Medical Marijuana: *Friend or Foe?*

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As of Dec 2018:
Medical: 32 States and DC
Recreational: 10 States and DC

**Marijuana Users, Treatment Admissions, and Average Potency: 1986-2010**

Sources: [NSDUH](#), [TEDS](#), National Seizure System
Main Effects of Marijuana

- **Active ingredients (similar structures):**
  - Delta-9 Tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)

- **Agonist to the cannabinoid (CB) receptors (CB₁ > CB₂)**
  - G protein- decrease adenylate cyclase, inhibit Ca channels, and modify K+ channels
  - THC >> CBD binding to CB1

- **Similar to naturally occurring anandamide (from arachidonic acid)**

Delta 9-THC is converted rapidly to 11-hydroxy THC which is also active and outlasts measurable THC

Major Brain Circuits Involved in Addiction

- Inhibitions
- Reward

Photo courtesy of the NIDA Web site. From A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana.
Inhibitions

Reward

Photo courtesy of the NIDA Web site.
Medical Marijuana
# THC Administration & FDA Approved THC-based medications

<table>
<thead>
<tr>
<th>TABLE 1 Cannabis Products</th>
<th>Cannabinoid Content</th>
<th>Administration Formulation and Dosage</th>
<th>FDA Approval</th>
<th>Indications</th>
<th>Approved Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dronabinol (Marinol and Syndros)</strong></td>
<td>Synthetic δ-9-THC</td>
<td>Oral capsule or solution 5–15 mg/m² per dose, up to 6 doses daily</td>
<td>Approved in 1985, Schedule III controlled substance</td>
<td>CINV (pediatric and adult), anorexia associated with weight loss in AIDS (adult)</td>
<td>United States, Australia, Germany, New Zealand, and South Africa</td>
</tr>
<tr>
<td><strong>Nabilone (Cesamet)</strong></td>
<td>Synthetic δ-9-THC</td>
<td>Oral capsule 1 or 2 mg twice a day, up to 6 mg daily (adult)</td>
<td>Approved in 1985, Schedule II controlled substance</td>
<td>CINV</td>
<td>United States, Canada, Ireland, Mexico, and United Kingdom</td>
</tr>
<tr>
<td><strong>Nabiximols (Sativex)</strong></td>
<td>Ratio of 2.7 δ-9-THC to 2.5 CBD, plant derived</td>
<td>Oromucosal spray 1 spray daily, up to 12 sprays daily with at least 15 min between sprays (adult)</td>
<td>Phase III trials</td>
<td>Neuropathic pain, cancer pain, multiple sclerosis spasticity</td>
<td>Canada, Czech Republic, United Kingdom, Denmark, Germany, Poland, Spain, and Sweden</td>
</tr>
<tr>
<td><strong>CBD (Epidiolex)</strong></td>
<td>CBD, plant derived</td>
<td>Oral solution 2 up to 50 mg/kg per day (research trials)</td>
<td>None, Schedule I controlled substance</td>
<td>Epilepsy</td>
<td>None</td>
</tr>
<tr>
<td><strong>Cannabis plant products (eg, marijuana and oral cannabis extracts)</strong></td>
<td>Varying concentration of plant-derived THC to CBD</td>
<td>Includes smoking (marijuana) and oral (cannabis extracts)</td>
<td>None approved</td>
<td>Medically and recreationally legal in certain states via physician certification</td>
<td></td>
</tr>
</tbody>
</table>

Efficacy of orally-administered cannabis extract for appetite stimulation and quality of life for patients with advanced cancer

Safety and efficacy of nabiximols

- 3 randomized, placebo-controlled, double-blind, parallel-group studies
  - n=666 (363 randomized to nabiximols) patients with MS and spasticity
- Outcome: spasticity
- Adverse events were recorded

Comparative effectiveness of pharmacological treatments for pain

Nabixomols (Sativex) least effective for pain reduction among individuals with diabetic peripheral neuropathy.
Efficacy of THC for HIV-positive patients with neuropathic pain

Over a 5-day inpatient intervention period, smoking cannabis cigarettes three times a day reduced HIV-SN pain by 34%, significantly more than the 17% reduction with placebo cigarettes. (p=.003) A 30% reduction in pain has been validated as a clinically significant level of improvement.

In the current study, half (52%) of those randomized to cannabis experienced at least a 30% reduction in pain, while a quarter (24%) of those randomized to placebo experienced a similar reduction in pain. (p=.004)

Significant benefit in reducing pain during active treatment phase, lasting up to 8 days after stopping smoking

**Figure 3.** Time course of the intensity of chronic neuropathic pain as rated on the daily VAS at 8 AM for the previous 24-hour period. Each point represents the group median. Study admission was at noon on study day -2, the first cigarette was smoked at 2 PM on study day 1, and the last cigarette was smoked at 2 PM on study day 5.

The present investigation aimed to provide an objective narrative review of the existing literature pertaining to the benefits and harms of marijuana use for the treatment of the most common medical and psychological conditions.

