“MEDICAL MARIJUANA”: WHAT IS THE THERAPEUTIC VALUE?

John F. Kelly
MGH Psychiatry Grand Rounds
September 12, 2013
Outline

• For what conditions might MJ/THC be beneficial?

• What are the current THC-based treatment options?

• What do we know from research how effective current THC-based and smoked MJ options are for commonly targeted medical conditions?
  • Anti-nausea(cancer/AIDS)/appetite (cancer)
  • Spasticity (multiple sclerosis)
  • Pain (neuropathy)

• What are some of the risks associated with (smoked) “medical marijuana”?

• What happens to MJ use rates in states that have implemented medical marijuana laws?
For which conditions *might* marijuana/THC have a therapeutic benefit?

Up to 259 conditions including:

- Alzheimer’s disease
- Anorexia
- HIV/AIDS
- Arthritis
- Cachexia
- Cancer
- Crohn’s Disease
- Epilepsy
- Glaucoma
- Migraines
- Multiple Sclerosis
- Nausea
- Pain
- Spasticity
- Wasting Syndrome

# 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 (Marinol)</td>
<td>Oral capsule</td>
<td>FDA-approved (1985)</td>
<td>USA, Germany</td>
<td>Nausea &amp; vomiting related to cancer chemotherapy and wasting associated with AIDS</td>
</tr>
<tr>
<td>Nabilone (Cesamet)</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>Nabiximols (Sativex)</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>
</tbody>
</table>

Abstract

In order to assess the current knowledge on the therapeutic potential of cannabinoids, a meta-analysis was performed through Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included the reports and reviews published in English, French and Spanish. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded.

Seventy-two controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Cannabinoids present an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of multiple sclerosis, spinal cord injuries, Tourette’s syndrome, epilepsy and glaucoma.

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Keywords: Cannabinoids; Cannabis; Therapeutic potential; Controlled clinical trials; Efficacy; Safety
Controlled studies evaluating the therapeutic effect of THC by administration type

Anti-nausea/emetic and appetite effects

(Oral THC in cancer patients)
Anti-emetic effect of oral THC vs. standard treatment

- **Sample**: 73 patients with neoplasms and inadequately controlled nausea and vomiting
- **Design**: Randomized, double-blind, crossover trial
- **Intervention**: Oral THC vs. prochlorperazine before and after chemotherapy
- **Follow-up**: 3 randomly assigned one-day courses
- **Outcomes**: Patient preference in ameliorating nausea & vomiting

### Antiemetics in Patients Receiving Chemotherapy for Cancer

A Randomized Comparison of Delta-9-Tetrahydrocannabinol and Prochlorperazine

Stephen E. Sallan, M.D., Carol Cronin, B.S., Marvin Zelen, Ph.D., and Norman E. Zinberg, M.D.

**Abstract**

Delta-9-tetrahydrocannabinol (THC) is an effective antiemetic as compared with placebos in patients receiving chemotherapy for cancer. In this study we compared THC with prochlorperazine (Compazine) in a randomized, double-blind, crossover trial with patients who had failed to benefit from standard antiemetic therapy. Regardless of the emetic activity of the chemotherapeutic agents, there were more complete responses to THC courses (in 36 of 79 courses) than to prochlorperazine (in 16 of 78 courses). Of 25 patients who were treated with both drugs and who expressed a preference, 20 preferred THC (P = 0.005). Among patients under 20 years of age there was a higher proportion of complete responses to THC courses (15 of 20) than among older patients (21 of 59 courses; P = 0.004).

Increased food intake occurred more frequently with THC (P = 0.008) and was associated with the presence of a “high.” Of 36 THC courses resulting in complete antiemetic responses, 32 were associated with a high.

We conclude that THC is an effective antiemetic in many patients who receive chemotherapy for cancer and for whom other antiemetics are ineffective. (N Engl J Med 302:135-138, 1980)

**Nausea** and vomiting of central origin occur after the administration of a variety of chemotherapeutic agents for cancer and frequently condition, THC has been proved to stimulate appetite and food consumption.

