Cannabis as a Potential Therapeutic Agent

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Funding and Conflicts of Interest

• I have no conflicts to report regarding this research
• I am Co-PI of a CDPHE funded study of cannabis use and sleep
Topics

• Background
  • History, Advocacy & Legislative Action

• Cannabinoids
  • Endocannabinoid system
  • Exogenous cannabinoids

• Cannabis Biology
  • Cannabis as a consumable product

• Cannabis as a potential Therapeutic Agent
Phytochemical and genetic analyses of ancient cannabis from Central Asia

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Abstract
The Yanghai Tombs near Turpan, Xinjiang-Uighur Autonomous Region, China have recently been excavated to reveal the 2700-year-old grave of a Caucasoid shaman whose accoutrements included a large cache of cannabis, superbly preserved by climatic and burial conditions. A multidisciplinary international team demonstrated through botanical examination, phytochemical investigation, and genetic deoxyribonucleic acid analysis by polymerase chain reaction that this material contained tetrahydrocannabinol, the psychoactive component of cannabis, its oxidative degradation product, cannabidiol, other metabolites, and its synthetic enzyme, tetrahydrocannabinolic acid synthase, as well as a novel genetic variant with two single nucleotide polymorphisms. The cannabis was presumably employed by this culture as a medicinal or psychoactive agent, or an aid to divination. To our knowledge, these investigations provide the oldest documentation of cannabis as a pharmacologically active agent, and contribute to the medical and archaeological record of this pre-Silk Road culture.

Key words: Archaeology, botany, cannabis, cannabinoids, archaeobotany, ethnopharmacology, genetics, medical history, phytochemistry.

Introduction
Uighur farmers cultivating the land at the base of the Huayan Shan ("Flaming Mountains") in the Gobi Desert near Turpan, Xinjiang-Uighur Autonomous Region, China some 20 years ago unearthed a vast ancient cemetery (54,000 m²) that seemingly corresponds to the nearby Aidinghu, Alagou, and

Discussion
The results presented collectively point to the most probable conclusion which is that the Gūshī culture cultivated cannabis for pharmaceutical, psychoactive or divinatory purposes. In examining the botanical evidence from this ‘old and cold’ site with its unique degree of preservation, the cannabis consisted of a processed (pounded) sample whose seed size, colour, and morphology, at least according to principles of Vavilov (Vavilov, 1926), suggest that it was cultivated rather than merely gathered from wild plants. The considerable amount of cannabis present (789 g) without any large stalks or branches would logically imply a pooled collection rather than one from a single plant. Importantly, no obvious male cannabis plant parts (e.g., staminate flowers, not infrequently observed in Indian herbal cannabis, or bhang (Russo, 2007) were evident, implying their exclusion or possible removal by human intervention, as these are pharmacologically less psychoactive.
Schedule I

Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Some examples of Schedule I drugs are:

heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote
### Criteria for Scheduling and Schedules under the Controlled Substance Act (CSA)

<table>
<thead>
<tr>
<th>Abuse Potential</th>
<th>SCHEDULE I</th>
<th>SCHEDULE II</th>
<th>SCHEDULE III</th>
<th>SCHEDULE IV</th>
<th>SCHEDULE V</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Heroin</td>
<td>Opioids</td>
<td>Opioids (Codeine combinations, Buprenorphine)</td>
<td>Benzodiazepines and other depressants (Zaleplon, Zolpidem, Eszopiclone)</td>
<td>Opioids in limited quantities and in combinations (Codeine, Dihydrocodeine, Difenoxin)</td>
</tr>
<tr>
<td>High</td>
<td>Hallucinogens</td>
<td>Barbiturates</td>
<td>Barbiturates (combinations and products)</td>
<td>Fenfluramine Modafinil Butorphanol Tramadol</td>
<td>Pregabalin Lacosamide</td>
</tr>
<tr>
<td>Low relative to CII</td>
<td>Cocaine</td>
<td>Methamphetamine</td>
<td>Ketamine</td>
<td>GHBP Marinol Anabolic Steroids</td>
<td></td>
</tr>
<tr>
<td>Lack of accepted safety under medical supervision</td>
<td>Amphetamine</td>
<td>Methylphenidate</td>
<td>GHB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Use</td>
<td>Methylphenidate</td>
<td>Methamphetamine</td>
<td>Ketamine</td>
<td>GHBP Marinol Anabolic Steroids</td>
<td></td>
</tr>
<tr>
<td>Medical Use</td>
<td>PCP</td>
<td>Methamphetamine</td>
<td>Ketamine</td>
<td>GHBP Marinol Anabolic Steroids</td>
<td></td>
</tr>
<tr>
<td>Low relative to CIII</td>
<td>Severe Psych or Physical</td>
<td>High Psych or Moderate to low Physical</td>
<td>Ltd Psych or Physical relative to CIII</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low relative to CIV</td>
<td>Severe Psych or Physical</td>
<td>High Psych or Moderate to low Physical</td>
<td>Ltd Psych or Physical relative to CIII</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statutory Basis for Scheduling Recommendation

CSA requires HHS to consider 8 factors:
1. Actual or relative potential for abuse
2. Scientific evidence of pharmacological effect
3. Current scientific knowledge regarding the substance
4. History and current pattern of abuse
5. Scope, duration, and significance of abuse
6. Risk to public health
7. Psychiatric or physiological dependence liability
8. Immediate precursor of a substance already controlled
Case Law on Meaning of “Currently Accepted Medical Use”

1. The drug’s chemistry is known and reproducible
2. There are adequate safety studies
3. **There are adequate and well-controlled studies proving efficacy**
4. The drug is accepted by qualified experts
5. The scientific evidence is widely available

57 FR 10499, 10504-06 (March 26, 1992).
1. FDA has supported cannabis based drug development (dronabinol and nabilone) for specific treatment
2. FDA/DEA/HHS supports cannabis research by providing legally produced cannabis product to researchers what have that HHS has found to be scientifically meritorious.
3. NIDA will work to provide a variety of potencies of cannabis for research purposes
4. DEA considers cannabis to be less dangerous than other schedule 1 drugs but schedule 1 is not based on “relative danger”, rather that the drug meets “specific statutory criteria”.
5. “If the scientific understanding about cannabis changes” then the scheduling decision can change

AA-Rosenberg-Marijuana-Petition-Ltr-08-11-2016
The current state of affairs at the federal level

Drugs in development focus on two molecules specifically, Tetrahydrocannabinol and Cannabidiol, not the full botanical product based on “assured quality manufacturing”.

