Medical Marijuana: *Friend or Foe?*

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Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g. substance use disorders)

Special appreciation to J Kelly PhD (MGH) for use of some of the slides.
As of Dec 2017:
Medical: 29 States and DC
Recreational: 7 States and DC

MARIJUANA USERS, TREATMENT ADMISSIONS, AND AVERAGE POTENCY: 1986-2010

Sources: NSDUH, TEDS, National Seizure System
Main Effects of Marijuana

- Active ingredients: Delta-9 Tetrahydrocannabinol (THC), cannabidiol, tetrahydrocannabivarin
- Agonist to the cannabinoid (CB) receptors (CB_1 > CB_2)
  - G protein- decrease adenylate cyclase, inhibit calcium channels, and modify K+ channels
- 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

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.
## THC Administration & FDA Approved THC-based medications

<table>
<thead>
<tr>
<th>Compound</th>
<th>Administration</th>
<th>FDA Status</th>
<th>Approved Locations</th>
<th>Purposes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol</td>
<td>Oral capsule</td>
<td>FDA-approved (1985)</td>
<td>USA, Germany</td>
<td>1. Nausea &amp; vomiting related to cancer chemotherapy</td>
</tr>
<tr>
<td>(Marinol)</td>
<td></td>
<td></td>
<td></td>
<td>2. Wasting associated with AIDS</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Oral capsule</td>
<td>FDA-approved (1985)</td>
<td>USA, Canada, UK, Mexico</td>
<td>Nausea &amp; vomiting related to cancer chemotherapy</td>
</tr>
<tr>
<td>(Cesamet)</td>
<td></td>
<td>*Marketed in the US in 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>Oromucosal spray</td>
<td>Almost FDA-approved; late-stage clinical trials</td>
<td>Canada, UK, other European countries</td>
<td>Multiple sclerosis spasticity, cancer pain, neuropathic pain</td>
</tr>
<tr>
<td>(Sativex)</td>
<td></td>
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</tbody>
</table>

Effectiveness of THC compared to prochlorperazine (Compazine) for treating nausea and vomiting

Of the 25 who expressed preference, 20 preferred THC to prochlorperazine; (degree of preference for either antiemetic not dependent on class of emetic activity related to patient’s chemotherapy); increased appetite

Emetic Activity of Chemotherapeutic Agent

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

Efficacy of smoked marijuana for MS patients with spasticity (RCT; N=30)


Treatment with smoked cannabis resulted in a reduction in patient scores on the modified Ashworth scale by an average of 2.74 points more than placebo (p < 0.0001). In addition, treatment reduced pain scores on a visual analogue scale by an average of 5.28 points more than placebo (p = 0.008).

Figure 2: Spasticity as measured by mean combined scores on the modified Ashworth scale, before and after treatment, on each day of each phase of the trial. (A) Change in scores by phase, before and after crossover. (B) Change in scores before and after treatment with placebo versus cannabis.
Comparative effectiveness of pharmacological treatments for pain


Nabixomols (Sativex) least effective for pain reduction among individuals with diabetic peripheral neuropathy.
Efficacy of smoked THC for chronic neuropathic pain (N=23, cross-over RCT)

\[ p = 0.023 \]

\[ \text{Pain Score}^* \]

<table>
<thead>
<tr>
<th>THC Potency</th>
<th>Average Daily Pain</th>
<th>Highest Daily Pain</th>
<th>Lowest Daily Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00%</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>2.50%</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>6.00%</td>
<td>6</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>9.40%</td>
<td>7</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

\[ ^* \text{Pain was scored on a scale from 0 (no pain) to 11 (worst possible pain)} \]

Participants receiving the 9.4% THC compared to the placebo. No other comparisons were sig. Secondary outcomes: Patients assigned to 9.4% THC had sig better outcomes compared to placebo with respect to getting to sleep, quality of sleep (less periodic wakefulness), and lower proportion anxiety depression on the quality of life measure.

**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)

**Figure 3.** Time course of the intensity of chronic neuropathic pain as rated on the daily diary 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.

Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders

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.

Review: Cannabinoids reduce symptoms of Tourette’s syndrome


- Kirsten R Müller-Vahl

- Abstract
  
  Currently, the treatment of Tourette’s syndrome (TS) is unsatisfactory. Therefore, there is expanding interest in new therapeutical strategies. Anecdotal reports suggested that the use of cannabis might improve not only tics, but also behavioural problems in patients with TS. A single-dose, cross-over study in 12 patients, as well as a 6-week, randomised trial in 24 patients, demonstrated that Δ⁹-tetrahydrocannabinol (THC), the most psychoactive ingredient of cannabis, reduces tics in TS patients. No serious adverse effects occurred and no impairment on neuropsychological performance was observed. If well-established drugs either fail to improve tics or cause significant adverse effects, in adult patients, therapy with Δ-THC should be tried. At present, it remains unclear whether herbal cannabis, different natural or synthetic cannabinoid CB1-receptor agonists or agents that interfere with the inactivation of endocannabinoids, may have the best adverse effect profile in TS.
Medical Marijuana Extract in Pediatric Epilepsy

- N=213 subjects aged (pediatric/adult; mean age 11 years)
- DX: Dravet & Lennox-Gestault syndromes (seizures may lead to intellectual disabilities), and 11 other types of epilepsy
- Design: 12 week, open label study
- Preparation: Oral suspension of cannabidiol (sponsored by GW Pharma)
- Findings: In 137 of 213 completers, mean 54% reduction in seizure rate
- Conclusion: Cannabidiol may offer treatment to refractory seizures necessitating further RCT’s

(Devinsky et al, Am Acad Neurology Presentation, 2015)
Medical Cannabis in Children and Adolescents: A Systematic Review

• Evidence for benefit was strongest for chemotherapy-induced nausea and vomiting, with increasing evidence of benefit for 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.

American Academy of Pediatrics: Position Statement on Medical Marijuana for Children

- No accepted indications for medical marijuana in children
- Acknowledges that there may be exceptions for “compassionate use” of marijuana medically for children with debilitating diseases
- Recognizes small trials of CBD for seizures (Cochrane report 2012); work with dronabinol for nausea
- In general, does not support the legalization or medical use of marijuana in children
- Recommends scheduling from C-I to C-II to allow clinical trials

(Am Acad Peds: 2015)
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

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*"p<0.05
Adjusting for gender, age, current asthma; Marijuana analyses also controlled for tobacco

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

Getting the Jump on the Marijuana Problem

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

SOURCE: University of Michigan, 2013 Monitoring the Future Study
Gray Matter Density (N=20/group; 18-25 yr olds)
(Gilman et al. J Neurosci 34: 2014)
Marijuana > controls

Gray Matter Density in Nucleus Accumbens Increases with Marijuana Dose

$\rho = 0.001$

Smoking Occasions per day  Joints per Occasion
The Impacts of adolescent marijuana use onset on cognition, brain structure, and function


Gruber et al. *Drug Alcohol Depend.* 2012 121, 159–162

5 year Followup of New Onset Cases of Any Drug Use Disorder (Largely Marijuana) and Current Executive Function Deficits in Adolescence


Subjects With Current Executive Dysfunction (%)

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