The purpose of this study was to compare the ef-
Effectiveness of THC compared to prochlorperazine 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

Appetite & Quality of Life: Efficacy of oral THC vs. placebo

- **Sample**: 243 advanced cancer patients experiencing involuntary, unexplained weight loss
- **Design**: Randomized, placebo-controlled trial
- **Intervention**: Compared 3 conditions: Oral cannabis extract (2.5mg THC & 1mg CBD; similar to nabiximols [Sativex]) vs. THC (2.5mg; similar to dronabinol [Marinol]) vs. placebo
- **Follow-up**: 6-weeks
- **Outcomes**: Appetite stimulation, Quality of Life
Efficacy of orally-administered cannabis extract for appetite stimulation and quality of life for patients with cancer

• So, cancer pts may prefer THC-based medicine for anti-nausea, may stimulate appetite

• Effects may be moderated by cancer stage and may not stimulate appetite among more advance cancer patients
Spasticity

(oral spray THC in MS patients)
Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis

Derick T Wade, Christine Collin, Colin Stott and Paul Duncombe

Abstract
Objective: To determine the efficacy of Sativex (USAN: nabiximols) in the alleviation of spasticity in people with multiple sclerosis.
Methods: The results from three randomized, placebo-controlled, double-blind parallel group studies were combined for analysis.
 Patients: 666 patients with multiple sclerosis and spasticity.
Measures: A 0–100 mm Visual Analogue Scale (VAS, transformed to a 0–10 scale) or a 0–10 Numerical Rating Scale (0–10 NRS) was used to measure spasticity. Patients achieving a ≥30% improvement from baseline in their condition...
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

Figure 1. Change from baseline in spasticity over time.

Table 3. Responder analysis (30% or more reduction from baseline in spasticity assessment)

<table>
<thead>
<tr>
<th>Study</th>
<th>Nabiximols</th>
<th>Placebo</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis at study endpoint²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1¹</td>
<td>31/70 (44%)</td>
<td>21/63 (33%)</td>
<td>1.59</td>
<td>0.79, 3.22</td>
<td></td>
</tr>
<tr>
<td>Study 2¹</td>
<td>48/120 (40%)</td>
<td>14/64 (22%)</td>
<td>2.38</td>
<td>1.19, 4.78</td>
<td></td>
</tr>
<tr>
<td>Study 3¹</td>
<td>51/166 (31%)</td>
<td>42/169 (25%)</td>
<td>1.34</td>
<td>0.83, 2.17</td>
<td></td>
</tr>
<tr>
<td>Pooled analysis</td>
<td>130/356 (37%)</td>
<td>77/296 (26%)</td>
<td>1.62³</td>
<td>1.15, 2.28*</td>
<td>0.0073</td>
</tr>
<tr>
<td>Analysis at week 6³</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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<tr>
<td>Study 3¹</td>
<td>44/166 (27%)</td>
<td>38/169 (22%)</td>
<td>1.24</td>
<td>0.76, 2.05</td>
<td></td>
</tr>
<tr>
<td>Pooled analysis</td>
<td>123/356 (35%)</td>
<td>73/296 (25%)</td>
<td>1.57³</td>
<td>1.11, 2.23*</td>
<td>0.014</td>
</tr>
</tbody>
</table>

1. Intention-to-treat population; Timepoints: week 6 for Study 1 and Study 2 and weeks 13–14 for Study 3.
2. Intention-to-treat population; Timepoints week 6 for all three studies.
3. Adjusted for study.

