The Science of Cannabinoids:
A Critical Review of Selected Literature

THERESE MALLICK-SEARLE, ANP-BC
Stanford University Medical Center/ Division Pain Medicine
Tmallick@stanfordmed.org
Disclosures
What American's Know About Science

• H2O is Hot Water, CO2 is Cold Water.

• Water is composed of two gins, oxygen and hydrogen. Oxygen is pure gin and Hydrogen is gin & water.

• Three kinds if blood vessels: arteries, veins and caterpillars.

• Gonads are a tribe of wondering desert people.

• How does one keep milk from turning sour, keep it in the cow.
Objectives

• Explore history of cannabinoids & current science.

• Objectively evaluate clinical applications of cannabinoids, supported by the research.

• Verbalize the limitations of scientific research on cannabinoids/delta-9-tetrahydrocannabinol (THC).
• <1000 B.C. early writings in the Far and Middle East note the use of cannabis for medicinal purposes.

• In 1545 the Spanish brought cannabis to the New World.

• The late 1800’s William Brooke O’Shaughnessy, an Irish physician was the first to introduce the use of medicinal marijuana into Western Medicine.

• Cannabis was listed in the United States Pharmacopeia from 1850 until 1942.
A campaign conducted in the 1930s by the U.S. Federal Bureau of Narcotics (now the Bureau of Narcotics and Dangerous Drugs) sought to portray marijuana as a powerful, addicting substance that would lead users into narcotics addiction.

1937 Marijuana Tax Act

The Controlled Substances Act of 1970

“The bad news is the Court outlawed medical marijuana. The good news is your cancer will likely kill you before the prescription morphine.”
The Compassionate Investigational New Drug Program (1978), federally sponsored program allowing a limited number of patients to use medical marijuana grown at the University of Mississippi.

Closed to new entrants (1992), there are only seven surviving patients who were grandfathered into the program.

2009 - Obama Administration stopped raids on MM dispensaries.

2011/2012 - Era of decreased tolerance and increased scrutiny on states MM laws.
2009 Attorney General Eric Holder said that the Justice Department will no longer raid medical marijuana clubs that are established legally under state law. Marking a major shift from the previous administration.

2011 U.S. Attorney General Eric Holder promised to clarify the Justice Department's position on state medical marijuana laws after federal prosecutors warned they might prosecute everyone from licensed growers to regulators.
August 29, 2013

Memorandum For All US Attorneys
From The Office of the Deputy Attorney General

Guidance Regarding Marijuana Enforcement

1) Preventing the distribution of marijuana to minors.
2) Preventing revenue from the sale of marijuana from going to criminal enterprises, gangs, or cartels.
3) Preventing the diversion of marijuana from states where it is legal under state law in some form to other states.
4) Preventing state-authorized marijuana activity from being used as a cover for our pretext for the trafficking of other illegal drugs or other illegal activity.
5) Preventing violence and the use of firearms in the cultivation and distribution of marijuana.
6) Preventing drugged driving and the exacerbation of other adverse public health consequences associated with marijuana use.
7) Preventing the growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands.
8) Preventing marijuana possession or use on federal property.
August 29, 2013
Memorandum For All US Attorneys
From The Office of the Deputy Attorney General
Guidance Regarding Marijuana Enforcement

"This memorandum does not alter in any way the Department's authority to enforce federal law, including federal laws relating to marijuana regardless of the state law."

"Finally, nothing herein precludes investigation or prosecution, even the absence of any one of the factors listed above, in particular circumstances were investigation and prosecution otherwise serves an important federal interest."

Veterans Administration Marijuana Policy

... pursuant of Federal Law, VA physicians, nurse practitioners, or other licensed clinicians are not authorized or permitted to participate in the recommendation for treatment of or prescribing medical marijuana to a VA patient.

... it is acknowledged that testing positive for marijuana in a patient, based upon random drug screening, will not serve as a breach of the current pain management agreement if the patient submits documentation in support of the marijuana being prescribed and dispensed in conformity with state law.

http://www.va.gov/vhapublications/viewpublication.asp?pub_id=2362
<table>
<thead>
<tr>
<th>States</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaska</td>
<td>1998</td>
</tr>
<tr>
<td>Arizona</td>
<td>2010</td>
</tr>
<tr>
<td>California</td>
<td>1996</td>
</tr>
<tr>
<td>Colorado</td>
<td>2000</td>
</tr>
<tr>
<td>Connecticut</td>
<td>2012</td>
</tr>
<tr>
<td>Delaware</td>
<td>2011</td>
</tr>
<tr>
<td>DC</td>
<td>2010</td>
</tr>
<tr>
<td>Hawaii</td>
<td>2000</td>
</tr>
<tr>
<td>Illinois</td>
<td>2013</td>
</tr>
<tr>
<td>Maine</td>
<td>1999</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>2012</td>
</tr>
<tr>
<td>Michigan</td>
<td>2008</td>
</tr>
<tr>
<td>Montana</td>
<td>2004</td>
</tr>
<tr>
<td>Nevada</td>
<td>2000</td>
</tr>
<tr>
<td>New Hampshire</td>
<td>2013</td>
</tr>
<tr>
<td>New Jersey</td>
<td>2010</td>
</tr>
<tr>
<td>New Mexico</td>
<td>2007</td>
</tr>
<tr>
<td>Oregon</td>
<td>1998</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>2006</td>
</tr>
<tr>
<td>Vermont</td>
<td>2004</td>
</tr>
<tr>
<td>Washington</td>
<td>1998</td>
</tr>
</tbody>
</table>

8 states with pending legislation or ballot measures to legalize medical marijuana:

- Kentucky
- Minnesota
- Missouri
- New York
- Ohio
- Pennsylvania
- Tennessee
- West Virginia

“If laughter is the best medicine, why won’t my insurance pay for marijuana?”