Findings indicate that, for the majority of these conditions, there is insufficient evidence to support the recommendation of medical marijuana at this time. A significant amount of rigorous research is needed to definitively ascertain the potential implications of marijuana for these conditions. It is important for such work to not only examine the effects of smoked marijuana preparations, but also to compare its safety, tolerability, and efficacy in relation to existing pharmacological treatments.

Cannabidiol for Drug-Resistant Seizures (Dravet Syndrome)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cannabidiol</th>
<th>Placebo</th>
<th>Adjusted Median Difference (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of convulsive seizures per mo — median (range)</td>
<td>12.4 (3.9 to 1717)</td>
<td>14.9 (3.7 to 718)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>-38.9 (−100 to 337)</td>
<td>0.01</td>
</tr>
<tr>
<td>Treatment period</td>
<td>5.9 (0.0 to 2159)</td>
<td>14.1 (0.9 to 709)</td>
<td>-22.8 (−41.1 to −5.4)</td>
<td></td>
</tr>
<tr>
<td>Percentage change in seizure frequency — median (range)</td>
<td></td>
<td></td>
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</table>

* CI denotes confidence interval.
† The P value was calculated with the use of a Wilcoxon rank-sum test with the Hodges–Lehmann approach.

Medical Cannabis in Children and Adolescents: A Systematic Review

- Evidence for benefit was strongest for chemotherapy-induced nausea and vomiting, and refractory epilepsy.
- At this time, there is insufficient evidence to support use for spasticity, neuropathic pain, posttraumatic stress disorder, Tourette syndrome, or any psychiatric disorder in childhood.

Putative Medical Uses of THC vs CBD

THC
- Pain
- Nausea/Vomiting
- Spasticity
- Glaucoma
- Insomnia
- Appetite

CBD
- Seizures
- Pain
- Migraines
- Anxiety
- Depression
- Inflammatory diseases (IBD)
The controversy regarding medical marijuana

1. Health risks of smoked marijuana

2. Addictiveness of marijuana

3. Influence on youth drug use
Health risks of smoked marijuana

“3-4 cannabis cigarettes a day are associated with the same evidence of acute and chronic bronchitis and the same degree of damage to the bronchial mucosa as 20 or more tobacco cigarettes a day. Cannabis smoking is likely to weaken the immune system. Infections of the lung are due to a combination of smoking-related damage to the cells lining the bronchial passage and impairment of the principal immune cells in the small air sacs caused by cannabis.”

-- British Lung Foundation

Health risks of smoked marijuana

“There is very little evidence that smoking marijuana as a means of taking it represents a significant health risk...there have been no reported cases of lung cancer or emphysema....”

-- Lester Grinspoon, MD
Emeritus Professor of Psychiatry
Harvard Medical School

Adjusting for sociodemographic factors, alcohol and tobacco use
Health risks of smoked marijuana

Motor vehicle collision risk

Health (and societal) risks of smoked marijuana

20 drugs ranked by overall harm along 16 criteria

Marijuana Use in Teens is Directly Related to Perceived Risk

Marijuana Perceived Risk vs. Past Year Use by 12th Graders

SOURCE: University of Michigan, 2013 Monitoring the Future Study
Marijuana Use in Teens is Associated with Adverse Cognition, Brain structure, and Function

Gruber et al. *Drug Alcohol Depend.* 2012 121, 159–162
Marijuana is Related to New Onset Executive Dysfunction in Teens


5 Year Followup Study in Late Adolescence
(All subjects started without executive dysfunction).

<table>
<thead>
<tr>
<th>Subjects With Current Executive Dysfunction (%)</th>
<th>No Marijuana Use</th>
<th>Marijuana Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>N=154</td>
<td>N=92</td>
</tr>
<tr>
<td>ADHD</td>
<td>N=92</td>
<td>N=24</td>
</tr>
<tr>
<td>Control + Use</td>
<td>N=9</td>
<td></td>
</tr>
<tr>
<td>ADHD + Use</td>
<td>N=24</td>
<td></td>
</tr>
</tbody>
</table>

Pairwise Comparisons:

a p < 0.05 vs. Controls; b p < 0.05 vs. ADHD
Summary

• Marijuana confers therapeutic benefit
  – FDA-approved medications addressing nausea in AIDS/cancer
  – May not be as effective as other meds for chronic pain
  – Specific components (e.g. THC vs cannabidiol) relationship to efficacy unclear

• Strong evidence of both oral and smoked marijuana alleviating spasticity among MS patients

• Lack of trials comparing smoked MJ to oral/spray THC:CBD
  – Thus, it is currently unclear whether the benefits of smoked MJ (net of smoking-related risks) is greater than oral/other FDA-approved THC-based medications, and for which specific medical conditions

• Marijuana has substantial addiction potential

• Use in adolescents <16 years of age particularly problematic for potential structural brain changes and lasting neurocognitive dysfunction

• Given the paucity of well conducted trials for specific indications, physician recommendations for smoked MJ remains on a case-by-case basis