Cannabis as Medication

Kalpna Gupta, PhD
Vascular Biology Centre
Division of Hematology, Oncology and Transplantation
Department of Medicine
University of Minnesota Medical School
Minneapolis, MN
The starting point?

Medical and Scientific Nomenclature

- To be referred to as *Cannabis/cannabinoids* and NOT *Marijuana*
- To be called *Medicine* and NOT *Drug*
- To be thought of as *Plant* NOT *Weed*
- To treat the *Sick* NOT ----?
History of cannabis

Origin: North of the Himalayan region in India (in China)
First written account: In Chinese records in 28th century BCE

Proof of early existence: ~3,000 year old mummy in Egypt contained traces of THC
Medicinal use of Cannabis

2700 BC – China
1000 BC – India
19th to early 20th century – Cannabis extracts and medications in USA
1937: Marihuana Tax Act, Federal Restrictions
1942: Removed from US Pharmacopoeia
1970: Controlled Substance Act: Schedule I, not accepted for medical use, potential of abuse high and lack of safety for medical use
1996: Legalized in California
2014: Bill passed in Minnesota
2014: 24 States, USA
1963 structure of Cannabidiol (CBD): Israeli Scientist Raphael Mechoulam
1964: Isolated the active ingredient delta-9 tetrahydrocannabinol (THC)

480 natural compounds and 66 are “cannabinoids” including CBD and THC. Others are called Cannabigerols (CBG)
Cannabichromenones (CBC)
Other Cannabidiols (CBD)
Other THC
Cannabinol (CBN) and cannabinodiol (CBDL)

Many other non-cannabinoids such as proteins, carbohydrates, etc
Calyx: comprise the female flowers with tiny nodules under the leaf with high concentration of glands or trichromes that secrete THC and other bioactive compounds in the highest concentration.

Trichromes: Crystal resins secreted through transluscent, mushroom shaped glands on leaves, stems and calyxes on the buds, containing cannabinoids and terpenes.
Current Regulatory Status of Cannabis

Schedule 1

- Cannabis
- Hallucinogenic amphetamine derivatives
- Heroin
- LSD
- Barbiturates
Cannabinoids

Endogenous

Anandamide ("Supreme bliss")

Phytochemicals

Δ-9-tetrahydrocannabinol (THC)

Synthetic

Schedule I

UN-Scheduled
How do Cannabinoids act?

1. By binding to transmembrane G-Protein coupled receptors called cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R)
2. Activation of signaling pathways by the activated receptors

Entourage effect

Compounds working better together than in isolation. Therefore, the plant has greater beneficial effects as compared to an isolated cannabinoid.

Eg. Marinol (Dronabinol), delta-9 THC. Appetite stimulation (HIV-AIDS patients) and anti-emetic. Marinol and phenothiazine (prochlorperazine) may result in synergistic or additive effects and attenuate the toxicities associated with each other.
Why do we want to use Cannabis as medicine?
<table>
<thead>
<tr>
<th><strong>Opioid</strong></th>
<th><strong>Cannabinoid</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose opioids promote myoclonus and seizure activity through μ and κ receptors[69]</td>
<td>Endocannabinoids and CB1 agonists appear to have anticonvulsant activity [70], [71], [72]</td>
</tr>
<tr>
<td>Nausea, vomiting and constipation are common during opioid therapy [73]</td>
<td>Cannabinoids are used as anti-emetic, especially in chemotherapy induced nausea and vomiting [74]; In cases of chronic cannabis abuse, hyperemesis has been reported [75]; Constipation seen as a mild-moderate AE in some clinical trials</td>
</tr>
<tr>
<td>Chance of respiratory depression with opioid overdose, generally along with ethanol or sedative ingestion, postoperative scenario or opioid abuse; not commonly reported with the doses used in pain management [76]</td>
<td>No such risk</td>
</tr>
<tr>
<td>Risk of opioid induced hyperalgesia with sustained opioid administration [77], [78]</td>
<td>No reports of cannabinoid induced hyperalgesia in animal studies, but some human studies suggest a hyperalgesic effect [67], especially with higher doses of cannabinoids</td>
</tr>
<tr>
<td>Opioids induce renal abnormalities in mice [79], [80]</td>
<td>Cannabidiol attenuated chemotherapy induced renal abnormalities in mice [81]</td>
</tr>
<tr>
<td>Opioids have been shown to stimulate angiogenesis, which could be harmful in angiogenesis-dependent pathologies including cancer and metastases [82]</td>
<td>Endocannabinoids inhibit angiogenesis [83]</td>
</tr>
<tr>
<td>Opioids inhibit apoptosis and promote cell cycle progression via cyclin D1 [82]</td>
<td>Cannabinoids promote apoptosis via ceramide accumulation in transformed cells (especially glioma cells), and may possess anti-tumor activity [22]</td>
</tr>
</tbody>
</table>
Pain

