Medical Cannabis

Nuria Thusius, M.D.
Addiction Psychiatry

Psychiatry in Medical Settings
Mayo Clinic, Scottsdale, AZ
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Disclosure

• **Relevant Financial Relationship(s)**
  None

• **Off Label Usage**
  None
Learning Objectives

• Appreciate diverse uses of cannabis worldwide over its twelve-millennium history

• Learn the demographics, risks and benefits of medical and recreational cannabis

• Learn how evolving understanding of the endocannabinoid system holds pleiotropic promise for pharmaceutical development

• Discuss psychiatric indications for medical marijuana nationwide
Historical Context: Cannabis

- Grown for fiber and inebriation for 12,000 years (since last Ice Age)
- Emerged 36 million years ago in Central Asia
- Used as medicine in China 4700 years ago (Chinese emperor Shen-Nung, along with ginseng and ephedra)
- By 1st century CE: expanded to cover 100 medical conditions
- 1500 – 200 BCE: Egypt, Greece and India
- William O'Shaughnessy: Cannabis Indica to Western Medicine, 1838
From Prohibition to Present

• The U.K. banned cannabis in 1928
• By mid-1930s: banned in all 48 U.S. states. Remained in U.S. Pharmacopeia (USP), but access impossible
• Federal government banned with the Marijuana Tax Act in 1937
• Excised from the USP in 1942
• From WW II until 1960: any research as potential medicine discouraged
• 1964: THC discovered, the “modern” scientific era arrived
“Medical Marijuana”

marijuana* (Free Text Entry) by inhalation two times a day.
multivitamin tablet 1 tablet by mouth one time daily.
Indication, Site, and Additional Prescription Instructions
gummy formulation
Medical Cannabis: What Most People Mean
Medical Cannabis: Definition

• The use of the whole unprocessed cannabis plant or its basic extracts to treat a disease or symptom.
• The U.S. Food and Drug Administration (FDA) has not recognized or approved the marijuana plant as medicine.
Current Cannabis Legal Status

Marijuana Legalization by State

- States with Recreational Marijuana Laws
- States with Medical Marijuana Laws

Key Statistics

59.3% of the U.S. population now lives in a state where marijuana has been legalized.

- 29 states plus Washington DC have medical marijuana laws...
- 19 plus Washington DC have operating dispensaries
- 8 states plus Washington DC have recreational marijuana laws...
- 4 with operating retail stores
Opinions Vary Greatly Based on Age, Ethnicity and Political Party

- **Democrats**:
  - 18-24: 59%
  - 35-50: 52%
  - 51-69: 50%
  - 70-87: 29%

- **Republicans**:
  - 18-24: 39%
  - 35-50: 48%
  - 51-69: 50%
  - 70-87: 29%

- **Men**:
  - 18-24: 57%
  - 35-50: 49%
  - 51-69: 55%
  - 70-87: 40%

- **Women**:
  - 18-24: 49%
  - 35-50: 52%
  - 51-69: 50%
  - 70-87: 35%
Long-Term Trends in Annual* Marijuana Use Among 8th-, 10th-, and 12th-Graders

*use in the past 12 months
Source: University of Michigan, 2015 Monitoring the Future Survey.
Medical Marijuana Laws Don't Increase Cannabis Use Among Adolescents

- Examined behaviors, attitudes and values
- Marijuana use was higher among teenagers in states prior to approving MM laws than states that never enacted such legislation
- Marijuana use did not increase among adolescents after the laws were passed
Tax Revenue Raised in Colorado

Bar chart showing the revenue raised in Colorado from licenses and fees and sales and excise tax, from February 2014 to August 2015.
# Laws, Fees, and Possession Limits