This is in opposition to the common philosophy of supporters of cannabis as medicine who say that there is evidence of an “entourage effect” that is not duplicated by single molecule therapy.
Colorado Civics Lesson

1998; Amendment 19 trying to legalize Medical Marijuana in Colorado fails to make it onto the ballot*

2000; Amendment 20 makes it on the ballot and passes 54% to 46% legalizing Medical Marijuana

2005; Denver initiative I-100 passes allowing recreational use of one ounce for >21

2006; Amendment 44 to legalize recreational use fails 60% to 40%

2009; US Attorney General says that there will be no further action taken against dispensaries following state and local laws

2010; HB10-1284 creates a state regulatory agency and business licensing for full-scale dispensaries

2012; Amendment 64 passes 55% to 45% legalizing recreational cannabis

2013; regulation of A64 is enacted, SB13-317 (licensing and regulation), SB13-318 (taxation), SB13-238 (education and enforcement)

2014; SB14-215 allocates $9,000,000 to fund research administered through CDPHE to investigate potential therapeutic benefits of cannabis use (among other things)
19. The above-named patient has been diagnosed with and is currently undergoing treatment for the following chronic, debilitating medical condition or has a chronic, debilitating disease or medical condition that produces one or more of the following:

- a. Cancer
- d. Cachexia*
- g. Persistent muscle spasms*
- b. Glaucoma
- e. Severe nausea*
- h. Severe pain*
- c. HIV or AIDS positive
- f. Seizures*

20. Etiology is required for medical conditions with an asterisk (*), if known.
Etiology: ___________________________ or □ Etiology unknown.
Topics

• Background
  • History, Advocacy & Legislative Action

• **Cannabinoids**
  • **Endocannabinoid system**
  • **Exogenous cannabinoids**

• Cannabis Biology
  • Cannabis as a consumable product
  • Cannabis as a potential Therapeutic Agent
Endocannabinoid System

- 1964 THC is isolated, its believed to have non-specific activity
- In the mid 1980’s Allyn Howlett suggested that specific receptors existed
- 1990 Matsuda et al published a paper detailing the structure and function of a receptor that bound THC and was present in the central and peripheral nervous system eventually named CB-1
- A second receptor (CB-2) was identified in immune cells, various peripheral nerves and organ systems but also in CNS tissue
- 1992 Devane identifies the first endogenous molecule that binds to these receptors, eventually named Anandamide
- 1995 Mechoulam et al identified 1-arachidonoylglycerol (2-AG)
Table 2. Therapeutic applications of ECS-related drugs at the periphery

<table>
<thead>
<tr>
<th>Compound/category</th>
<th>ECS target</th>
<th>Model</th>
<th>Therapeutic indication</th>
<th>Clinical condition</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Peripherally restricted) CB₁ agonists</td>
<td>CB₁</td>
<td>Dog/human</td>
<td>Transient lower esophageal relaxation</td>
<td>Gastroesophageal reflux disease</td>
<td>[161,162]</td>
</tr>
<tr>
<td>(Peripherally restricted) CB₁ agonists</td>
<td>CB₁</td>
<td>Mouse/rat</td>
<td>Diarrhea, Inflammation, Visceral pain</td>
<td>Irritable bowel syndrome, Inflammatory bowel disease, Gastric ulcer</td>
<td>[163,164,165]</td>
</tr>
<tr>
<td>(Peripherally restricted) CB₁ antagonists</td>
<td>CB₁</td>
<td>Mouse</td>
<td>Metabolic endotoxemia, Food intake, Dysmotility</td>
<td>Obesity, Paralytic ileus</td>
<td>[43,40,168,169]</td>
</tr>
<tr>
<td>CB₂ agonists</td>
<td>CB₂</td>
<td>Mouse/rat</td>
<td>Diarrhea, Inflammation, Visceral pain</td>
<td>Irritable bowel syndrome, Inflammatory bowel disease</td>
<td>[44,170]</td>
</tr>
<tr>
<td>FAAH inhibitors</td>
<td>CB₁, CB₂, PPARs</td>
<td>Mouse</td>
<td>Diarrhea, Inflammation, Visceral pain</td>
<td>Irritable bowel syndrome, Inflammatory bowel disease</td>
<td>[45,171]</td>
</tr>
<tr>
<td>MAQIL inhibitors</td>
<td>CB₁, CB₂, PPARs</td>
<td>Mouse/rat</td>
<td>Diarrhea, Inflammation, Visceral pain</td>
<td>Irritable bowel syndrome, Inflammatory bowel disease, Gastric ulcer</td>
<td>[174]</td>
</tr>
<tr>
<td>Peripherally restricted CB₁ antagonists</td>
<td>CB₁</td>
<td>DIO mice, ob/ob mice, ob/db mice, db/db mice, ZDF rats</td>
<td>Lipogenesis, inflammation</td>
<td>Obesity, Metabolic liver disease, Type 2 diabetes</td>
<td>[61,172,178]</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>CB₁</td>
<td>Mouse</td>
<td>Defective myotube differentiation and muscle regeneration</td>
<td>Muscular dystrophy</td>
<td>[100]</td>
</tr>
<tr>
<td>Synthetic CB₂ agonists</td>
<td>CB₂</td>
<td>Mouse</td>
<td>Bone mineralization</td>
<td>Osteoporosis</td>
<td>[113]</td>
</tr>
<tr>
<td>PEA</td>
<td>CB₁, CB₂, TRPV₁, PPARs, GPR55</td>
<td>Human</td>
<td>Vestibulodynia, vestibulodynia, proctodynia</td>
<td>Infertility</td>
<td>[178,180]</td>
</tr>
<tr>
<td>THC</td>
<td>CB₁</td>
<td>Mouse</td>
<td>Purification</td>
<td>Infertility</td>
<td>[125,128]</td>
</tr>
<tr>
<td>PEA</td>
<td>CB₁, CB₂, TRPV₁, PPARs, GPR55</td>
<td>Human</td>
<td>Inflammation, pruritus</td>
<td>Atopic dermatitis, prurigo, urticaria itch</td>
<td>[140,141]</td>
</tr>
<tr>
<td>(Peripherally restricted) CB₁ antagonists</td>
<td>CB₁</td>
<td>Rodent</td>
<td>Diabetic and other nephropathies and tubulopathies</td>
<td>Diabetic and other nephropathies and tubulopathies</td>
<td>[151,152,154]</td>
</tr>
<tr>
<td>CB₂ agonists</td>
<td>CB₂</td>
<td>Rodent</td>
<td>Diabetic and other nephropathies and tubulopathies</td>
<td>Diabetic and other nephropathies and tubulopathies</td>
<td>[153,154]</td>
</tr>
</tbody>
</table>