- Pain is the leading reason for seeing a doctor
- Costs the nation >$635 billion/year
- 40% of the adult population in the United States suffers with chronic pain
Why do we need to address pain in cancer?

- Approximately 30% - 50% people with cancer experience pain while undergoing treatment.
- 70 – 90% of people with advance cancer experience pain.
- Chemotherapy induces peripheral neuropathy (numbness and pain in fingers, feet, arms).
Currently opioids are the commonly used analgesics to treat severe pain. These are associated with liabilities, such as [a] addiction [b] tolerance [c] side-effects

Therefore, newer targets are required to treat pain without the liabilities associated with opioid analgesia.
University of Minnesota

- Leaders in pain research
- Leading NIH funded Cancer Center
- Leading Sickle research program
Leaders in research on pain


- **Interactions between cancer cells and peripheral nerves that lead to pain**: Donald Simone, PhD (Cain et al., J Neurosc 2001: 21:9367)

- **Pro-angiogenic signaling of morphine**: Kalpna Gupta, PhD (Gupta et al., Cancer Res 2012)

- **Understanding of sickle pain initiated**: Kalpna Gupta, PhD (Kohli et al., Blood 2010)
Morphine Signaling in Endothelium

OPIOIDS

GPCR

GTP Ras

VEGF-receptor (PTK)

PI-3Kinase

Akt

Apoptosis

NOS

NO

Cell cycle progression & survival

COX-2

MAPK

Cell proliferation

Angiogenesis


Cellular Basic studies
Are opioids ideal analgesics to treat chronic pain?


Based on Mouse Studies
Poorer outcomes in patients with greater opioid requirement and/or higher mu opioid receptor in the tumors


Research Goals/Vision

- Identify novel targets to treat pain
- Development of new drugs to treat chemotherapy induced neuropathy.
- Development of novel analgesics to treat pain without an inadvertent effect on disease progression.
- Development of drug delivery approaches to improve analgesia
- Does pain contribute to disease progression?
Weiblen laboratory at the University of Minnesota

Home to one of the only two academic laboratories to grow Cannabis with Federal permission

**Goal:** To produce new Cannabis varieties suitable for cultivation in the United States. This is important because presently all Cannabis plants containing >0.03% THC are considered schedule I controlled substances that cannot be cultivated without a DEA permit.

George Weiblen, PhD, Distinguished McKnight University Professor, Plant Biology Herbarium Curator, Bell Museum of Natural History, with Cannabis seeds in his laboratory.
Cannabinoids for analgesia and chemotherapy induced neuropathy

Iryna Khasabova, PhD

Donald A Simone, PhD
Murine model of bone cancer hyperalgesia

NCTC clone 2472 fibrosarcoma cells injected into and around calcaneous bone of C3H/He mice

Osteolysis of bone at PID 6

Little infiltration of inflammatory cells of the tumor site (Wacnik et al., 2005)

Phenotypic changes in nociceptors contributes to the mechanical hypersensitivity (Khasabova et al., J Neuroscience, 2007) and spontaneous nocifensive behavior
Does increasing AEA locally attenuate nociception in tumor-bearing mice?