<table>
<thead>
<tr>
<th>State</th>
<th>Mature Plants</th>
<th>Immature Plants</th>
<th>Possession Limits</th>
<th>Mandatory Registry?</th>
<th>Registry Card Cost</th>
<th>Avg Ounce Cost</th>
<th>Big 8 Conditions</th>
<th>Other Conditions</th>
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<tbody>
<tr>
<td>Michigan</td>
<td>12</td>
<td></td>
<td>2.5 oz</td>
<td>Mandatory</td>
<td>$ 60.00</td>
<td>$ 272.50</td>
<td>8</td>
<td>9</td>
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<tr>
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<td>$ 282.50</td>
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<tr>
<td>Hawaii</td>
<td>7</td>
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<td>4.0 oz</td>
<td>Mandatory</td>
<td>$ 25.00</td>
<td>$ 280.00</td>
<td>8</td>
<td>3</td>
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<tr>
<td>Oregon</td>
<td>6</td>
<td>18</td>
<td>24.0 oz</td>
<td>Mandatory</td>
<td>$ 200.00</td>
<td>$ 190.00</td>
<td>8</td>
<td>3</td>
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<tr>
<td>California</td>
<td>6</td>
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<td>8.0 oz</td>
<td>Voluntary</td>
<td>$ 66.00</td>
<td>$ 300.00</td>
<td>8</td>
<td>46</td>
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<tr>
<td>Washington</td>
<td>6</td>
<td></td>
<td>3.0 oz</td>
<td>Voluntary</td>
<td>$ 207.50</td>
<td></td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Maine</td>
<td>6</td>
<td></td>
<td>2.5 oz</td>
<td>Voluntary</td>
<td>$ -</td>
<td>$ 265.00</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>New Mexico</td>
<td>4</td>
<td>12</td>
<td>6.0 oz</td>
<td>Mandatory</td>
<td>$ -</td>
<td>$ 250.00</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Montana</td>
<td>4</td>
<td>12</td>
<td>1.0 oz</td>
<td>Mandatory</td>
<td>$ 75.00</td>
<td>$ 252.50</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Nevada</td>
<td>3</td>
<td>4</td>
<td>1.0 oz</td>
<td>Mandatory</td>
<td>$ 100.00</td>
<td>$ 245.00</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Colorado</td>
<td>3</td>
<td>3</td>
<td>2.0 oz</td>
<td>Mandatory</td>
<td>$ 15.00</td>
<td>$ 217.50</td>
<td>8</td>
<td>2</td>
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<tr>
<td>Alaska</td>
<td>3</td>
<td>3</td>
<td>1.0 oz</td>
<td>Mandatory</td>
<td>$ 25.00</td>
<td>$ 280.00</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Vermont</td>
<td>2</td>
<td>7</td>
<td>2.0 oz</td>
<td>Mandatory</td>
<td>$ 50.00</td>
<td>$ 332.50</td>
<td>6</td>
<td>2</td>
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<tr>
<td>New York</td>
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<td></td>
<td>No Bud</td>
<td>Mandatory</td>
<td>$ 50.00</td>
<td>$ 300.00</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Louisiana</td>
<td></td>
<td></td>
<td>No Bud</td>
<td>Mandatory</td>
<td>TBD</td>
<td>$ 300.00</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Minnesota</td>
<td></td>
<td></td>
<td>No Bud</td>
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<td>$ 200.00</td>
<td>$ 305.00</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>60d</td>
<td></td>
<td></td>
<td>Mandatory</td>
<td>$ 50.00</td>
<td>$ 310.00</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Connecticut</td>
<td>30d</td>
<td></td>
<td></td>
<td>Mandatory</td>
<td>$ 100.00</td>
<td>$ 297.50</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Maryland</td>
<td>30d</td>
<td></td>
<td></td>
<td>Mandatory</td>
<td>TBD</td>
<td>$ 312.50</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Delaware</td>
<td>6.0 oz</td>
<td></td>
<td></td>
<td>Mandatory</td>
<td>$ 125.00</td>
<td>$ 300.00</td>
<td>7</td>
<td>6</td>
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<tr>
<td>Arizona</td>
<td>2.5 oz</td>
<td></td>
<td></td>
<td>Mandatory</td>
<td>$ 150.00</td>
<td>$ 255.00</td>
<td>8</td>
<td>7</td>
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<tr>
<td>Illinois</td>
<td>2.5 oz</td>
<td></td>
<td></td>
<td>Mandatory</td>
<td>$ 100.00</td>
<td>$ 315.00</td>
<td>5</td>
<td>35</td>
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<tr>
<td>New Jersey</td>
<td>2.0 oz</td>
<td></td>
<td></td>
<td>Mandatory</td>
<td>$ 200.00</td>
<td>$ 312.50</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>DC</td>
<td>2.0 oz</td>
<td></td>
<td></td>
<td>Mandatory</td>
<td>$ 100.00</td>
<td>$ 312.50</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>New Hampshire</td>
<td>2.0 oz</td>
<td></td>
<td></td>
<td>Mandatory</td>
<td>TBD</td>
<td>$ 317.50</td>
<td>8</td>
<td>11</td>
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<tr>
<td><strong>Averages</strong></td>
<td><strong>5.7</strong></td>
<td><strong>8.4</strong></td>
<td><strong>4.0 oz</strong></td>
<td><strong>22 Mandatory</strong></td>
<td><strong>$ 84.10</strong></td>
<td><strong>$ 280.50</strong></td>
<td><strong>6.4</strong></td>
<td><strong>8.4</strong></td>
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</table>
## Dispensary Prices vs. Street Prices

### In Which States Are Dispensary Prices Most Expensive Compared to Street Prices

Based on Average Price of an Ounce for Midlevel Marijuana

<table>
<thead>
<tr>
<th>Rank</th>
<th>State</th>
<th>Dispensary Price</th>
<th>Street Price</th>
<th>% Saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>California</td>
<td>$299</td>
<td>$218</td>
<td>27%</td>
</tr>
<tr>
<td>2</td>
<td>Arizona</td>
<td>$290</td>
<td>$254</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>Washington</td>
<td>$238</td>
<td>$210</td>
<td>12%</td>
</tr>
<tr>
<td>4</td>
<td>Oregon</td>
<td>$214</td>
<td>$191</td>
<td>11%</td>
</tr>
<tr>
<td>5</td>
<td>Michigan</td>
<td>$301</td>
<td>$274</td>
<td>9%</td>
</tr>
<tr>
<td>6</td>
<td>Colorado</td>
<td>$223</td>
<td>$219</td>
<td>2%</td>
</tr>
</tbody>
</table>
Cannabis Industry

MARIJUANA STOCKS

IF YOU HAD $100 IN THE FOLLOWING MARIJUANA STOCKS ON JANUARY 2, 2014, THIS IS WHAT YOUR INVESTMENT MAY HAVE LOOKED LIKE ON MARCH 21, 2014*

<table>
<thead>
<tr>
<th>Ticker</th>
<th>Stock</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>BRDT</td>
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<td>$632</td>
</tr>
<tr>
<td>CANN</td>
<td></td>
<td>$697</td>
</tr>
<tr>
<td>ICBU</td>
<td></td>
<td>$750</td>
</tr>
<tr>
<td>GRNH</td>
<td></td>
<td>$770</td>
</tr>
<tr>
<td>FSPM</td>
<td></td>
<td>$1,014</td>
</tr>
<tr>
<td>LXRP</td>
<td></td>
<td>$1,173</td>
</tr>
<tr>
<td>TAUG</td>
<td></td>
<td>$1,517</td>
</tr>
<tr>
<td>FITX</td>
<td></td>
<td>$1,532</td>
</tr>
<tr>
<td>MNTR</td>
<td></td>
<td>$1,672</td>
</tr>
<tr>
<td>CYBK</td>
<td></td>
<td>$1,909</td>
</tr>
<tr>
<td>EAPH</td>
<td></td>
<td>$1,967</td>
</tr>
<tr>
<td>ERBB</td>
<td></td>
<td>$2,493</td>
</tr>
<tr>
<td>CBGI</td>
<td></td>
<td>$2,928</td>
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<tr>
<td>GHIL</td>
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<td>$2,980</td>
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<tr>
<td>ZDPY</td>
<td></td>
<td>$4,263</td>
</tr>
<tr>
<td>ATTBF</td>
<td></td>
<td>$7,620</td>
</tr>
<tr>
<td>SPLI</td>
<td></td>
<td>$35,500</td>
</tr>
</tbody>
</table>