Endocannabinoid signaling at the periphery: 50 years after THC
## Taxonomic Hierarchy

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Plantae – plantes, Planta, Vegetal, plants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subkingdom</td>
<td>Viridiplantae</td>
</tr>
<tr>
<td>Infrakingdom</td>
<td>Streptophyta – land plants</td>
</tr>
<tr>
<td>Superdivision</td>
<td>Embryophyta</td>
</tr>
<tr>
<td>Division</td>
<td>Tracheophyta – vascular plants, tracheophytes</td>
</tr>
<tr>
<td>Subdivision</td>
<td>Spermatophytina – spermatophytes, seed plants, phanérogames</td>
</tr>
<tr>
<td>Class</td>
<td>Magnoliopsida</td>
</tr>
<tr>
<td>Superorder</td>
<td>Rosanae</td>
</tr>
<tr>
<td>Order</td>
<td>Rosales</td>
</tr>
<tr>
<td>Family</td>
<td>Cannabaceae – hemp</td>
</tr>
<tr>
<td>Genus</td>
<td>Cannabis L. – hemp</td>
</tr>
<tr>
<td>Species</td>
<td>Cannabis sativa L. – hemp, grass, hashish, Mary Jane, pot, marijuana</td>
</tr>
</tbody>
</table>

**Direct Children:**

- **Subspecies** *Cannabis sativa ssp. indica* (Lam.) E. Small & Cronquist – hemp, grass, hashish, Mary Jane, pot, marijuana
- **Subspecies** *Cannabis sativa ssp. sativa* L. – hemp, grass, hashish, Mary Jane, pot, marijuana
Hemp Plant Chemistry Is Complex

Terpenes / Terpenoids
- α-Bisabolol
- Borneol
- Camphene
- Campher
- Δ²-Carene
- β-Caryophyllene
- α-Cedrene
- β-Eudesmol
- Geraniol
- Guaiol
- α-Humulene
- Limonene
- Linalool
- Menthol
- Myrcene
- Nerol
- α-Pinene
- α-Terpinene
- Over 150 more

Cannabinoids
- Cannabidiol
- Cannabichromene
- Cannabichromevarin
- Cannabicyclol
- Cannabitriol
- Cannabidivarin
- Cannabidiodiol
- Cannabigerol
- Cannabigerovarin
- Cannabinol
- Cannabinvarin
- Tetrahydrocannabinol
- Tetrahydrocannabivarin