Intraplantar injection of AEA

Reduces mechanical hypersensitivity and attenuates nocifensive behavior

The inhibitory effect was calculated:

\[
\left( \frac{(\text{PD lifting time} - \text{post-drug lifting time})}{(\text{PD lifting time} - \text{PT lifting time})} \right) \times 100\%
\]
Peripheral cannabinoids attenuate cancer pain

WIN 55,212-2 dose-dependently attenuates mechanical hyperalgesia in a murine model of cancer pain. Local injection of 2.5, 5, or 10 μg of WIN 55,212-2 into the tumor-bearing hindpaw reduced the mean paw withdrawal frequency evoked by a suprathreshold von Frey monofilament (3.4 mN). indicates a significant difference from vehicle ($p < 0.05$).

Potenzieri et al., 2008.
Cannabinoids decrease activity of nociceptors

ACEA attenuated responses of A-delta nociceptors in inflamed skin.

Vehicle, ACEA, or ACEA + AM251 was injected into the plantar skin.

Line above each trace is the time of mechanical stimulation (156 mN).

Potenzieri et al., 2008
Sickle Cell Disease

- Most widespread genetic disease which is on the rise
- Vasoocclusion: Sickle RBCs cluster together occluding blood vessels
- Vasculopathy: Endothelial dysfunction
- Inflammation: Cytokine storm and neuropeptides
- Hypoxia/reperfusion injury: following VOC
- Oxidative Stress: ROS
Sickle Cell Anemia: Molecular Basis

Courtesy, Robert P Hebbel MD
Normal Hemoglobin

Sickle Hemoglobin

Note: The Sickle hemoglobin image is drawn at 50% of the size of the Normal hemoglobin
Clinical Features of SCD

Pain: Chronic and acute

Nephropathy

Pulmonary hypertension

Stroke

Retinopathy

Priapism

Leg Ulcers

Reduced Survival
Pain in sickle cell disease

- Pain can start during infancy and increases in severity throughout life, reaching levels considered higher than labor pain during childbirth. Hence, sickle patients often require hospitalization and chronic opioids.

- Long-term opioid usage, however, creates a high risk of addiction, tolerance and side effects that pose a major obstacle for pain management.

- Recurrent episodes of crises and pain lead to increased hospitalization, poor quality of life, morbidity and mortality, resulting in reduced lifespan of patients with sickle cell disease.
Cannabinoids as potential analgesics to treat pain in SCD

- Cannabinoid receptors (CB1 & CB2) are located in the brain, nerve fibers & inflammatory cells in the periphery and CNS.
- Activation of peripheral cannabinoid receptors attenuates inflammatory & neuropathic pain.
- Since pain in sickle cell disease may have both inflammatory & neuropathic components, cannabinoids may provide pain relief.
- Cannabinoids can be used via oral, oro-mucosal, respiratory or systemic routes.
- Some preparations like Sativex, an oro-mucosal spray, are approved for clinical use in Canada & Europe.
Antidromic release from DRG may contribute to increased neuropeptides ion the periphery.
Neuromodulators

**CGRP**: Calcitonin gene-related peptide, a vasoactive peptide, upregulated in the peripheral nerves in inflammatory and neuropathic pain.

**SP**: substance P, pro-inflammatory and vasoactive peptide that is upregulated by central nociceptive activation in inflammatory and neuropathic pain.

**MOR**: mu opioid receptor, mediates opioid analgesia.
Mouse model

- **Sickle** (HbSS-BERK) and **Control** (HbAA-BERK) mice (Paszty et al., Science 1997): These mice show reduced mu opioid receptor expression and pain (Kohli et al, Blood 2010; Cain et al., Br J Hematol 2011).

- **Opioid receptor knockout mice**: deleted for mu, delta or kappa and wild type 129S6.
Substance P and CGRP are increased in the skin of sickle (BERK) mice

(Kohli et al. Blood, 2010)
Substance P and CGRP, mediators of pain are upregulated in the periphery (skin) via a centrally mediated mechanism in chronic pain.