*These calculations and figures are approximations and depend on the time of day the shares were purchased. If the data was unavailable, data for the next closest available date was used. All stocks are from companies which are believed to have at least some affiliation with the cannabis industry. Disclosure: At the time this chart was created, the designer was long: ERBB and FITX. The designer is not affiliated and receives no compensation from any of the companies. The infographic was designed by John Tommervik.

WWW.JOINTINDUSTRIES.COM
Cannabinoids

- **Endocannabinoids**
  - Produced in human tissue as neurotransmitters
  - Anandamide (arachidonic acid derivatives)

- **Phytocannabinoids**
  - Produced in C. Sativa and Indica plants
  - THC (tetrahydrocannabinol-psychoactive) and CBD (cannabidiol)

- **Synthetic and pharmaceutical cannabinoids**
  - Synthesized in labs (K2, Spice, Spike)
  - Dronabinol (Marinol), Nabilone (Cesamet)
The Cannabis Plant

• Two species:
  • Cannabis Sativa:
    • Fiber type
    • More CBD
    • Less than 1% of THC
    • Broad-leafleted, taller, tropical climes
  • Fiber, food source (fatty acids, Mg, Fe, K+)

• Cannabis Indica:
  • Drug-rich: up to 25% of THC
  • Broad-leafleted, shorter, Afghanistan, Pakistan
  • Cultivation: sun, water, well-drained soil, annual
Phytocannabinoids

• THC (tetrahydrocannabinol):
  • Most commonly produced by Indica (up to 25%)
  • Psychoactive
  • Anti-inflammatory
  • Analgesic
  • Neuroprotective
  • Spasticity
  • IO pressure reduction
  • Interacts with CB1 and CB2

• CBD (cannabidiol):
  • 2nd most common in Indica, MC by fiber (hemp) or Sativa
  • Eliminates THC’s adverse effects
  • Anti-inflammatory
  • Analgesic
  • In vitro: anti-cancer
  • Anti-convulsant
  • Antibiotic (MRSA)
  • No CB1, CB2
Cannabis Uses: Past and Present

**Know Your Cannabis**

**Sativa**
- Taller & Slimmer
- Leaves are Longer & Thinner
- Head High
- Alertness
- Uplifting & Euphoric
- Creativity
- Increased Energy
- Best for Daytime Use

**Indica**
- Shorter & Bushier
- Leaves are Shorter & Wider
- Body High
- Relaxation
- Appetite Stimulator
- Sleep Aid
- Pain Relief
- Best for Nighttime Use

- Paper Products
- Moulded Plastics
- Textiles
- Body Care Products
- Construction
- Nutritional Supplements
- Essential Oils
- Animal Bedding
- Animal Feed
- Foods
- Medicines
Survey by International Association for Cannabinoid Medicine (IACM)

- Survey of medical conditions and the number of people treating them
- Survey of symptoms and the number of people seeking alleviation

<table>
<thead>
<tr>
<th>Condition</th>
<th>#</th>
<th>Condition</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>113</td>
<td>Pain from injury</td>
<td>59</td>
</tr>
<tr>
<td>Sleep d/o</td>
<td>66</td>
<td>MS</td>
<td>39</td>
</tr>
<tr>
<td>Depression</td>
<td>64</td>
<td>Anxiety</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom</th>
<th>#</th>
<th>Symptom</th>
<th>#</th>
</tr>
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<tbody>
<tr>
<td>Chronic pain</td>
<td>278</td>
<td>Depression</td>
<td>49</td>
</tr>
<tr>
<td>Anxiety</td>
<td>174</td>
<td>Sleep d/o</td>
<td>49</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>102</td>
<td>Chronic inflammation</td>
<td>35</td>
</tr>
</tbody>
</table>
While in the Washington Post...

**Fewer pills prescribed in medical pot states**

Difference between annual drug doses prescribed per physician in medical marijuana states, and in states without medical marijuana laws, by drug category.

- **Pain**: 1,826 fewer doses
- **Anxiety**: 562 fewer doses
- **Nausea**: 541 fewer doses
- **Psychosis**: 519 fewer doses
- **Seizures**: 486 fewer doses
- **Sleep disorders**: 362 fewer doses
- **Depression**: 265 fewer doses
- **Spasticity**: 32 fewer doses
- **Glaucoma**: 35 more doses

*Source: Bradford and Bradford, Health Affairs, July 2016*
Endocannabinoid System: Ubiquitous Network
AREAS OF THE BRAIN AFFECTED BY CANNABINOIDS