Other Substances
- Apigenin
- Borneol
- α-Cadinene
- Cannabisin-A
- Cannflavin-A
- N-trans-Caffeoyltymamine
- Docosnoic Acid
- Epifriedelanol
- N-trans-Feruloytymamine
- β-Eudesmol
- Grossamide
- Kaempferol
- Orientin
- Quebrachol
- β-Selinene
- α-Spinasterol
- Stigmasterol
- Vitexin
- Vomifoliol
- Hundreds more
<table>
<thead>
<tr>
<th>Compound</th>
<th>C. indica Hemp Biotype (N = 45^a)</th>
<th>C. indica Feral Biotype (N = 14)</th>
<th>C. indica NLD Biotype (N = 68)</th>
<th>C. indica WLD Biotype (N = 40^a)</th>
<th>C. indica Hemp Biotype (N = 62)</th>
<th>C. indica Feral Biotype (N = 16)</th>
<th>C. ruderalis (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC%</td>
<td>0.34 A</td>
<td>0.18 AB</td>
<td>0.19 B</td>
<td>0.17 B</td>
<td>0.18 B</td>
<td>0.13 B</td>
<td>0.07 B</td>
</tr>
<tr>
<td>(SD)</td>
<td>(0.47)</td>
<td>(0.27)</td>
<td>(0.21)</td>
<td>(0.25)</td>
<td>(0.24)</td>
<td>(0.20)</td>
<td>(0.10)</td>
</tr>
<tr>
<td>Range%</td>
<td>0.0–1.9</td>
<td>0.0–0.9</td>
<td>0.0–0.9</td>
<td>0.0–1.4</td>
<td>0.0–1.2</td>
<td>0.0–0.8</td>
<td>0.0–0.2</td>
</tr>
<tr>
<td>CBD%</td>
<td>1.43 BC</td>
<td>1.95 BC</td>
<td>0.02 D</td>
<td>1.21 C</td>
<td>4.01 A</td>
<td>3.62 A</td>
<td>3.02 AB</td>
</tr>
<tr>
<td>(SD)</td>
<td>(2.45)</td>
<td>(2.82)</td>
<td>(0.02)</td>
<td>(2.78)</td>
<td>(2.66)</td>
<td>(1.80)</td>
<td>(1.29)</td>
</tr>
<tr>
<td>Range%</td>
<td>0.0–8.5</td>
<td>0.0–7.9</td>
<td>0.0–0.1</td>
<td>0.0–11.0</td>
<td>0.0–13.6</td>
<td>1.7–8.3</td>
<td>1.0–4.6</td>
</tr>
<tr>
<td>CBG%</td>
<td>0.18 AB</td>
<td>0.22 AB</td>
<td>0.24 A</td>
<td>0.19 AB</td>
<td>0.14 B</td>
<td>0.08 B</td>
<td>0.11 AB</td>
</tr>
<tr>
<td>(SD)</td>
<td>(0.20)</td>
<td>(0.23)</td>
<td>(0.27)</td>
<td>(0.32)</td>
<td>(0.27)</td>
<td>(0.16)</td>
<td>(0.11)</td>
</tr>
<tr>
<td>Range%</td>
<td>0.0–1.0</td>
<td>0.0–0.7</td>
<td>0.0–1.1</td>
<td>0.0–1.8</td>
<td>0.0–0.7</td>
<td>0.0–0.3</td>
<td>0.0–0.5</td>
</tr>
<tr>
<td>THC%</td>
<td>3.54 B</td>
<td>3.04 B</td>
<td>5.48 A</td>
<td>6.49 A</td>
<td>1.16 C</td>
<td>0.39 C</td>
<td>0.17 C</td>
</tr>
<tr>
<td>(SD)</td>
<td>(2.58)</td>
<td>(2.12)</td>
<td>(2.41)</td>
<td>(4.09)</td>
<td>(2.05)</td>
<td>(0.61)</td>
<td>(0.08)</td>
</tr>
<tr>
<td>Range%</td>
<td>0.1–9.3</td>
<td>0.3–6.0</td>
<td>1.4–12.4</td>
<td>0.1–14.7</td>
<td>0.1–11.5</td>
<td>0.1–2.5</td>
<td>0.1–0.3</td>
</tr>
<tr>
<td>(CBD + THC)%</td>
<td>4.97 BC</td>
<td>4.99 BC</td>
<td>5.50 B</td>
<td>7.70 A</td>
<td>5.17 BC</td>
<td>4.01 C</td>
<td>3.19 C</td>
</tr>
<tr>
<td>(SD)</td>
<td>(2.61)</td>
<td>(1.91)</td>
<td>(2.42)</td>
<td>(3.45)</td>
<td>(2.59)</td>
<td>(1.83)</td>
<td>(1.37)</td>
</tr>
<tr>
<td>Range%</td>
<td>0.6–11.4</td>
<td>1.7–8.2</td>
<td>1.4–12.4</td>
<td>1.7–14.8</td>
<td>1.2–14.3</td>
<td>1.7–8.8</td>
<td>1.0–4.8</td>
</tr>
<tr>
<td>(CBDV + THCV)/i.s.</td>
<td>0.19 B</td>
<td>0.90 A</td>
<td>0.25 B</td>
<td>0.14 BC</td>
<td>0.05 C</td>
<td>0.09 BC</td>
<td>0.05 BC</td>
</tr>
<tr>
<td>(SD)</td>
<td>(0.35)</td>
<td>(0.80)</td>
<td>(0.40)</td>
<td>(0.30)</td>
<td>(0.06)</td>
<td>(0.10)</td>
<td>(0.05)</td>
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<tr>
<td>Range%</td>
<td>0.0–1.6</td>
<td>0.0–2.7</td>
<td>0.0–2.1</td>
<td>0.0–1.4</td>
<td>0.0–0.3</td>
<td>0.0–0.3</td>
<td>0.0–0.1</td>
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<tr>
<td>CBGM/i.s.</td>
<td>0.05 A</td>
<td>0.00 C</td>
<td>0.01 C</td>
<td>0.02 B</td>
<td>0.01 BC</td>
<td>0.00 BC</td>
<td>0.01 BC</td>
</tr>
<tr>
<td>(SD)</td>
<td>(0.05)</td>
<td>(0.01)</td>
<td>(0.01)</td>
<td>(0.03)</td>
<td>(0.03)</td>
<td>(0.01)</td>
<td>(0.01)</td>
</tr>
<tr>
<td>Range%</td>
<td>0.0–0.18</td>
<td>0.0–0.02</td>
<td>0.0–0.05</td>
<td>0.0–0.14</td>
<td>0.0–0.15</td>
<td>0.0–0.03</td>
<td>0.0–0.03</td>
</tr>
</tbody>
</table>