MS Spasticity: Efficacy of THC/CBD spray vs. placebo

- **Sample**: 572 MS patients with spasticity
- **Design**: Randomized, placebo-controlled trial
- **Intervention**: Nabiximols (2.7 mg THC + 2.5 mg CBD) oromucosal spray vs. placebo
- **Follow-up**: 12 weeks
- **Outcome**: Change in spasticity from baseline

A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis


*Krajša nemocnice Pardubice, Neurologie odd. Pardubice, Czech Republic; BNeurologická klinika Olomouc, Czech Republic; CMAC UK Neuroscience Ltd, Manchester, UK; DMS Centrum, Neurologická klinika, Prague, Czech Republic; EMS Centre of Hospital Toplice, Toplice, Czech Republic; FNeurologická klinika FN Ostrava, Ostrava, Czech Republic; GRipar Neurologico LANCISI Day Hospital, Centro Sclerosi Multipla, Rome, Italy; HDipartimento di Scienze Neurologiche, Universita degli Studi, Rome, Italy; ISant’Andrea Multiple Sclerosis Centre, Universita La Sapienza, Rome, Italy; JCentro Sclerosi Multipla Ospedale S. Raffaele, Milan, Italy; KNeurologická klinika FN Plzen, Plzen, Czech Republic; LKatedra i Klinika Neurologii Akademii Medycznej, Lublin, Poland; MEdin Clinic F, Edin Cowl Hospital, Peterborough, UK; NHospital Universitari de la Vall d’Hebron, Antigua Escola de Enfermeria, Barcelona, Spain; KL’inika Neurologii i Epileptologii z Oddzialem Udarowym, Lodz, Poland; and ODepartment of Neurology, Northampton General Hospital, Northampton, UK

See editorial by Claudio Solaro, on page 1113.

**Keywords**: cannabidiol, cannabinoids, delta-9-tetrahydrocannabinol, endocannabinoid system, multiple sclerosis, nabiximols, Sativex, spasticity

**Background**: Spasticity is a disabling complication of multiple sclerosis, affecting many patients with the condition. We report the first Phase 3 placebo-controlled study of an oral antispasticity agent to use an enriched study design.

**Methods**: A 19-week follow-up, multicentre, double-blind, randomized, placebo-controlled, parallel-group study in subjects with multiple sclerosis spasticity not fully relieved with current antispasticity therapy. Subjects were treated with nabiximols, as add-on therapy, in a single-blind manner for 4 weeks, after which those achieving an
Efficacy of oral spray nabiximols for MS patients with spasticity

Spasticity

(Smoked THC in MS patients)
MS Spasticity: Efficacy of smoked THC vs. placebo

- **Sample**: 30 MS patients with spasticity
- **Design**: Randomized, double-blind, placebo-controlled crossover trial
- **Intervention**: 800mg 4% THC cigarettes vs placebo
- **Follow-up**: 6 assessments
- **Outcome**: Change in spasticity

**Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial**

Jody Corey-Bloom MD PhD, Tanya Wolfson MA, Anthony Gamst PhD, Sheila Jin MD MPH, Thomas D. Marcotte PhD, Heather Bentley BA, Ben Gouaux BA

**Abstract**

**Background**: Spasticity is a common and poorly controlled symptom of multiple sclerosis. Our objective was to determine the short-term effect of smoked cannabis on this symptom.

**Methods**: We conducted a placebo-controlled, crossover trial involving adult patients with multiple sclerosis and spasticity. We recruited participants from a regional clinic or by referral from specialists. We randomly assigned participants to either the intervention (smoked cannabis, once daily for three days) or control (identical placebo cigarettes, once daily for three days). Each participant was assessed daily before and after treatment.

**Results**: Thirty-seven participants were randomized at the start of the study, 30 of whom completed the trial. 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 ($p = 0.008$). Scores for the timed walk did not differ significantly between treatment and placebo ($p = 0.2$). Scores on the Paced Auditory Serial Addition Test decreased by 8.67 points more with treatment.
Efficacy of smoked THC for MS patients with spasticity


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.
Issues with blinding in medical marijuana RCTs

The use of cannabis and rapidly acting cannabinoids pose considerable challenges for blinding, as the psychoactive effects are expected to be quickly discernible to study participants, particularly those who have been previous users of such products.