CEREBRAL CORTEX
PLAYS A ROLE IN MEMORY, THINKING, PERCEPTUAL AWARENESS AND CONSCIOUSNESS

HYPOTHALAMUS
GOVERNS METABOLIC PROCESSES SUCH AS APETITE

AMYGDALA
PLAYS A ROLE IN EMOTIONS

HIPPOCAMPUS
IS KEY TO MEMORY STORAGE AND RECALL

BASAL GANGLIA
GOVERNS MOTOR SKILLS AND LEARNING

CEREBELLUM
GOVERNS COORDINATION AND MUSCLE CONTROL

BRAIN STEM
CONTROLS MANY BASIC FUNCTIONS INCLUDING AROUSING, THE VOMITING REFLEX, BLOOD PRESSURE AND HEART RATE

ALSO PLAYS A ROLE IN PAIN SENSATION, MUSCLE TONE AND MOVEMENT
Receptor Specificity and Diversity

• Cannabinoid receptors characterized in 1980s

• **CB1**: brain, psychoactive effects (release of neurotransmitters):
  • decision making, cognition, emotions, learning, memory, anxiety, fear, pain, body temp, appetite, reward, motor control

• **CB2**: blood cells, tonsils, spleen:
  • cytokine release, inflammation, immune function

• Cannabinoid medicines can enhance or interfere: **Rimonabant** for obesity (CB1 antagonist)
Cannabis Contaminants, Pathogens, Pesticides, Adulterants

• Fungal diseases:
  • Powdery Mildew: indoor cultivation
  • Gray mold: outdoor cultivation with rain
  • No health risk, bad taste

• Pesticides:
  • Rarely toxic to mammals, but toxic to bees and fish

• Synthetic Plant Growth Regulators (PGR)-plant steroids
  • Toxic, carcinogens

• Pathogenic Molds and Bacteria: Aspergillus, Fuzarium
  • Too wet for too long during curing process
  • Aflatoxins: toxic and carcinogenic
  • E. coli, MRSA, anaerobic bacteria, hair, pests
Synthetics and Pharmaceuticals

- **Marinol (dronabinol):** synthetic THC analog
  - First FDA-approved cannabinoid, 1985
  - RX: Chemotherapy-induced nausea, HIV/AIDS cachexia
  - THC only → adverse effects more than herbal formulation
  - Generic. 2.5, 5, 10 mg

- **Cesamet (nabilone):** synthetic THC analog
  - FDA-approved 1985
  - RX: Chemotherapy-induced nausea and vomiting
  - Later onset, longer action
  - 1, 2 mg

  - More effective than phenothiazines
  - Use limited by psychoactive effects
Synthetics and Pharmaceuticals

• **Sativex (nabiximols):** extracted from cannabis plants
  - Equal amounts of THC and CBD: modulatory “entourage effect” (CBD as anxiolytic, antipsychotic)
  - Oromucosal absorption: rapid absorption, less psychoactivity, less risk of dependence
  - RX: cancer pain, MS spasticity
  - Since 2010, approved in UK, Canada, 25 other countries
  - Phase III clinical trials in US, 2006- present
  - One spray: THC 2.7 mg + CBD 2.5 mg

• **Rimonabant: synthetic cannabinoid receptor blocker**
  - RX: obesity
  - 50 countries
  - Acute depression, SI, withdrawn in 2009
Cannabis Within the Body

• Cannabis plant >700 chemical compounds

• Absorption of MC:
  • Smoked/vaporized:
    • THC is detectable within few seconds
    • Peak blood plasma concentrations within 6-7 minutes
  • Sublingual (SL), oromucosal, oral:
    • Absorption within 5-15 minutes
    • Peak within 2-7 hours
    • Slow, inconsistent (THC destroyed by stomach acid, first pass metabolism)
  • Topical:
    • Difficult, not efficient. Blending into a fatty acid
    • Treatment of psoriasis, osteoarthritis
Before Using Cannabis: Contraindications

- Schizophrenia, bipolar d/o, severe depression
- Heart disease, hypertension, angina, arrhythmia
- COPD
- An immune disorder
- Under 22 years old
- Family history of psychotic disorders
- Addictive disorders
Psychiatric Co-Morbidity

Mood & Anxiety Disorders Among Respondents with Marijuana Dependence (NESARC)

- Any Mood Disorder: Marijuana dependence 61%, General Population 20%
- Any Anxiety Disorder: Marijuana dependence 49%, General Population 16%
- Depression: Marijuana dependence 47%, General Population 17%
- Dysthymia: Marijuana dependence 20%, General Population 4%
- Mania: Marijuana dependence 24%, General Population 3%
- Hypomania: Marijuana dependence 17%, General Population 10%
- Panic w/ Agoraphobia: Marijuana dependence 8%, General Population 1%
- Panic w/o Agoraphobia: Marijuana dependence 14%, General Population 5%
- Social Phobia: Marijuana dependence 21%, General Population 4%
- Specific Phobia: Marijuana dependence 27%, General Population 9%
- Generalized Anxiety: Marijuana dependence 21%, General Population 4%
Marijuana Use and Psychosis

**AKT1 Gene Variations and Psychosis**

- Never used cannabis
- Used cannabis at weekends or less
- Used cannabis everyday

**Genetic Variations in COMT Influences the Harmful Effects of Abused Drugs**

- Percent with schizophreniform disorder at age 26
- No adolescent marijuana use
- Adolescent marijuana use

<table>
<thead>
<tr>
<th>COMT genotype</th>
<th>n=</th>
<th>No adolescent marijuana use</th>
<th>Adolescent marijuana use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met/Met</td>
<td>(151) (48)</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Val/Met</td>
<td>(311) (91)</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Val/Val</td>
<td>(148) (54)</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>
Adverse Effects of Medical Cannabis

- Most associated with THC (psychoactive). Never fatal
- CBD might reduce or eliminate adverse effects
  - Orthostatic hypotension ➔ lightheadedness, LOC
    (Tx: keep eyes open, focus on something)
  - Tachycardia: subsides within 15-20 mins (Tx: slow, steady breathing)
  - If reclining ➔ upward spike of BP
  - “Cottonmouth” (Tx: water, lemonade)
  - Red, irritated eyes (Tx: Visine, eye drops)
  - Coughing (Tx: reduce the amount inhaled, water, explore oral or SL cannabis)
Long-Term Adverse Effects