(Editorial Commentary: New Era dawns on pain in sickle cell disease)

Red, SP

Blue, CGRP

Green, blood vessel

Kohli et al., Gupta laboratory
Blood 2010
Determination of deep tissue/ musculoskeletal pain using grip force

- Mice are held by the tail & made to pull on a wire grid
- Peak grip force exerted by the mouse is recorded

Lower grip force is indicative of increased pain
High dose of morphine is required to reduce hyperalgesia in sickle mice, but a relatively low dose of cannabinoids is effective.

\[(0.3 \text{ mg/Kg})\]

*Kohli et al. Blood, 2010*
Cannabinoid treatment ameliorates pain incited by hypoxia-reoxygenation in sickle mice

Cain et al., Br J Hematology 2011

Higher Grip Force = Less Pain
Cannabinoids as analgesics

- Cannabinoids offer a novel approach to treat chronic pain and hyperalgesia (Khasabova et al, 2008; Cheng & Hitchcock, 2007; Anand et al, 2009; Elikkottil et al, 2009; Kohli et al, 2010; Cain et al., 2011)

- Act via 2 main receptors: CB1-receptor (CB1-R) and CB2-receptor (CB2-R)

- Effective in treating pain in multiple sclerosis (Rog et al, 2007)
  Attenuate pain that persisted on opioids in cancer, fibromyalgia, and rheumatoid arthritis (Elikkottil et al, 2009; Johnson et al, 2010)

- Potential therapeutic option to protect organs from hypoxia/reperfusion injury (Fouad & Jresat, 2011; Gonzales et al, 2011), oxidative stress (Booz, 2011; Cassol et al, 2010) and inflammation (Ribeiro et al, 2012)
We therefore speculate that the use of cannabinoid receptor agonists may be beneficial in treating neurogenic inflammation and pain in SCD.

A retrospective study of Cannabis users showed that 52% of SCD patients reported decrease in pain, anxiety and depression.

Howard et al., Br J Hematology 2005
Proof of Principle Trial of cannabis to treat pain in SCD

University of Minnesota: Kalpna Gupta, PhD and John Connett, PhD
with UCSF: Donald Abrams, MD

ClinicalTrials.gov (identifier: NCT01771731).

Funded by NHLBI, UO1 HL117664 (Kalpna Gupta, Lead Principal Investigator)

Cannabis Provided by : NIDA
Vaporized Cannabis: 4.7% THC and 5.1% CBD
Cannabis Vaporizer
SCD: Study Design

1. Effect of 5-day treatment with vaporized Cannabis or Placebo on pain and other associated disorders (sleep, Anxiety, depression, etc) in patients with SCD.

2. Determine the short-term side effects associated with inhaled Cannabis treatment in association with opioids.

3. Examine the markers of pain, inflammation and disease progression.
From concept to realization

2010-2011: Gupta K, U of M, Efforts to obtain a license
2011: Approached Donald Abrams, UCSF
2012: Applied for funding to NHLBI, NIH
2012-2013: Grant competed in the top ranks but funding delayed until Sept 2013 due to Government issues.
7/19/2013: UCSF, CTSI approves the trial
7/23/2013: UCSF General Hospital; IRB approves the trial (approval number 13-10526).
11/7/2103: IND 119158 for the study agent, cannabis, was activated by the FDA on
11/14/2013: DEA form submitted
2/19/2014: DEA responds field investigation required
4/2014: Field investigation completed
May 2014: Research Advisory Panel of California, a regulatory body within the office of the state Attorney General that authorizes academic research involving Schedule I medications.
July 2014: Cannabis received from NIDA
Safety and efficacy of vaporized Cannabis

Vaporization is a safe mode of delivery: Physiologic THC levels are comparable
Expired carbon monoxide is decreased

Participants preferred vaporized Cannabis Vs smoked

Co-administration with opioids is safe and enhances analgesia in patients with chronic pain.

Abrams et al, Clin Pharm and Therap 2011
HIV-associated Neuropathy

- Smoked Cannabis effective in treating peripheral neuropathy
- Smoked Cannabis effective in attenuating central sensitization
- Effectiveness of smoked Cannabis comparable to trials with Gabapentin

Abrams et al., Neurology 2007
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 cannabinoidv 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/capsaicin 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
Review Article

Adverse Health Effects of Marijuana Use

Nora D. Volkow, M.D., Ruben D. Baler, Ph.D., Wilson M. Compton, M.D., and Susan R.B. Weiss, Ph.D.