Neuropathic Pain
(Oral spray THC in diabetic patients)
Systematic Review and Meta-Analysis of Pharmacological Therapies for Painful Diabetic Peripheral Neuropathy

Sonya J. Snedecor, PhD*; Lavanya Sudharshan, MS*; Joseph C. Cappelleri, PhD†; Alesia Sadosky, PhD‡; Sonam Mehta, MS*; Marc Botteman, MSc*

*Pharmerit International, Bethesda, MD; †Pfizer Inc, Groton, CT; ‡Pfizer Inc, New York, NY, U.S.A.

Abstract

Background: Painful diabetic peripheral neuropathy (pDPN) is prevalent among persons with diabetes and smaller Cis. Pregabalin (≥ 300 mg/day) was the most effective on the 100-point visual analog scale (−21.88; [−27.06, −16.68]); topiramate was the least (−3.09; [−3.99, −2.18]). Relative risks (RRs) of 30% pain reduction ranged
Comparative effectiveness of pharmacological treatments for pain

Pain: Efficacy of smoked cannabis vs. placebo

- **Sample**: 23 adults with neuropathic pain
- **Design**: Randomized, placebo-controlled, crossover trial
- **Intervention**: Four doses of THC 0.0, 2.5, 6.0 or 9.4%THC administered using a single-smoke inhalation 3 times per day
- **Follow-up**: 8-weeks
- **Outcome**: Change in average daily pain

**Research**

**Smoked cannabis for chronic neuropathic pain: a randomized controlled trial**

Mark A. Ware MBBS, Tongtong Wang PhD, Stan Shapiro PhD, Ann Robinson RN, Thierry Ducruet MSc, Thao Huynh MD, Ann Gamsa PhD, Gary J. Bennett PhD, Jean-Paul Collet MD PhD

Previously published at www.cmaj.ca

See related commentary by McQuay at www.cmaj.ca

**ABSTRACT**

**Background**: Chronic neuropathic pain affects 1%-2% of the adult population and is often refractory to standard pharmacologic treatment. Patients with chronic pain have reported using smoked cannabis to relieve pain, improve sleep and improve mood.

**Methods**: Adults with post-traumatic or postsurgical neuropathic pain were randomly assigned to receive cannabis at four potencies (0%, 2.5%, 6% and 9.4% tetrahydrocannabinol) over four 14-day periods in a crossover trial. Participants inhaled a single 25-mg dose through a pipe three times daily for the first five days in each cycle, followed by a nine-day washout period to assess carry-over pain intensity was measured.

**Cannabis sativa** has been used to treat pain since the third millennium BC. An endogenous pain-processing system has been identified, mediated by endogenous cannabinoid ligands acting on specific cannabinoid receptors. These findings, coupled with anecdotal evidence of the analgesic effects of smoked cannabis, support a reconsideration of cannabinoid agents as analgesics.

Oral cannabinoids such as tetrahydrocannabinol, cannabidiol and nabulone have, alone and in combination, shown efficacy in central and peripheral neuropathic pain, rheumatoid arthritis and fibromyalgia.

The analgesic effects of smoked cannabis remain controversial although, it is used by 10%–10% of patients with...
Efficacy of smoked THC for chronic neuropathic pain

$p = 0.023$

Pain was scored on a scale from 0 (no pain) to 11 (worst possible pain)

Pain: Efficacy of smoked THC vs. placebo

- **Sample**: 55 patients with HIV-associated sensory neuropathy
- **Design**: Randomized, double-blind, placebo-controlled trial
- **Intervention**: 900 mg 3.56% THC cigarettes vs placebo
- **Follow-up**: 3 weeks
- **Outcome**: Neuropathic pain

Cannabis in painful HIV-associated sensory neuropathy

A randomized placebo-controlled trial

D.I. Abrams, MD; C.A. Jay, MD; S.B. Shade, MPH; H. Vizoso, RN; H. Reda, BA; S. Press, BS; M.E. Kelly, MPH; M.C. Rowbotham, MD; and K.L. Petersen, MD