- Severe chronic bronchitis
- Cognitive deficits (might be reversible)
- Drug interactions
- **Cannabis Hyperemesis:**
  - vomiting and abdominal pain
  - relieved by hot bath or shower
  - resolved completely upon cessation
- Heart attack, stroke
- **OD:** 3-8 hours:
  - hallucinations, panic, nausea, tachycardia, paranoia
  - never fatal
  - call 911 if victim is a child

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Early-Onset, Regular Cannabis Use Is Linked to IQ Decline
Qualifying Conditions

- Cancer, Cachexia,
- Terminal illness, Hospice patients
- Glaucoma
- HIV/AIDS, Hepatitis C (AR)
- Nausea, Crohn’s disease
- Seizures (TBI, epilepsy)
- Muscle spasms, Multiple sclerosis, ALS
- Tourette’s Syndrome
- Parkinson’s disease
- Arnold-Chiari malformation
- Causalgia

- Myoclonus (IL)
- Nail-patella sd (IL)
- Neurofibromatosis (IL)
- Post-concussion syndrome (IL)
- Residual limb pain (IL)
- Huntington’s disease (NY, PA)
- Spinal stenosis (ND)
- Lennox-Gastaut syndrome (OK), Dravet syndrome (OK), Severe myoclonic epilepsy of infancy (OK)
- Dystonia
- Spinal cord disease (arachnoiditis, Tarlov cysts, hydromyelia & syringomelia) (IL)
Qualifying Conditions: continued

- Intractable pain, Migraines
- Fibromyalgia
- Peripheral neuropathy
- CRPS (Complex Regional Pain Syndrome) (IL)
- Hydrocephalus (IL)
- Spinal cord injury (IL)
- Spinocerebellar ataxia (SCA) (IL)
- Traumatic brain injury (TBI) (IL)
- Spastic quadriplegia (IL)
- PTSD
- Alzheimer’s disease
- Autism (PA)
- ADHD
- Mitochondrial disease (GA)
- Sickle cell disease (GA, PA)
- Lupus (IL)
- Muscular dystrophy (IL)
- Myasthenia gravis (IL)
- Fibrous dysplasia (IL)
- Interstitial cystitis (IL)
- Rheumatoid arthritis (RA, IL)
- Sjogren’s syndrome (IL)
- Any condition diagnosed as “debilitating” by a licensed physician
### Qualifying “Psychiatric” Conditions by State

<table>
<thead>
<tr>
<th>Alzheimer’s Disease</th>
<th>Severe or chronic pain</th>
<th>PTSD</th>
<th>TBI</th>
<th>ADHD</th>
<th>Autism</th>
<th>Fibro</th>
<th>Chronic traumatic encephalopathy</th>
<th>“Determined by MD”, treatable by MM</th>
</tr>
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<tbody>
<tr>
<td>AZ</td>
<td>AK</td>
<td>CT</td>
<td>IL</td>
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<td>WA</td>
</tr>
</tbody>
</table>
Cannabis and Pregnancy

• Risk of infertility (ovulatory abnormalities)
  • CC: nausea, depression

• Negative effects on prenatal, neonatal and child development (2014 Swedish animal study): THC interferes with fetal brain development

• Study of 600 British women who smoked Cannabis: NO: risk of infant mortality; reduced birth weight

• Ottawa Prenatal prospective study (OPPS), Maternal health practices study and child development study (MHPCD): NO: higher rates of miscarriage, premature birth, childbirth complications. YES: For 3-4 year olds: impaired verbal and memory domains, short-term memory, verbal reasoning, attention-deficit, executive functioning (smokers in 1-2 trimester)
Medical Cannabis in the Workplace

- Many corporate zero-tolerance drug policies
  - No detectable amount of illegal drugs
  - No accommodations, users may lose employment
- AZ, CT, DE, ME, RI: laws protect from hiring discrimination or disciplining if UDAS is (+) for cannabis
- No protection if the patient is “impaired”
Driving and Cannabis

• Dose-dependent impairment of automatic skills, but generally mild, cautious “insightful” style, compensate
  • max in 20-40 minutes after smoking
  • vanishes in 2.5 hours

• Cannabis (automatic) + alcohol (complex) = more severe impairment even at low doses of both

• Decreased driving speed, time and distance perception, coordination, decision making, concentration

• Blood concentration 13 ug/L → weaving similar to EtOH of 0.08 (5 ug/L is a limit in CO, WA)

• If drunk – you run the RED lights;
  if stoned – you stop at the GREEN lights
Cannabis Dependence and Withdrawal

- 9% dependence
  - 17% in those who start using young (in their teens)
  - 25 to 50% among daily users
- 2013 NSDUH: marijuana accounted for 4.2 million of the estimated 6.9 million Americans dependent on illicit drugs
- In the US, 49% of people have used cannabis.

- Cannabis withdrawal:
  - Insomnia
  - Irritability, anxiety
  - Reduced appetite
  - Mild depression
  - GI, nausea
  - 14 days
  - Tx: stress management, sleep, appetite
"Legal yet illegal. Is there a sane solution?"