\(^a\)Means (in rows) not connected by the same letter are significantly different using Student’s \(t\) test \((P \leq 0.05)\).
<table>
<thead>
<tr>
<th>Sample</th>
<th>Indoor/Outdoor</th>
<th>THCA (mg/g)</th>
<th>THC (mg/g)</th>
<th>CBG (mg/g)</th>
<th>THCV (µg/g)</th>
<th>CBN (µg/g)</th>
<th>CBD (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamír</td>
<td>I</td>
<td>81±4</td>
<td>2.6±0.2</td>
<td>0.37±0.03</td>
<td>35±2</td>
<td>112±0.8</td>
<td>1.6±0.2</td>
</tr>
<tr>
<td>Great White Sugar</td>
<td>12</td>
<td>99±5</td>
<td>3.7±0.2</td>
<td>0.37±0.03</td>
<td>56±3</td>
<td>7.5±0.5</td>
<td>2.9±0.3</td>
</tr>
<tr>
<td>Power Plant</td>
<td>13</td>
<td>107±5</td>
<td>2.0±0.1</td>
<td>0.30±0.03</td>
<td>70±4</td>
<td>11.6±0.8</td>
<td>1.8±0.2</td>
</tr>
<tr>
<td>AK 47</td>
<td>14</td>
<td>74±4</td>
<td>1.2±0.1</td>
<td>0.39±0.02</td>
<td>33±2</td>
<td>7.4±0.5</td>
<td>0.67±0.07</td>
</tr>
<tr>
<td>N.Y.C. Diesel</td>
<td>15</td>
<td>114±6</td>
<td>2.2±0.1</td>
<td>1.14±0.08</td>
<td>35±2</td>
<td>7.0±0.5</td>
<td>2.4±0.2</td>
</tr>
<tr>
<td>Jaggie</td>
<td>16</td>
<td>91±5</td>
<td>2.9±0.2</td>
<td>0.67±0.05</td>
<td>62±4</td>
<td>10.2±0.7</td>
<td>2.1±0.2</td>
</tr>
<tr>
<td>Medicine Woman</td>
<td>17</td>
<td>119±6</td>
<td>3.6±0.2</td>
<td>1.23±0.08</td>
<td>60±4</td>
<td>11.1±0.8</td>
<td>2.5±0.2</td>
</tr>
<tr>
<td>Amnesia</td>
<td>18</td>
<td>117±6</td>
<td>2.7±0.2</td>
<td>1.04±0.07</td>
<td>97±6</td>
<td>18±1</td>
<td>3.9±0.4</td>
</tr>
<tr>
<td>Cheese</td>
<td>19</td>
<td>70±4</td>
<td>1.1±0.1</td>
<td>0.54±0.04</td>
<td>13.7±0.8</td>
<td>4.6±0.3</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>Chocolope</td>
<td>110</td>
<td>94±5</td>
<td>2.9±0.2</td>
<td>0.55±0.04</td>
<td>12.4±0.8</td>
<td>10.9±0.8</td>
<td>3.4±0.3</td>
</tr>
<tr>
<td>Deep Chunk</td>
<td>111</td>
<td>71±4</td>
<td>1.3±0.1</td>
<td>0.16±0.01</td>
<td>31±2</td>
<td>6.1±0.4</td>
<td>1.9±0.2</td>
</tr>
<tr>
<td>OG Kush</td>
<td>112</td>
<td>67±3</td>
<td>1.8±0.1</td>
<td>0.34±0.02</td>
<td>27±2</td>
<td>2.4±0.2</td>
<td>1.9±0.2</td>
</tr>
<tr>
<td>Soul Diesel</td>
<td>113</td>
<td>70±4</td>
<td>1.4±0.1</td>
<td>0.19±0.01</td>
<td>26±2</td>
<td>4.5±0.3</td>
<td>2.5±0.2</td>
</tr>
<tr>
<td>Skunk Green</td>
<td>114</td>
<td>80±4</td>
<td>2.0±0.1</td>
<td>0.076±0.005</td>
<td>38±2</td>
<td>15±1</td>
<td>2.8±0.3</td>
</tr>
<tr>
<td>Super Lemon Haze</td>
<td>115</td>
<td>69±3</td>
<td>3.5±0.2</td>
<td>0.30±0.02</td>
<td>310±20</td>
<td>130±0.9</td>
<td>3.6±0.4</td>
</tr>
<tr>
<td>Super Silver Haze</td>
<td>116</td>
<td>105±5</td>
<td>3.2±0.2</td>
<td>0.53±0.04</td>
<td>134±8</td>
<td>9.1±0.6</td>
<td>3.5±0.4</td>
</tr>
<tr>
<td>Tijuana</td>
<td>117</td>
<td>92±5</td>
<td>3.6±0.2</td>
<td>0.73±0.05</td>
<td>153±8</td>
<td>130±0.9</td>
<td>4.5±0.4</td>
</tr>
<tr>
<td>Nevilles Haze</td>
<td>118</td>
<td>63±3</td>
<td>1.9±0.1</td>
<td>0.067±0.005</td>
<td>63±4</td>
<td>59±0.4</td>
<td>2.2±0.2</td>
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<tr>
<td>Somango</td>
<td>119</td>
<td>86±4</td>
<td>4.6±0.3</td>
<td>0.68±0.05</td>
<td>240±10</td>
<td>10.0±0.07</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td>Amnesia</td>
<td>01</td>
<td>91±5</td>
<td>16±1</td>
<td>0.74±0.05</td>
<td>94±6</td>
<td>91±6</td>
<td>9.1±0.9</td>
</tr>
<tr>
<td>Critical</td>
<td>02</td>
<td>112±6</td>
<td>7.6±0.5</td>
<td>0.38±0.03</td>
<td>153±9</td>
<td>61±4</td>
<td>5.0±0.5</td>
</tr>
<tr>
<td>Blueberry</td>
<td>03</td>
<td>30±2</td>
<td>6.5±0.4</td>
<td>0.100±0.007</td>
<td>28±2</td>
<td>60±4</td>
<td>3.3±0.3</td>
</tr>
<tr>
<td>Chocolope</td>
<td>04</td>
<td>80±4</td>
<td>25±2</td>
<td>0.75±0.05</td>
<td>5.8±0.3</td>
<td>84±6</td>
<td>14±1</td>
</tr>
<tr>
<td>Cream Carmel</td>
<td>05</td>
<td>113±6</td>
<td>10.8±0.7</td>
<td>1.17±0.08</td>
<td>103±6</td>
<td>63±4</td>
<td>6.9±0.7</td>
</tr>
<tr>
<td>Bubba Kush</td>
<td>06</td>
<td>69±3</td>
<td>9.1±0.5</td>
<td>0.018±0.001</td>
<td>52±3</td>
<td>61±4</td>
<td>6.0±0.6</td>
</tr>
<tr>
<td>Super Lemon Skunk</td>
<td>07</td>
<td>51±3</td>
<td>17±1</td>
<td>0.54±0.04</td>
<td>4.5±0.3</td>
<td>91±6</td>
<td>10±1</td>
</tr>
<tr>
<td>Super Skunk</td>
<td>08</td>
<td>76±3</td>
<td>5.0±0.3</td>
<td>0.39±0.03</td>
<td>69±4</td>
<td>59±4</td>
<td>6.0±0.6</td>
</tr>
<tr>
<td>Trainwreck</td>
<td>09</td>
<td>65±3</td>
<td>22±1</td>
<td>0.48±0.03</td>
<td>3.6±0.2</td>
<td>73±5</td>
<td>12±1</td>
</tr>
<tr>
<td>Trainwreck X HP</td>
<td>10</td>
<td>71±4</td>
<td>60±0.4</td>
<td>0.33±0.02</td>
<td>98±6</td>
<td>58±4</td>
<td>3.4±0.3</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>011</td>
<td>73±4</td>
<td>9.6±0.6</td>
<td>0.39±0.03</td>
<td>107±6</td>
<td>470±30</td>
<td>10±1</td>
</tr>
</tbody>
</table>

I: Indoor; O: Outdoor
Topics

- Background
  - History, Advocacy & Legislative Action
- Cannabinoids
  - Endocannabinoid system
  - Exogenous cannabinoids

- **Cannabis Biology**
  - **Cannabis as a consumable product**
  - Cannabis as a potential Therapeutic Agent
This is not what a modern cannabis grow typically looks like

http://www.cannabis-pictures.com/34notminey8OzOutdoorBogglegumBush.jpg
This is a modern industrial grow
### Indica
- Triangle Kush X
- Ghost OG
- Rugburn
- Emerald OG
- Purple Urkle
- Kurple Fantasy
- OG Chem #3
- Shaw #4