N Engl J Med
Volume 370(23):2219-2227
June 5, 2014
Increases over Time in the Potency of Tetrahydrocannabinol (THC) in Marijuana and the Number of Emergency Department Visits Involving Marijuana, Cocaine, or Heroin.

Use of Marijuana in Relation to Perceived Risk and Daily Use of Tobacco Cigarettes or Marijuana among U.S. Students in Grade 12, 1975–2013.

Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

<table>
<thead>
<tr>
<th>Effects of short-term use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired short-term memory, making it difficult to learn and to retain information</td>
</tr>
<tr>
<td>Impaired motor coordination, interfering with driving skills and increasing the risk of injuries</td>
</tr>
<tr>
<td>Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases</td>
</tr>
<tr>
<td>In high doses, paranoia and psychosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects of long-term or heavy use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*</td>
</tr>
<tr>
<td>Altered brain development*</td>
</tr>
<tr>
<td>Poor educational outcome, with increased likelihood of dropping out of school*</td>
</tr>
<tr>
<td>Cognitive impairment, with lower IQ among those who were frequent users during adolescence*</td>
</tr>
<tr>
<td>Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
</tr>
<tr>
<td>Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders</td>
</tr>
</tbody>
</table>

* The effect is strongly associated with initial marijuana use early in adolescence.

# Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Medium</td>
</tr>
<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>

* The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.

### Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Primary Analysis Estimate (95% CI)</th>
<th>Secondary Analyses Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical cannabis law</td>
<td>-24.8 (-37.5 to -9.5)*</td>
<td>-31.0 (-42.2 to -17.6)f</td>
</tr>
<tr>
<td>Prescription drug monitoring program</td>
<td>3.7 (-12.7 to 23.3)</td>
<td>3.5 (-13.4 to 23.7)</td>
</tr>
<tr>
<td>Law requiring or allowing pharmacists to request patient identification</td>
<td>5.0 (-10.4 to 23.1)</td>
<td>4.1 (-11.4 to 22.5)</td>
</tr>
<tr>
<td>Increased state oversight of pain management clinics</td>
<td>-7.6 (-19.1 to 5.6)</td>
<td>-11.7 (-20.7 to -1.7)c</td>
</tr>
<tr>
<td>Annual state unemployment ratea</td>
<td>4.4 (-0.3 to 9.3)</td>
<td>5.2 (0.1 to 10.6)c</td>
</tr>
</tbody>
</table>

* All models adjusted for state and year (fixed effects).

b $R^2 = 0.876$.

c All intentional (suicide) overdose deaths were excluded from the dependent variable; opioid analgesic overdose mortality is therefore deaths that are unintentional or of undetermined intent. All covariates were the same as in the primary analysis; $R^2 = 0.873$.

d Findings include all heroin overdose deaths, even if no opioid analgesic was involved. All covariates were the same as in the primary analysis. $R^2 = 0.842$.

P ≤ .05.

f P ≤ .001.

g An association was calculated for a 1-percentage-point increase in the state unemployment rate.

### Figure Legend:

Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010
From: Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010


Figure Legend:
Association Between Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in Each Year After Implementation of Laws in the United States, 1999-2010Point estimate of the mean difference in the opioid analgesic overdose mortality rate in states with medical cannabis laws compared with states without such laws; whiskers indicate 95% CIs.
Multiple Sclerosis

Spasticity is one of the most common disabling symptoms associated with multiple sclerosis. The European working group EUPASM recently proposed the following definition for spasticity: “disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles”.