- Schedule I status

- To do clinical research, approval of:
  - DEA for issuance of a license
  - FDA for approval of a protocol
  - NIDA to use botanical cannabis

- Little financial incentive to launch multimillion-dollar studies on a ubiquitous plant

- States with MC legalized: in defiance with federal constraints. Federal statutes trumps the state statutes

- MDs Rx MC violate federal law: risk of losing DEA license, face criminal prosecution; no clear guidance for practitioners and patients

- Rescheduling to Sch II: research to develop meds, improve efficacy and minimize side effects
Name Games and Strain Identification

• 100s of MC varieties marketed by dispensaries
• What are the chemically distinct varieties? Nobody knows! No standards or certification procedures
• CT, 2013, legislature: to have brand names with chemical and genetic fingerprinting
• Need component analysis to understand the complex interactions of plant constituents
• Cannabis chemistry manifests in appearance and aroma:
  • Piney scent: stimulating
  • Lavender/grape: sedating
• Gamble: fraud and ignorance
• Use remains controversial
• More research is needed
• Not FDA approved
Alzheimer’s disease

• **Effect:** calm agitation, increase sleep, appetite
  - **Dosage:** For sedation: THC 5-10 mg PO (edibles);
  - High doses → agitation, disorientation.
  - For inflammation: CBD 160 mg (600 mg)

• **Future:** slow the buildup of beta-amyloid plaques and tangles. **MOA:** THC lowers amyloid-beta levels and enhancing mitochondrial function (Cao, et al., 2014) (Currais, et al., 2016 (Eubanks, et al., 2006)).
  - **CBD** modulates microglial function, controls neuroinflammation (Martin-Moreno, et al., 2011). **CBD:** neuroprotective, anti-oxidative, anti-inflammatory and anti-apoptotic effects (Iuvone, et al., 2004). **CBD** promotes regeneration of brain cells (Cheng, et al., 2014). **CBD** increases glucose uptake (Köfalvi, et al., 2016).
ADHD (AR)

• Can encourage “hyper focus” 90 minutes. Less successful than Rx meds. Reduce “jitters” of stimulants.

• ADHD:
  1. Dysfunction of DA system. DA receptors interact with endocannabinoid system, CB1 in limbic system (amygdala, hippocampus)
  2. Endocannabinoid (EC) deficiency -> restlessness, impulsivity, and inattention. Cannabis -> activates EC system -> DA release -> slows the speed of neural impulses

• Dosage: micro-doses THC 2.5 mg

• Methods: oral—sedating, SL better, smoking--bad

• No effect on attention without ADHD Dx
Autism Spectrum Disorders (PA)

- Rimland’s Autism Research Institute: current use
  - Aggression, violence, tantrums, self-injury
  - Anxiety, panic

- 2013: ECS is different in ASD: current research

1. ASD: 5 times the number of CB2 receptors
   - CB1 and CB2 receptor abnormalities → to social and emotional disturbances. Poor functioning CB2 → response to increase CB2 receptor count

2. NL3 mutations inhibit secretion and signaling of endocannabinoids → increase in pro-inflammatory cytokines levels in ASD → CB2 upregulation in response to inflammatory stimuli as neuroprotection

- Methods: oral, vap for teens, THC+CBD
Posttraumatic Stress Disorder (PTSD)

- Vietnam War: smoked during and after war
- PTSD patients 3 times more likely to have cannabis dependence
- 2012 petition signed by 8000 veterans to legalize MC for PTSD: denied
- **Effect**: Alters fear conditioning, memory, arousal, mood and sleep, nightmares
- **MOA**: CB1 in amygdala (emotional memory and fear), memory processing
- **Dosage**: dose-dependent response.
PTSD: Current Research

- Preliminary, open-label, pilot study of add-on oral Δ9-tTHC in chronic PTSD. Roitman P et. al. Hadassah Hebrew University Medical: 10 PTSD, on stable medication; THC 5 mg BID as add-on treatment.
  - Mild adverse effects in 3 patients
  - Improvement in global symptom severity, sleep quality, frequency of nightmares, and hyperarousal
  - THC was safe and well tolerated by patients

- DEA approves a controlled clinical trial. Funded by $2.156 million grant from Colorado DPH
  - 76 veterans with TX-resistant PTSD in MD and AZ
  - Smoked cannabis with varying THC/CBD ratio
  - Naturalistic data on dosing, composition, side effects, benefits
Traumatic Brain Injury

- **Effect of marijuana use on outcomes in traumatic brain injury**, Nguyen et al. UCLA, 2014 Oct. N=446, 3 year retrospective review. Overall mortality was 9.9%, mortality in THC group 2.4% → A positive THC screen is associated with decreased mortality in adult TBI patients.

- **MOA: Mouse model of closed head injury**: Br J Pharmacol 2011 Aug
  - Reduces glutamate, a toxic molecule
  - Decreases free radicals and TNF
  - Increases blood supply to the brain
  - Limits damage and edema
  - CB2 reduce white blood cell rolling and adhesion → reduce infarct size, improve motor function.
Chronic Traumatic Encephalopathy (CTE)

- Progressive degenerative disease. Severe TBI or repeated TBI to the head. Tauopathy
- Dementia pugilistica (DP), i.e. "punch-drunk"
- Football, rugby, ice hockey, boxing, professional wrestling, bull riding, rodeo…
- KannaLife Sciences, Inc. CTE and hepatic encephalopathy (HE) study. NIH license patent #6630507, “Cannabinoids as Antioxidants and Neuroprotectants”.
  - reduction of oxidative stress
Cancer

- **Animal models:** cannabinoids inhibit tumor growth
  - **Human trials:** not demonstrated

- **MOA:** Could inhibit one cancer and promote the growth of another:
  - high doses → inhibit growth
  - low doses → proliferation of the same tumors

- May protect against head, neck, lung cancers

- May increase incidence of prostate, cervical, brain cancers

- **Cancer pain:** THC+CBD > effective THC alone
  - THC>25 mg/day is poorly tolerated
  - 2/3 studies: Sativex is effective, max dose 10 sprays/day (THC 27 mg+ CBD 25 mg/day)
Cancer: continued