### Sativa
- Sharks Breath
- Glass Slipper

### Hybrid
- White Master Kush
- Blue Dream
- Chem 91
- KING CHEM Lemonhead
- Purple Dream
- SFV OG Kush
- Mixed Buds

### Edible
- CBD Capsules 10 pack
- 80mg CBD/40mg THC/40mg Dr. J's capsules
- Highly Edible 100mg
- Dixie Meda Mints 80mg
- 70mg Dixie Rolls
- Incredible's Boulder Bar 100mg
- Incredibles Affogato 100mg
- Edi-Pure 100mg
- 84mg Dixie Toasted Rooster Bar
- Incredible's Monkey Bar 50mg
- 80 mg Dr. J's PM Health Capsules
- 80 mg Dr. J’s AM capsules
- Gaia's Garden 80mg Garden Drops
- Incredibles Peanut Budda 50mg
- Blue Kudu 80mg
- 40mg Blue Kudu Chocolate
- Gaia's Garden Single Serving Lollipop
- Sweetgrass 10mg Snickerdoodle Cookie
- Sweet Grass 10mg Peanut Butter Cookie
- 10mg Ganjala Taffy

### Concentrate
- O-Pen Vape Cartridge 500mg
- Co2 Oil
- Hummingbird Brand Co2 Cannabis Oil
- Mahatma Shatter
- TC Labs Shatter (Strain Specific)
- O-Pen Vape Cartridge 250mg
- O-Pen Vape Pen

### Drink
- Canna Punch 100mg
- Dixie Elixir 90 mg
- 10mg Keef Kola Orange Krush, Root Beer

### Tincture
- 200mg Charlotte’s Web CBD Hemp Extract
- Dixie Dew Drops 90mg

### Topicals
- Dixie Synergy Relief Balm
- Dixie 100mg Muscle Relief Lotion
The bioavailability of those molecules is based on how the plant is ingested.
Measuring cannabis use; we need to update Donald Tashkin’s 1993 survey used by UCLA

29. Now we would like to find out something about the type of marijuana that is generally available in Southern California. Thinking about the last time you bought marijuana, what kind of marijuana did you buy?

(PROBE FOR NAME AND/OR LOCATION IN WHICH GROWN.)

<table>
<thead>
<tr>
<th>SINSEILLA</th>
<th>JAMAICAN</th>
<th>COLOMBIAN</th>
<th>HAWAIIAN</th>
<th>PANAMANIAN</th>
<th>DOMESTIC/COMMERCIAL/MEXICAN</th>
<th>HOME GROWN</th>
<th>AFGHANISTAN</th>
<th>THAI</th>
<th>OTHER</th>
<th>DON'T KNOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>99</td>
</tr>
</tbody>
</table>
6(b) We would like you to tell us about how you use cannabis specifically. Please describe how you use cannabis frequently on days when you do. If you use cannabis during the night please indicate that in the "Time of day used" field:

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Cannabis Species (Indica, Sativa, Or Hybrid)</th>
<th>Form of Cannabis (bud, edible, Concentrate, etc.)</th>
<th>Name of Product or Strain (for edibles please include concentration)</th>
<th>Method of Use (Smoke, Vaporize, Water Pipe, Eat or Drink, etc.)</th>
<th>Amount Used (a Puff, a Few Puffs, a Bowl, a Bite etc)</th>
<th>Reason for Use (Sleep, Nausea, Pain, Recreation, etc)</th>
<th>Dispensary (Name, private, home grow, etc)</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First use</td>
<td>6AM All</td>
<td>Bud</td>
<td>Blue Dream San Diego</td>
<td>Smoke + Vape</td>
<td>Joint</td>
<td>Anxiety</td>
<td>Livewell</td>
<td></td>
</tr>
<tr>
<td>Second use</td>
<td>8 AM All</td>
<td>Bud + Concentrate</td>
<td>&quot;</td>
<td>Smoke + Vape</td>
<td>Joint+</td>
<td>Anxiety</td>
<td>Livewell</td>
<td></td>
</tr>
<tr>
<td>Third Use</td>
<td>12pm Both + Hybrid</td>
<td>Bud + Concentrate</td>
<td>&quot;</td>
<td>Smoke</td>
<td>&quot;</td>
<td>&quot;</td>
<td>Livewell</td>
<td></td>
</tr>
<tr>
<td>Fourth Use</td>
<td>2PM Indica</td>
<td>Bud</td>
<td>&quot;</td>
<td>Smoke</td>
<td>Joint</td>
<td>&quot;</td>
<td>Livewell</td>
<td></td>
</tr>
<tr>
<td>Fifth Use</td>
<td>4PM Indica</td>
<td>Bud</td>
<td>&quot;</td>
<td>Smoke</td>
<td>Joint+</td>
<td>&quot;</td>
<td>Livewell</td>
<td></td>
</tr>
<tr>
<td>Sixth Use</td>
<td>6PM Indica</td>
<td>Bud</td>
<td>&quot;</td>
<td>Smoke</td>
<td>Joint+</td>
<td>&quot;</td>
<td>Livewell</td>
<td></td>
</tr>
<tr>
<td>Seventh Use</td>
<td>7PM Indica</td>
<td>Bud</td>
<td>Sweet Grass</td>
<td>Smoke + Eat</td>
<td>Joint+</td>
<td>10-30mg</td>
<td>Livewell</td>
<td></td>
</tr>
<tr>
<td>Final Use of the Day</td>
<td>8PM - 12PM Indica</td>
<td>Bud</td>
<td>Sweet Grass</td>
<td>Smoke + Eat</td>
<td>Joint+</td>
<td>10-30mg</td>
<td>Livewell</td>
<td></td>
</tr>
</tbody>
</table>
Cannabis Self-Titration

Recreation vs Medical differ in the target result of the exposure, being high/calm/sedated/relaxed vs achieving a therapeutic effect such as control of pain or anxiety but they have things in common

Self-Titration is complex and is effected by many factors;

What is used
- Strain; cannabinoid composition, other molecular factors
- Form; bud, concentrate, other forms

How is it used
- Temperature effects the exposure so method of use effects exposure
- smoke vs filtering through liquid vs vape vs eat vs tincture vs dab vs....