MS patient-level definition of spasticity: “an unusual tightening of muscles that feels like leg stiffness, jumping of legs, a repetitive bouncing of the foot, muscle cramping in the legs or arms, legs going out tight and straight or drawing up”
Largest pivotal study of Sativex, a Phase III placebo-controlled trial for MS in Spain

Out of ~571 patients only those who responded (20% reduction in mean spasticity score) to Sativex in the first 4 weeks were included (241 patients)

Garcia-Merino A et al., Expert Rev Neurother 13 (3 suppl) 9-13 (2013)
After 12 weeks of treatment Sativex was significantly superior to placebo for overall spasticity numerical rating scale scores ($p = 0.0002$), spasm frequency ($p = 0.005$), sleep disruption ($p < 0.0001$), Barthel Activities of Daily Living score ($p = 0.0067$), Physician Global Impression of Change score ($p = 0.005$), Subject Global Impression of Change score ($p = 0.023$) and Carer Global Impression of Change in Function score ($p = 0.005$).
“Even after more than 2 years of use, no new safety/tolerability signals have emerged with Sativex, including no evidence of driving impairment and no relevant incidence of falls or other adverse events of concern, such as psychiatric or nervous system events.

Sativex appears to be a well-tolerated and useful add-on therapy in patients who have not achieved an adequate response with traditional antispastic agents.”

Garcia-Merino A et al., Expert Rev Neurother 13 (3 suppl) 9-13 (2013)
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatments</th>
<th>Duration</th>
<th>Outcome</th>
<th>Toxicity</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechoulam and Carlini, (1978)²²</td>
<td>TRE –</td>
<td>3 months</td>
<td>CBD: 2 seizure free; 1 partial improvement; 1 no change</td>
<td>None</td>
<td>No baseline seizure frequency, no definition of improvement; unclear if AEDs were changed; small N/limited power; not truly randomized-blinded; unknown if groups were matched</td>
</tr>
<tr>
<td></td>
<td>CBD 200 mg/day (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TRE –</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo (5)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cunha et al. (1980)⁷³</td>
<td>TRE-TLE CBD (7)³²ab</td>
<td>200–300 mg/day for 3–18 weeks</td>
<td>Last visit: 4 CBD, 1 placebo</td>
<td>Somnolence</td>
<td>Not clearly blinded, since one patient transferred groups and doses were adjusted in CBD, but no mention of this in placebo group and CBD group received had longer average treatment</td>
</tr>
<tr>
<td></td>
<td>TRE-TLE Placebo (8)³²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ames and Cridland (1986)⁷⁴</td>
<td>IDD-TRE CBD (6)³²c</td>
<td>CBD 300/day × 1 week; 200/day × 3 weeks</td>
<td>No difference between CBD v. Placebo</td>
<td>Somnolence</td>
<td>This was a letter to the editor and details are lacking</td>
</tr>
<tr>
<td></td>
<td>IDD-TRE Placebo (6)³²</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>× 4 weeks</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tremblay and Sherman (1990)⁷⁵</td>
<td>TRE (10 or 12)³²</td>
<td>3 months baseline; 6 months placebo: Randomized to either 6 months placebo v. CBD 100 t.i.d.; then crossover for 6 months on alternative treatment</td>
<td>No change in seizure frequency or cognitive/behavioral tests</td>
<td>None</td>
<td>Only truly double blind study. Unclear why sample size differed in two reports. Data reported is incomplete</td>
</tr>
</tbody>
</table>

TRE, treatment-resistant epilepsy; TLE, temporal lobe epilepsy; IDD, intellectual/developmental disability.

³²Frequent convulsions for ≥1 year; – 1 GTCSz per week.

³³One patient transferred from placebo to treatment after 1 month.

³⁴12 subjects were divided into two groups, but distribution uncertain.

³⁵Abstract and subsequent book chapter have different N's (10 and 12).
Table 2. (A) Proposed molecular targets for plant cannabinoids investigated in animal models of seizure and (B) Cannabinoid efficacy in animal models of seizure and epilepsy