• **Cancer nausea and vomiting:** Plant THC, 1970s: 10-18 mg THC 1-2 hrs before chemo, repeat Q2-4 hrs, 2-4 doses over 12-24 hrs.
  - Clinical trials of dronabinol 30 to 80 mg/day in divided doses: intolerable side effects.
  - FDA: Marinol 5 mg TID/QID

• **Cancer cachexia/wasting:** Small trials: effectiveness with plant-THC 10-15 mg TID/QID on days of chemo.
  - Later trials with Marinol: less encouraging.
  - A large trial of THC only (2.5 mg BID) or THC + CBD (2.5 mg THC/1.0 mg CBD BID):
    ✓ stopped early for lack of effectiveness
    ✓ dose reductions in 1/3 of both groups due to intolerance.
Cachexia and Appetite

- Popular culture “munchies”
- 2006 Cannabis in Cachexia Study Group: little advantage over placebo in cancer patients + side effects
- Recent Israeli study: effective in reducing weight loss in cancer patients

- Mechanism:
  - CB1 in hypothalamus: appetite regulation
  - Reduction of cytokine activity (interleukins, interferon)

- Dosage: Marinol 2.5 mg before meals
- Methods: PO, SL, vap/smoke
Non-Cancer Pain

• The literature is sparse and patchy. 19 articles on 21 studies. No studies for pediatric populations.
  • Broad categories → difficult to group studies by type of pain or patient population
  • MC as an adjunctive treatment: nabiximols (Sativex)
  • No difference between nabiximols and placebo for MS and central neuropathic pain
  • Improvement in neuropathic pain

• 1 small study compared nabilone AE to dihydrocodeine and AE to opioids or other analgesics

• Treatment durations examined are too short. Unknown if benefits diminish over time.
  • Duration and population sizes limit the ability to identify uncommon or difficult to detect harms.
Pain: continued

• The most common symptom for which patients report using MC
  • Adjunct TX for opioid medications
  • Reduce the amount of opioid
  • Restore opioid pain relief, reduce opioid tolerance, reduce opioid withdrawal severity
  • Reduce GI bleed from nonsteroidal

• Dosage: UCASD human study, Sativex study:
  • Small dose: no effect
  • Medium dose: reduced pain significantly
  • High dose: increased pain significantly

• Method: oral for chronic pain, Inhaled: titration
Headaches and Migraine

• Has been used for 1,500 years. **MOA:**

1. Migrainers release less endocannabinoids → release neuropeptides → dilation of blood vessels.

2. Headache Group’s study, activation of the CB1 reduced the amount of A delta fibers by 19%

• **Prophylaxis:** TCH 2.5 mg daily
  • **Symptomatic migraine:**
    - Take early up to 10 mg THC if vomiting
    - THC 25 mg for progressed migraine to reduce vomiting and to sedate
    - Add CBD to prevent psychoactivity
    - Tension HA: 2.5-5 mg THC. Add CBD 2.5 mg
    - CBD alone can cause HA
Glaucoma

- CBD: not effective, may increase IOP
- Some studies: THC 5 mg may reduce IOP for 4-5 hrs (not consistent)
- Large doses (20-25 mg) reduce IOP for 10 hrs, but with intolerable side effects
HIV/AIDS

- **Effect:** wasting SD → increased caloric intake, stimulated appetite
  - 2007, San Francisco: effective for neuropathic pain
  - No HIV drug interactions
  - Rhesus Monkeys with SIV: THC → decline in mortality rate and viral load

- **MOA:** hypothalamus and enteric nervous system CB1 and CB2

- **Dosage:** Marinol appetite stimulation: 5-12.5 mg BID (3 studies: could tolerate up to 20-40 mg/day)

- **Methods:** oral: appetite, rest, sleep, analgesia. Smoke/vap: neuropathic pain
HIV/AIDS: Research

- Improvements in appetite, muscle pain levels, nausea, anxiety, depression and skin tingling (Woodridge, et al., 2005).


- Medical marijuana boosts appetite and daily functioning, weight loss and muscle breakdown (Haney, Rabkin, Gunderson & Foltin, 2005).

- No significant association with cannabis use and the CD4 T-cell count of patients co-infected with HIV and HCV (Marcellin, et al., 2016).

- HIV/HCV co-infection that smoked marijuana were at no greater risk of liver fibrosis (Brunet, et al., 2013).

- Marijuana-like compounds blocked the spread of HIV virus during the infection’s late stages (Costantino, et al., 2012).
Multiple Sclerosis and Movement Disorders

- Numerous trials: THC 20-25 mg/day in divided doses.
- Slow titration over weeks to reduce AE
- THC in high doses works better for spasticity (better tolerated with THC/CBD 1:1 ratio.
- Effective in 50% patients
- U of CA Center for Medical Cannabis Research (CMCR): 30 MS patients, placebo-controlled study, significant reduction in spasticity, pain reduced by 50%
- MOA: Regulate neurotransmission, limit excessive glutamate release (reduce neuronal damage)
Seizure Disorders

- Israeli: CBD, N=74 children, 1–18 years, with intractable epilepsy resistant to >7 AED. 66% failed a ketogenic diet, VNS, or both

- TX: 2–11/2014, for 3-6 months. CBD/THC 20:1. CBD dose 1-20 mg/kg/d

- Results: 66/74, 89%: reduction in seizure frequency:
  - 13 (18%): 75–100% reduction, 25 (34%): 50–75% reduction, 9 (12%): 25–50% reduction, 19 (26%) <25% reduction
  - Five (7%): aggravation of seizures
  - Improvement in behavior and alertness, language, communication, motor skills and sleep
  - Adverse reactions: somnolence, fatigue, GI disturbances and irritability
Seizure Disorders. Pipeline: Epidiolex

