Cannabis/Marijuana contains ~100 cannabinoids plus other chemicals in varying concentrations

- Plant with long history of use worldwide
- Illegal under Federal law (Schedule I substance—not FDA approved)
- Legal for medical use in 28 States + D.C.
- High CBD variety (or extracts) legal in 16 states for medical use
- Versions of active ingredients approved (or in clinical trials) for medical indications in U.S. and other countries
  - Synthetic - Marinol, Syndros, Cesamet
  - Plant Derived- Sativex (THC/CBD)
  - Plant Derived-Epidiolex (CBD: Phase III trials)
Medical Marijuana Laws In the U.S.

States vary on:
- Allowable conditions
- Routes of administration
- Dispensaries/home growth
- Registries
- Amount of cannabis
- Testing, regulatory requirements

28 Legal Medical Marijuana States and DC

Source: ProCon.org
51 Medical Conditions For Which Marijuana Is Approved by a State

1. Alzheimer's Disease
2. Anorexia
3. Arnold-Chiari malformation
4. Arthritis
5. Ataxia
6. Cachexia
7. Cancer
8. Cardiopulmonary respiratory syndrome
9. Causalgia
10. Cervical dystonia
11. Crohn's disease
12. Decompensated cirrhosis
13. Dystonia
14. Epilepsy
15. Fibromyalgia
16. Glaucoma
17. Hepatitis C
18. HIV/AIDS
19. Huntington’s disease
20. Hydrocephalus
21. Inflammatory autoimmune-mediated arthritis
22. Inflammatory bowel disease (IBS)
23. Inflammatory demyelinating polyneuropathy
24. Interstitial cystitis
25. Lou Gehrig’s disease (amyotrophic lateral sclerosis, ALS)
26. Migraines
27. Multiple Sclerosis
28. Muscle spasms
29. Muscular dystrophy
30. Myasthenia gravis
31. Myoclonus
32. Nail-patella syndrome
33. Nausea or vomiting
34. Neurofibromatosis
35. Neuropathy
36. Pain

37. Pancreatitis
38. Parkinson's disease
39. Peripheral neuropathy
40. Post-traumatic stress disorder (PTSD)
41. Reflex sympathetic dystrophy
42. Residual limb pain from amputation
43. Seizure disorders
44. Sjogren's syndrome
45. Spasticity
46. Spinal cord damage with intractable spasticity
47. Syringomyelia
48. Terminal illness
49. Tourette’s syndrome
50. Traumatic brain injury

The Medical Cannabis “Store”...
# Level of Confidence in the Evidence for *Adverse* Effects of Chronic *Marijuana* Use on Health and Well-Being

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Low</td>
</tr>
<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>

# Strength of the Evidence For Marijuana/Cannabinoid Medical Applications

<table>
<thead>
<tr>
<th>Strongest Evidence</th>
<th>Modest Evidence</th>
<th>Weakest Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nausea (Cancer chemotherapy)</td>
<td>• Anticonvulsant (CBD)</td>
<td>• PTSD</td>
</tr>
<tr>
<td>• Spasticity and Pain (MS)</td>
<td>• Anti-inflammatory (CBD)</td>
<td>• ADHD</td>
</tr>
<tr>
<td>• Appetite Stimulant (AIDS-associated wasting)</td>
<td>• Antitumor (THC/CBD)</td>
<td>• Alzheimer’s</td>
</tr>
<tr>
<td>• <strong>Pain</strong> esp. neuropathic</td>
<td>(animal models/cell cultures: glioblastoma; breast cancer cells; others (mechanisms: apoptosis; inhibition of tumor angiogenesis)</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Glaucoma (decreases intraocular pressure; no evidence it slows disease progression; and short acting)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Recent Meta-Analyses Support the use of Cannabinoids for Chronic Neuropathic Non Cancer Pain, but.....

- Studies generally short, small, with modest effect sizes.

- "There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics."
  - A. Deshpande et al; CFP 2015

- "Currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain."
  - M.E. Lynch & M.A. Ware; J Neuroimmune Pharmacology 2015
Increasing Rx Opioid Overdose Deaths: Urgent Need for Alternative Pain Management

States with MML/Dispensaries report:
- Decreasing rates OD deaths
- Fewer opioid treatment admissions
- Fewer opioid Rxs
- Savings in Medicare spending
- Patient – reported decreases in opioid and other pain medication use

Source: CDC Wonder
Policy, Evidence & Public Health: Where are We Now?

✓ Cannabis is a plant, lacking FDA approval, but widely available for medical use
✓ Physicians recommend it without evidence-based guidelines to inform practice.
✓ Patients obtain it from dispensaries (or grow their own) → choose preferred strain, formulation, dosage, and route of administration (sometimes on the advice of “budtenders”).

But....

• Opioid Epidemic – nearly 19,000 deaths in the U.S. (2014)
• Chronic pain: patients continue to suffer from unrelenting severe pain.
• Among medical cannabis users, most common reason for use is pain.
  o Significant preclinical and clinical data supporting efficacy of cannabinoids
  o Preliminary data that cannabis/cannabinoids may enhance the anti-nociceptive effects of opioids, or reduce (eliminate?) the need for them.
• On the horizon- cannabis products (e.g., nabiximols), currently going through the FDA approval process.