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Molecular target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ⁶-Tetrahydrocannabinol (Δ⁶-THC)</td>
<td>CB1R, CB2R, TRPV1, TRPV2</td>
</tr>
<tr>
<td>Δ⁶-Tetrahydrocannabinvarin (Δ⁶-THCV)</td>
<td>CBI, CB2, TRPV1, TRPV3, TRPV4</td>
</tr>
<tr>
<td>Cannabidiol (CBD)</td>
<td>ENT, GPR55, TRPV1, TRPV2, TRPV3, TRPA1, FAAH, TRPM8, adenosine, SHT1α</td>
</tr>
<tr>
<td>Cannabidivarin (CBDV)</td>
<td>TRPV4, DAGLα</td>
</tr>
<tr>
<td>Cannabinol (CBN)</td>
<td>CB1R, TRPV4, TRPA1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plant cannabinoid</th>
<th>Model</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ⁶-Tetrahydrocannabinol (Δ⁶-THC)</td>
<td>Generalized seizure (e.g., MES, PTZ, 6 Hz, 60 Hz, nicotine, and strychnine)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Temporal lobe epilepsy</td>
<td>Y</td>
</tr>
<tr>
<td>Synthetic CB1R agonists (e.g., WIN55-212)</td>
<td>Generalized seizure (MES, PTZ, amygdala kindling)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Partial seizure with secondary generalization (penicillin and maximal dentate gyrus activation)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Temporal lobe epilepsy</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Absence epilepsy (WAG/Rij)</td>
<td>Mixed effect</td>
</tr>
<tr>
<td>Synthetic CB1R antagonists (e.g., SR141716A)</td>
<td>Generalized seizure (MES and PTZ)</td>
<td>N⁹</td>
</tr>
<tr>
<td></td>
<td>Absence epilepsy (WAG/Rij)</td>
<td>N⁹</td>
</tr>
<tr>
<td></td>
<td>Partial seizures with secondary generalization (penicillin but not maximal dentate gyrus activation)</td>
<td>N⁹</td>
</tr>
<tr>
<td>Δ⁶-Tetrahydrocannabinvarin (Δ⁶-THCV)</td>
<td>Epileptogenesis (juvenile head trauma but not kainic acid)</td>
<td>Y</td>
</tr>
<tr>
<td>Cannabidiol (CBD)</td>
<td>Generalized seizure (MES, PTZ, 6 Hz, 60 Hz, picrotoxin, isonicotinic acid, bicuculline, hydrazine, limbic kindling (electrical), and strychnine but not 3-mercaptopropionic acid)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Temporal lobe convulsions/status epilepticus</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Partial seizures with secondary generalization (penicillin but not cobalt)</td>
<td>Y</td>
</tr>
<tr>
<td>Cannabidivarin (CBDV)</td>
<td>Generalized seizure (MES, PTZ, and audiogenic)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Temporal lobe convulsions/status epilepticus</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Partial seizures with secondary generalization (penicillin only)</td>
<td>Y</td>
</tr>
<tr>
<td>Cannabinol (CBN)</td>
<td>Generalized seizure (MES only)</td>
<td>Y</td>
</tr>
</tbody>
</table>

⁹Indicates a proconvulsant effect.
Cannabis derived medicines may be useful in many different ways

- As an adjunct to opioids
- In opioid-induced tolerance
  - For mood elevation?
- As an appetite stimulant
  - Relieving nausea
- To relieve stress
  - Sleep
Randomized controlled trials examining cannabinoids in treatment of chronic non-cancer pain

Lynch et al., Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

Br J Clin Pharmacol 2011
Treatment of a number of debilitating conditions. Some of these symptoms can be treated with Cannabis medications.

Therefore, evidence based review and regulatory oversight should be similar for cannabis and other medications prescribed by physicians.

Research and appropriately designed clinical trials.

Approval of these compounds by FDA.

Manufacturing following good practice standards and distributed by regulated pharmacies.
Dispensing via conventional and safe route of administration (oral pills or inhalation in quantifiable amounts)

Database to record outcomes of medical cannabis for objective assessment of individual and multiple symptom and pathological outcomes following informatics approaches in future.

Collaboration of a dedicated team of scientists, physicians, community participants, patient advocates, law makers and industry.

Funding and policies to facilitate fast-track research and medical use.
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Collaborators
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- George Weiblen, PhD
- Pankaj Gupta, MD
- Donald Abrams, MD (UCSF)

Members of Gupta Laboratory

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