- Cannabinoids are both pro- and anticonvulsants
- **Epidiolex**: 98-99% plant-derived CBD (start 2-5 mg/kg/day → goal 25-50 mg/kg/day)
  - 50% of 137 pts: decrease in seizures
  - GW Pharmaceuticals: Ph3 trials in Dravet syndrome, Ph2 in Lennox-Gastaut syndrome, Ph1 in Tuberous Sclerosis Complex, Ph1 in Infantile Spasms
- Might be effective for schizophrenia
- **GWP42006 (CBDV)**: Ph1-Ph2 clinical trials for:
  - Epilepsy, Autism Spectrum Disorders
  - Neonatal Hypoxic-ischemic Encephalopathy
  - Glioma, Schizophrenia
Anxiety Disorders

• Used widely, not a qualifying condition

• **Effect:** Biphasic & bidirectional: increase or reduce anxiety (chemistry, dose, mind-set)

• **MOA:** CB1 in amygdala, hippocampus, anterior cingulate cortex

• **Dosage:**
  - Both THC and CBD. More effective separately
  - THC 1-3 mg, CBD 2.5-10 mg
  - High CBD: “mental sedation”. Drug holidays.
  - Panic, phobia, social: CBD 600 mg, not practical, scarce

• **Methods:** oral
  - smoke/vap most common, titration to proper dose
Autoimmune Disorders

• CB2: modulation of the function of all immune system cells in the body

• Endocannabinoid system plays a key role in many autoimmune d/o: MS, RA, DM

• MOA:
  • Reduction of production of inflammatory interleukin-2
  • Increase of production of anti-inflammatory interleukin-10
Insomnia and Sleep Disorders

- **Effect:** sedating, not a qualifying condition
  - restful sleep w/o AM grogginess
  - no tolerance
- **MOA:**
  - TCH: residual sedation
  - CBD: wake promoting, anxiety-reducing (initiation), Sativa not recommended
- **Dosage:** low (psychoactivator on high)
- **Methods:** oral is longer-acting
  - vap/smoke: effective, Sativex
Schizophrenia

- THC is pro-psychotic, CBD is antipsychotic
- Cannabinoid ratio of today’s cannabis is skewed completely toward THC
- **Effect**: schizophrenics use THC to relax, sedate; have lower incidence of diabetes
- **MOA**: Robson: schizophrenia-metabolic inflammatory disease: THC/CBD anti-inflamm, anti-metabolic, adjunct to anti-psychotics; s/e
- **Dosage**: preliminary: high CBD (1.5 mg/day), Epidiolex, GWP42006
Asthma

- **Effect**: Not a qualifying condition. “Nature” 2000: strong bronchodilator when smoked or vaporized (lung damage from tobacco constituents and inflammation)
  - Short term: improve, long term use may damage lung function

- **MOA**: Tashkin, 1975: immediate bronchodilation in asthma attack vs placebo in 30-60 min

- **Dosage**: 2% THC, start with a very low dose

- **Methods**: oral – too long to work,
  - SL – more effective
  - smoke/vap – try before bronchospasm, use clean cannabis without mold/yeast
Synthetic Cannabinoids: Not Marijuana
Not So Nice Spice, K2, Bliss, Mojo, Skunk

- MS: 1243 ED visits April 1 – May 31, 2015
  - 10% ICU, 11% non-ICU, 17 deaths

- **229% increase** in poisoning January-May 2015

- Collection of lab chemicals. Interact with cannabinoid and other receptors: stronger bind – full agonist

- **SX:** mild to severe. “Excited delirium”: agitation, sweating, arrhythmias, MI, psychosis, resp/depression, flaccid paralysis, hyperthermia, rhabdomyolysis, seizures, coma and death

- **TX:** ABC, fluids, electrolyte correction, anti-psychotics >benzos (seizure potential), poison control

- UDAS: (-) for cannabis, frequent change in formulation, laced with drugs, rat poison, embalming fluids
# Modern Cannabis Varieties

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Medical Use</th>
<th>Aroma</th>
<th>Potency</th>
<th>Duration</th>
<th>Psychoactivity</th>
<th>Analgesia/muscle relaxation</th>
<th>Dissociation</th>
<th>Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghan (Affie)</td>
<td>BL indica</td>
<td>Pain, relax, app, N/V,</td>
<td>Skunk, spice, coffee</td>
<td>17-20% THC</td>
<td>Long</td>
<td>Strong</td>
<td>Excellent/strong</td>
<td>Strong</td>
<td>Strong</td>
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<tr>
<td>Blueberry</td>
<td>NL indica</td>
<td>App, GI</td>
<td>Pungent, fruity</td>
<td>20%</td>
<td>Long</td>
<td>Clear-headed high</td>
<td>Excellent/good</td>
<td>Strong</td>
<td>No sedation, disorientation some</td>
</tr>
<tr>
<td>Bubba kush</td>
<td>BL indica</td>
<td>Pain, nausea, chemo-TX</td>
<td>Spice, citrus, wood, pepper, coffee</td>
<td>14-20%, no CBD</td>
<td>Long</td>
<td>Most stony: stimulating but body paralysis</td>
<td>Very strong/lethargic</td>
<td>Rare</td>
<td>Sedation high, mentally stimulating</td>
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<tr>
<td>Cannatonic</td>
<td>NL hemp (sativa+ indica)</td>
<td>Anxiety</td>
<td>Not pleasant</td>
<td>22% CBD (5% THC)</td>
<td>Several hours</td>
<td>None</td>
<td>Effective/relaxing</td>
<td>Slight</td>
<td>Never sleepy/not stimulating</td>
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</tbody>
</table>
References


References

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