What do we do now???
Policy, Evidence & Public Health: Leveraging the Current Landscape to Collect the Evidence

Exploit new policies and regulations in U.S. and Other Countries

- Patient characteristics
- Conditions/symptoms being treated
- Cannabis products used (high THC/high CBD)
- How much/often being consumed
- How being administered
- Clinical outcomes/adverse effects
- Tolerance development

- How cannabis use affects use of other medications/other abused substances?
- Are there groups that are high risk (based on: age, gender, pregnancy status, comorbid conditions, drug interactions)?

Potential Opportunities

- Create Patient Registries (Canada, Germany)
- New DEA Policy: multiple manufacturers → clearer path towards medication development
# Cannabinoids in RCTs

**Nabilone**

- Neuropathic pain (Frank 2008)
- Fibromyalgia pain (Skrabek 2008) and sleep (Ware 2010)
- Spinal cord injury (Pooyania 2010)

**Dronabinol**

- MS spasticity (Svensen 2004)
- Chronic pain + opioids (Narang 2008)
- Spinal cord injury (Rinatala 2010)

**Cannabis (2.5mg THC + 1.2mg CBD)**

- Spasticity in MS (Zajicek 2003, 2005, 2012)

**Nabiximols (2.5mg THC + 2.5mg CBD)**

- Brachial plexus avulsion (Berman 2004)
- Rheumatoid arthritis (Blake 2005)
- MS neuropathic pain (Rog 2007)
- MS Spasticity (Novotna 2011)
- Cancer pain (Portnoy 2012)

**Herbal cannabis (1.8-9.4%THC)**

- HIV neuropathy (Abrams 2007, Ellis 2009)
- Neuropathic pain (Wilsey 2009, 2013; Eisenberg 2014)
- Post traumatic neuropathy (Ware 2010)
- MS spasticity (Corey-Bloom 2012)
<table>
<thead>
<tr>
<th>Secure storage</th>
<th>“Start low, go slow”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional outcomes</td>
<td>Try prescription cannabinoids</td>
</tr>
<tr>
<td>Precautions</td>
<td>Withdrawal syndrome</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Regular re-evaluation</td>
</tr>
<tr>
<td>Heart disease</td>
<td>No use in public</td>
</tr>
<tr>
<td>Serious mental illness</td>
<td>Awareness of positive Urine Drug Test</td>
</tr>
<tr>
<td>Avoid smoking</td>
<td>Reduce opioid/benzo/alcohol</td>
</tr>
<tr>
<td>Wait 3-4h before driving</td>
<td></td>
</tr>
</tbody>
</table>

Ware, 2016
The Endocannabinoid System: Therapeutic Potential of Cannabis

Exogenous compounds
- Phytocannabinoids
  - THC, CBD, combinations
- Synthetic cannabinoids
  - Dronabinol

Endogenous manipulation
- FAAH inhibitors
- MAGL inhibitors
- Allosteric modulators

Receptor targets
- CB1, CB2, TRPV1, PPAR, 5-HT, peripheral, others...

Source: Canadian Consortium for the Investigation of Cannabinoids, http://www.ccic.net/
Medical Cannabis Use is Associated with Decreased Opiate Medication Use

Medical Marijuana Laws Reduce Prescription Medication Use in Medicare Part D

Estimated savings between 2010-2013: $515,000


Table 5. Medication Classes Used Before and After Initiation of Cannabis Among the Study Population

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Use Before Initiation of Cannabis, n/N (%)</th>
<th>Use After Initiation of Cannabis, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>119/184 (65)</td>
<td>33/184 (18)</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>115/184 (62)</td>
<td>38/184 (21)</td>
</tr>
<tr>
<td>Disease-modifying antirheumatic drugs</td>
<td>15/184 (8)</td>
<td>3/184 (2)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>72/184 (39)</td>
<td>25/184 (14)</td>
</tr>
<tr>
<td>Serotonin–norepinephrine reuptake inhibitors</td>
<td>13/184 (7)</td>
<td>3/184 (2)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>34/184 (18)</td>
<td>8/184 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>69/184 (38)</td>
<td>40/184 (22)</td>
</tr>
</tbody>
</table>
is a riddle wrapped in a mystery inside an enigma.

WINSTON CHURCHILL

But perhaps there is a key.
Cannabis: Most Commonly Used “Illicit” Drug In the U.S.

- Over **22 million** Americans 12 and older were past month marijuana users.
- Approximately **4.0 million** Americans met criteria for cannabis use disorders in 2015.
- An estimated **2.6 million** Americans used it for the first time; **1.2 million** were between the ages of 12 and 17.

**Tetrahydrocannabinol (THC)**
Psychoactive Ingredient in Marijuana

Source: 2016 National Survey on Drug Use and Health, SAMHSA