Route of exposure
- lungs vs skin vs digestion
Cannabis and Self-Titration

In the real world

A convenience sample of 121 current and former cigarette smokers surveyed, participants in a lung health study in Denver at NJH. 33 reported cannabis use >1 day per month the number of uses per day and the reason for that use.

<table>
<thead>
<tr>
<th>Uses Per Month</th>
<th>Uses Per Day</th>
<th>Reason For Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>sleep, rec, pain, relax</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>rec</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>sleep, nausea, pain, rec</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>pain</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>pain</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>sleep, pain</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>rec</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>pain</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>anxiety, rec</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>pain</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>rec</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>sleep, pain, rec</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>sleep, pain</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>pain</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>pain</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>rec</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>sleep, anxiety</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>rec</td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td>rec</td>
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<td>20</td>
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<td>pain, rec</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>sleep, pain</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>relax, appetite, pain</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
<td>rec</td>
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<tr>
<td>25</td>
<td>3</td>
<td>pain</td>
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<td>26</td>
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<td>29</td>
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<td>pain</td>
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<tr>
<td>30</td>
<td>1</td>
<td>pain</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
<td>sleep, pain</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>pain, PTSD</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>sleep, appetite, relax</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>sleep, nausea, stress, anxiety, appetite</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>pain</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>pain, cancer, sleep</td>
</tr>
</tbody>
</table>
Cannabis Pharmacokinetics

- Smoking turns ~50% of the THC into smoke that is inhaled
  - Remainder lost to heat and smoke that isn’t inhaled
- ~50% of smoke that is inhaled is exhaled
- The bioavailability of THC is between 10% and 25%
- Serum THC levels rise immediately and fall rapidly back to baseline ~3 hours later
- Edible bioavailability is 5-20%
- Serum THC peaks after edible consumption between 1 and 3 hours later
Dosage – industry  http://www.cheebachews.com

• Each Cheeba Chew is cut within precise weight tolerances, ensuring consistent medicinal effects every time for patients. We have perfected our process to consistently make the safest pharmaceutical grade cannabis extract possible, while activating 98%+ of the available cannabinoids. Every single batch of extract is tested for THC, CBD, and CBN content. We also test with edibles on a monthly basis to ensure that we are sticking to our promise of making the most potent and consistent cannabis edible on the market.

• *Dosage Information (these are estimates for an average tolerance, effects can vary greatly from one person to another)*
  • Single Dose (17.5mg THC) – 1-2 bowl hits
  • Double Dose (35mg THC) – 3-4 bowl hits
  • Quad Dose (70mg THC)- Joint to yourself
  • Deca Dose (175mg THC) – High Tolerance Patients Only

• If it’s your first time trying a Cheeba Chew we recommend 17.5mg THC/single dose, or 1/4 of a Quad Dose Chew. We never recommend consuming a whole Quad Dose your first time taking Cheeba Chews. With the correct dose, effects typically last between 2 – 6 hours.

• Time for Cheeba Chews effects to be felt vary greatly from one patient to another. Most will start to feel the effects around 30mins, but sometimes it can take 3hrs. This is dependent on how your individual body reacts to Cannabinoids. What you ate, and the amount of cannabis you smoked/consumed during the past 24 hours play a major role. Every patient is different.
Topics

• Background
  • History, Advocacy & Legislative Action
• Cannabinoids
  • Endocannabinoid system
  • Exogenous cannabinoids
• Cannabis Biology
  • Cannabis as a consumable product

• Cannabis as a potential Therapeutic Agent
What is a therapeutic agent; a therapeutic agent is a compound with a beneficial and desirable effect when used in some way.
19. The above-named patient has been diagnosed with and is currently undergoing treatment for the following chronic, debilitating medical condition or has a chronic, debilitating disease or medical condition that produces one or more of the following:

- a. Cancer
- b. Glaucoma
- c. HIV or AIDS positive
- d. Cachexia*
- e. Severe nausea*
- f. Seizures*
- g. Persistent muscle spasms*
- h. Severe pain*

20. Etiology is required for medical conditions with an asterisk (*), if known.
Etiology: ___________________ or ☐ Etiology unknown.
Potential Negative Associations

• Addiction potential; heavily investigated and published broadly
• Pulmonary effects; primarily symptomatic (e.g. cough and phlegm) and not functional (e.g. FEV$_1$, FVC or FEV$_1$/FVC) or causative for emphysema outside of cigarette smoking
• Cardiovascular; evidence to show a negative effect of overstimulation of the endocannabinoid system (opposing effects of CB-1 vs CB-2 in cardiac tissue possibly associated with exogenous cannabinoids)
Nausea and Appetite

• Cancer chemotherapy related nausea
• HIV/AIDS related cachexia
Pain

• Neuropathic pain (RTC trials of cannabis)
  • Diabetic neuropathy
  • HIV/AIDS
  • Post-traumatic injury
  • Cancer
  • Dental
  • Multiple Sclerosis
Muscle

- Multiple Sclerosis spasticity and tremors
- Parkinson’s Disease tremors
Gastrointestinal

• The gut is strongly effected by the endocannabinoid system making diseases effecting the gut potential targets of endocannabinoid modulating medications or exogenous cannabis
  • Crohn’s Disease
  • Celiac Disease
  • Inflammatory Bowel Disease
Sleep

• Many studies, trials and observational measures of cannabis users mention altered sleep, many positive (sleep onset), some negative (sleep quality).

• Our study is investigating sleep in people using cannabis specifically to effect their sleep.
Neurological effect

- CBD decreased risk for impairment due to stroke in CB-1 ablated animals
- CB-2 receptor stimulation may provide neural anti-inflammatory effects
- CBD may be neuroprotective through other pathways outside of directly binding CB-1 and CB-2 (e.g. other endocannabinoid triggers and receptors)
- These effects are altered by tolerance and “the psychoactive effects of cannabis may be prohibitive for neuroprotection “
- Cannabis impairs cognition and its use in people with existing cognitive impairment may not be warranted
In summary

• Cannabis is a botanical that is very complicated and we have a long way to go to understand how the hundreds of molecules in the plant interact to generate effects in humans

• The endocannabinoid system is very complex and some drugs attempting to access it have failed due to cardiovascular and other adverse effects

• Self-titration of cannabis exposure in people is complex and subject to change due to tolerance

• Edible exposure can vary by person
Questions?
Ongoing Studies in Colorado

**Project title**

Do Adolescents and Young Adults with Inflammatory Bowel Disease Benefit from Use of Marijuana?