Abstract—Objective: To determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model. Methods: Prospective randomized placebo-controlled trial conducted in the inpatient General Clinical Research Center between May 2003 and May 2005 involving adults with painful HIV-associated sensory neuropathy. Patients were randomly assigned to smoke either cannabis (3.56% tetrahydrocannabinol) or identical placebo cigarettes with the cannabinoids extracted three times daily for 5 days. Primary outcome measures included ratings of chronic pain and the percentage achieving >30% reduction in pain intensity. Acute analgesic and anti-hyperalgesic effects of smoked cannabis were assessed using a cutaneous heat stimulation procedure and the heat/eccapsin sensitization model. Results: Fifty patients completed the entire trial. Smoked cannabis reduced daily pain by 34% (median reduction; IQR = –71, –16) vs 17% (IQR = –29, 8) with placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo ($p < 0.001$). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($p < 0.05$) but appeared to have little effect on the painfulness of noxious heat stimulation. No serious adverse events were reported. Conclusion: Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

NEUROLOGY 2007;68:515–521

HIV-associated sensory neuropathy (HIV-SN) is the most common peripheral nerve disorder complicating pain and analgesia. The need for a greater variety of effective therapeutic options has led to height-
Efficacy of THC for HIV-positive patients with neuropathic pain

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 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.

So, oral spray THC (Sativex) may help reduce spasticity in MS patients, but be unhelpful with chronic pain among diabetic pts with peripheral neuropathic pain.

Unclear whether smoked THC may help in this population.

Smoked THC may help reduce experience of chronic among certain clinical populations (e.g., HIV pts).
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

* $p<0.05$

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. I suspect that a day’s breathing in any city with poor air quality poses more of a threat than inhaling a day’s dose – which for many ailments is just a portion of a joint – of marijuana.”

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

Adjusting for sociodemographic factors, alcohol and tobacco use

Addictiveness of marijuana

“Adolescents, especially troubled ones, and people with psychiatric disorders (including substance abuse) appear more likely than the general population to become dependent on marijuana… Some controlled substances that are approved medications produce dependence after long-term use; this, however, is a normal part of patient management and does not generally present undue risk to the patient”

-- Institute of Medicine

Hall, W.; and Degenhardt, L. Adverse health effects of non-medical cannabis use. Lancet 374:1383–1391, 2009;
Health (and societal) risks of smoked marijuana

20 drugs ranked by overall harm along 16 criteria

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

Sources: NSDUH, TEDS, National Seizure System
Influence on youth drug use

“While it is not possible with existing data to determine conclusively that state medical marijuana laws caused the documented declines in adolescent marijuana use, the overwhelming downward trend strongly suggests that the effect of state medical marijuana laws on teen marijuana use has been either neutral or positive, discouraging youthful experimentation with the drug.”

-- Mitch Earlywine, SUNY Albany; Karen O'Keeffe, Marijuana Policy Project

“By characterizing the use of illegal drugs as quasi-legal, state-sanctioned, Saturday afternoon fun, legalizers destabilize the societal norm that drug use is dangerous. They undercut the goals of stopping the initiation of drug use to prevent addiction.... Children entering drug abuse treatment routinely report that they heard that 'pot is medicine' and, therefore, believed it to be good for them.”

-- Andrea Barthwell
Former Deputy Director
White House Office of National Drug Control Policy (ONDCP)

Conclusions

• THC confers therapeutic benefit
  • FDA-approved medications addressing nausea in AIDS/cancer
  • May not be as effective as other pharm. agents for chronic pain

• Some evidence of both oral THC-based meds and smoked MJ, relative to placebo, alleviating spasticity among MS patients

• Levels of THC and CBD (and other cannabinoids) likely differ between different batches of MJ used across studies, making generalizability about potential benefit difficult; dosing regimen also differs from the way it may be smoked for medical reasons in the real world

• Lack of trials comparing smoked MJ to oral/spray THC for any ailment

• 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

• Physician recommendations for smoked MJ for any medical purpose lacks clear systematic empirical basis

• Somewhat unclear also is the relationship between state medical MJ implementation and its potential effect on changing perceptions/attitudes and increasing MJ use, especially among teens/young people