</td>
<td>Collet et al.,127 2007</td>
<td>102</td>
<td>124</td>
<td>46</td>
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<td></td>
<td></td>
<td>Collet et al.,123 2010</td>
<td>156</td>
<td>167</td>
<td>132</td>
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<tr>
<td></td>
<td></td>
<td>Langford et al.,65 2013</td>
<td>120</td>
<td>167</td>
<td>106</td>
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<td></td>
<td></td>
<td>Wade et al.,123 2004</td>
<td>67</td>
<td>80</td>
<td>57</td>
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<td></td>
<td></td>
<td>Duran et al.,24 2010</td>
<td>6</td>
<td>7</td>
<td>6</td>
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<td></td>
<td></td>
<td>Subtotal</td>
<td>931</td>
<td>1101</td>
<td>727</td>
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<td></td>
<td></td>
<td>Nausea and vomiting</td>
<td>0.74</td>
<td>55.32</td>
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Intermountain Healthcare
Healthcare for Life
<table>
<thead>
<tr>
<th>General AE categories</th>
<th>No. of Studies (No. of Patients)</th>
<th>Summary OR (95% CI)</th>
<th>$I^2$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>29 (3714)</td>
<td>3.03 (2.42-3.80)</td>
<td>31</td>
</tr>
<tr>
<td>Serious</td>
<td>34 (3248)</td>
<td>1.41 (1.04-1.92)</td>
<td>0</td>
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<tr>
<td>Withdrawal due to AE</td>
<td>23 (2755)</td>
<td>2.94 (2.18-3.96)</td>
<td>2</td>
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<tr>
<td>MedDRA high-level grouping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10 (1960)</td>
<td>1.78 (1.43-2.22)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>7 (1681)</td>
<td>1.13 (0.87-1.46)</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>8 (1672)</td>
<td>3.10 (1.81-5.29)</td>
<td>55</td>
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<tr>
<td>Nervous system disorders</td>
<td>10 (1521)</td>
<td>3.17 (2.20-4.58)</td>
<td>46</td>
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<tr>
<td>Musculoskeletal and connective tissues disorders</td>
<td>7 (1310)</td>
<td>1.32 (0.75-2.32)</td>
<td>34</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>6 (1208)</td>
<td>1.78 (1.34-2.36)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>5 (929)</td>
<td>1.01 (0.51-2.00)</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>3 (922)</td>
<td>2.72 (1.55-4.75)</td>
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<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>5 (851)</td>
<td>0.80 (0.46-1.39)</td>
<td>0</td>
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<tr>
<td>Cardiac disorders</td>
<td>7 (833)</td>
<td>1.42 (0.58-3.48)</td>
<td>0</td>
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<td>Blood disorders</td>
<td>3 (543)</td>
<td>1.42 (0.20-10.25)</td>
<td>18</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
<td>3 (543)</td>
<td>1.18 (0.48-2.93)</td>
<td>0</td>
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<tr>
<td>Renal and urinary disorders</td>
<td>3 (470)</td>
<td>2.45 (2.27-2.65)</td>
<td>0</td>
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<tr>
<td>Investigations</td>
<td>2 (427)</td>
<td>1.55 (0.36-6.71)</td>
<td>0</td>
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<td>Metabolism and nutrition</td>
<td>2 (427)</td>
<td>2.37 (1.00-5.61)</td>
<td>0</td>
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<tr>
<td>Neoplasms, benign, malignant, and unspecified</td>
<td>2 (427)</td>
<td>0.99 (0.47-2.08)</td>
<td>0</td>
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<tr>
<td>Skin and subcutaneous</td>
<td>3 (405)</td>
<td>0.85 (0.34-2.13)</td>
<td>0</td>
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<tr>
<td>Eye disorders</td>
<td>1 (339)</td>
<td>1.42 (0.46-4.33)</td>
<td>NA</td>
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<td>Reproductive system</td>
<td>1 (246)</td>
<td>1.55 (0.20-11.92)</td>
<td>NA</td>
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<td>Hepatobiliary disorders</td>
<td>1 (181)</td>
<td>3.07 (0.12-76.29)</td>
<td>NA</td>
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<td>Mental status change</td>
<td>3 (106)</td>
<td>2.49 (0.49-12.54)</td>
<td>0</td>
</tr>
<tr>
<td>Other body systems</td>
<td>1 (42)</td>
<td>2.59 (0.34-19.47)</td>
<td>NA</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (32)</td>
<td>2.49 (0.02-6.68)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Individual AEs

- Dizziness: 41 (4243) 5.09 (4.10-6.32) 18
- Dry mouth: 36 (4181) 3.50 (2.58-4.75) 28
- Nausea: 30 (3579) 2.08 (1.63-2.65) 0
- Fatigue: 20 (2717) 2.00 (1.54-2.62) 0
- Somnolence: 26 (3168) 2.83 (2.05-3.91) 27
- Euphoria: 27 (2420) 4.08 (2.18-7.64) 49
- Depression: 15 (2353) 1.32 (0.87-2.01) 0
- Vomiting: 17 (2191) 1.67 (1.13-2.47) 0
- Diarrhea: 17 (2077) 1.65 (1.04-2.62) 15
- Disorientation: 12 (1736) 5.41 (2.61-11.19) 0
- Asthenia: 15 (1717) 2.03 (1.35-3.06) 0
- Drowsiness: 18 (1272) 3.68 (2.24-6.01) 44
- Anxiety: 12 (1242) 1.98 (0.73-5.35) 54
- Confusion: 13 (1160) 4.03 (2.05-7.97) 0
- Balance: 6 (920) 2.62 (1.12-6.13) 0
- Hallucination: 10 (898) 2.19 (1.02-4.70) 0
- Dyspnea: 4 (375) 0.83 (0.26-2.63) 0
- Paranoia: 4 (492) 2.05 (0.42-10.10) 0
- Psychosis: 2 (37) 1.09 (0.07-16.35) 25
- Seizures: 2 (42) 0.91 (0.05-15.66) 0

Abbreviations: AE, adverse event; $I^2$, measures of heterogeneity; NA, not applicable; OR, odds ratio. MedDRA, medical dictionary for regulatory activities.
Questions

• Dispensary vs Pharmacy
• What do we say to patients that want to know if Marijuana is a safe option?
• Should THC be available, as opposed to just CBD?
• How do we monitor for diversion and misuse?
• CBD vs Opioids
• Should the state legislature “legalize” medical marijuana in Utah?
  – CBD only? THC also?
  – If so who regulates or directs its use?
• Should providers “prescribe it?”
  – Or should it be treated like any other non-pharmaceutical “supplement”?*
• Do the benefits outweigh the risks?
• What is the providers role in this?
• What about “medical evidence”?
  – How can we study this?
  – Is it providers responsibility to educate our patients about this?