A Randomized, Double-blind, Placebo-controlled Crossover Study of Tolerability and Efficacy of Cannabidiol (CBD) on Tremor in Parkinson's Disease

Treating PTSD with Marijuana: Clinical and Functional Outcomes

Cannabidiol (CBD) and Pediatric Epilepsy

Medical Marijuana in the Pediatric Brain Tumor Population (palliative care)

Use of Medicinal Cannabinoids as Adjunctive Treatment for Medically Refractory Epilepsy (pediatric epilepsy)

Placebo-controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Potencies of Smoked Marijuana in 76 Veterans with Chronic, Treatment-Resistant Post Traumatic Stress Disorder (PTSD)

A Double Blind, Placebo-Controlled Cross Study Comparing the Analgesic Efficacy of Cannabis versus Oxycodone

Colorado Cannabis Cohort: Efficacy, Safety, and Usage Patterns of Medical Marijuana for Sleep

**Primary Investigator**

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CDPHE and Retail Marijuana (C.R.S. 25-1.5-111 & SB-13-283)

Retail Marijuana Public Health Advisory Committee

An appointed panel of scientists and health care professionals with expertise in cannabinoid physiology to monitor emerging health effects and other information.

• Systematically review the scientific literature
• Review public health surveillance data
• Recommend public health related policies
• Recommend public health surveillance activities
• Identify research gaps important to public health
CDPHE Goal
Translate Science into Public Health

• Develop consensus statements that convey the quality and quantity of scientific evidence behind a finding
• Translate consensus statements into plain language statements in a standardized way
• Guide the development of evidence-based prevention campaigns
• Analyze surveillance data using high quality methods
Potential targets of medical marijuana research

• Positive effects:
  • Stroke recovery
  • Glaucoma
  • Pain management
  • Nausea reduction for chemo patients
  • Muscle relaxant for spastic muscles
  • Seizure control

• Negative effects:
  – Drugged driving
  – Impaired brain development from long term use in teenagers
  – Lung damage from the smoke
  – ER visits for children consuming edibles
What can we learn from this natural experiment?

- Large population
- Long term self titration of treatment
- Consistent patterns of treatment aimed at therapeutic benefit
- Broad public communication

Potential Weaknesses

- Tolerance
- Abuse
- Exposure of at risk populations
- Difficulty moving beyond anecdotal data
**Table 1. Effects of regular use of marijuana alone on chronic respiratory symptoms and lung function in comparison with nonsmoking control subjects**

<table>
<thead>
<tr>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased prevalence of chronic cough or sputum (17, 18, 20–22), wheezing (17, 18, 20–22), and shortness of breath (20)</td>
</tr>
<tr>
<td>Increased incidence of acute bronchitic episodes (17) or clinic visits for acute respiratory illness (19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>No difference in FEV$_1$ or FVC (17, 20, 21)</td>
</tr>
<tr>
<td>Increase in FVC (23, 27, 29)</td>
</tr>
<tr>
<td>Increase in FEV$_1$ (23)</td>
</tr>
<tr>
<td>Decrease in FEV$_1$/FVC (18, 20)</td>
</tr>
<tr>
<td>No difference in single-breath nitrogen washout measures (17, 25)</td>
</tr>
<tr>
<td>No differences in FRC, TLC, or RV (17, 21)</td>
</tr>
<tr>
<td>Increases in FRC, TLC, and RV (27)</td>
</tr>
<tr>
<td>Increase in Raw and decrease in SGaw (17, 25, 27)</td>
</tr>
<tr>
<td>No difference in D$_{LCO}$ (17, 21, 27)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: D$_{LCO}$ = single-breath diffusing capacity for carbon monoxide; FRC = functional residual capacity; Raw = airway resistance; RV = residual volume; SGaw = specific airway conductance; TLC = total lung capacity.*
Research Gaps

• Research studies on all outcomes should evaluate occasional users, separate from regular or heavy users.

• Research studies on all outcomes should include former users and continuing users with comparable prior use frequency and age of onset to help separate long-term effects from the effects of current use.

• Additional studies with more varied time periods of abstinence are needed to assess the duration of cognitive impact of marijuana use.

• Studies evaluating the potential psychological outcomes of marijuana use should have separate evaluations of males and females.

• More studies are needed to assess the risk of increasing use or becoming addicted for occasional users, based on age of onset.
<table>
<thead>
<tr>
<th>Name</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td><img src="image" alt="Chemical structure of THC" /></td>
</tr>
<tr>
<td>AEA</td>
<td><img src="image" alt="Chemical structure of AEA" /></td>
</tr>
<tr>
<td>2-AG</td>
<td><img src="image" alt="Chemical structure of 2-AG" /></td>
</tr>
<tr>
<td>OEA</td>
<td><img src="image" alt="Chemical structure of OEA" /></td>
</tr>
<tr>
<td>PEA</td>
<td><img src="image" alt="Chemical structure of PEA" /></td>
</tr>
</tbody>
</table>
Spinal Pain Pilot Data

- Asked 150 participants in a spinal pain clinic whether they used cannabis for pain management, 35 reporting cannabis use for pain management
  - 45% had a red card
  - 90% reported smoking, 45% eating and 29% vaporizing
  - 81% reported “cannabis is more effective than narcotics”
  - 89% reported “cannabis is more effective than NSAID”
  - 88% reported “cannabis is more effective than nerve targeted pharmaceuticals”

Emily Lindley, University of Colorado Denver
THC vs. THCa

Marijuana flower is often said to contain THC, but this is not technically true. The plant contains “THCa”, which is not psychoactive in its natural state. THC is created through decarboxylation.

Decarboxylation is the process of heating THCa, which naturally occurs in cannabis plants, to activate THC that can be absorbed in the body through ingestion. In the process, the THCa loses carbon and oxygen molecules, and about 12.3 percent of its weight.

This weight reduction is calculated using the molecular weight of THCa and THC.

Although the report authors refer to both THC and THCa throughout the report, the reader can interpret the terms as synonymous.