ProCon.org December 2013
"For states such as Colorado and Washington that have enacted laws to authorize the production, distribution and possession of marijuana, The Department expects these states to establish strict regulatory schemes that protect the eight federal interests identified in The Department’s guidance."
The cannabis plant contains more than 400 chemicals. Approximately 60 are called cannabinoids. Marijuana is a cannabinoid drug.

1964, Rafael Mechoulam discovered the chemical structure of the THC molecule.

- THC = delta-9-tetrahydrocannabinol
- CBD = cannabidiol
Mechanism of action

- 1988 discovery of the cannabinoid receptor site in the brain @St. Louis University Medical School (Howlett & Devane).

- High density of receptor sites in the CNS, account for the effects seen by (THC): euphoria, anxiety, anxiolysis, antinociception, cognitive disturbances, etc.
Mechanism of action

- CB₁ receptors: Expressed by central & peripheral neurons.
- CB₂ receptors: Expressed mostly by cells of the immune system.
HYPOTHALAMUS
Controls appetite, hormonal levels and sexual behavior

BASAL GANGLIA
Involved in motor control and planning, as well as the initiation and termination of action

AMYGDALA
Responsible for anxiety, emotion and fear

NEOCORTEX
Responsible for higher cognitive functions and the integration of sensory information

HIPPOCAMPUS
Important for memory and the learning of facts, sequences and places

CEREBELLUM
Center for motor control and coordination

BRAIN STEM AND SPINAL CORD
Important in the vomiting reflex and the sensation of pain
Endocannabinoid System/Simplified (?)

- The endocannabinoid system - endogenous, previously unknown neurotransmitter system, that modulate multiple systems throughout the body.

- Cannabinoid receptors, CB1 and CB2.


- The exposure to exogenous cannabinoids (THC, CBD), can have similar effects on these systems.

- Cognition and memory
- Appetite
- Stress response
- Inflammation
- Exploration, social behavior, & anxiety
- Immune/Endocrine function
- Autonomic nervous system
- Antinociception
Endocannabinoid System

- Discovery of the endocannabinoid system and cannabindiol (non-psychoactive cannabinoid), that has driven much of the current research on cannabinoids (1990s).

- The endocannabinoid system is present and has important physiological functions not only in the central nervous system but also in peripheral tissues.
Endocannabinoid System

• Our endocannabinoid system works to modulate the sensitivity of our brain to many of the other neurotransmitters that are present, such as dopamine and serotonin.

• Our experience of pain, especially from inflammation (the endocannabinoid system interacts with our endorphin system to reduce pain).

• Our response to stress (the entire stress response, from brain (hypothalamus) to endocrine glands (adrenal cortisol secretion) is regulated by the endocannabinoid system).

• Phytocannabinoids (THC, CBD) can bind to the cannabinoid receptor sites (CB1, CB2), and mimic the physiological processes seen with binding of the endocannabinoids (anandamide, 2-AG).

• Clinical Endocannabinoid Deficiency Syndrome (Russo, E. 2008).
http://youtu.be/QGKpbqXwg84

YouTube - Cannabinoid Receptors - Horizon: Cannabis - The Evil Weed
**Pharmacokinetics**

**delta-9-tetrahydrocannabinol**

* Highly lipophilic.
* THC psychoactive cannabinoid.
* Rapidly absorbed through lungs after inhalation, quickly reaching high serum concentration.
* Systemic bioavailability is ~23-27% for daily users, ~10-14% occasional users.
* Extensive liver (first pass) metabolism; cytochrome P450.
* >65% excreted in the feces, ~20% urine.
* t1/2 occasional users is 1-2 days, daily users up to 2 weeks.
Pharmacokinetics

delta-9-tetrahydrocannabinol

- Cannabinoids appear to effect the same reward systems as alcohol, cocaine and opioids.

- Evidence for cannabis dependence is now available from epidemiological studies of long-term users. (Miller & Plant 1996; Malhotra & Parthasarathy 2006)

- Tolerance to cannabis can occur in relation to mood, psychomotor performance, sleep, arterial pressure, body temperature and antiemetic properties.

- Symptoms such as irritability, anxiety, craving and disturb sleep have been reported in 60 to 90% of cannabis users during abstinence.

- Common adverse effects: blurred vision, dry mouth and eyes, tachycardia, hypo/hypertension, somnolence, urinary retention, cognitive dysfunction, hallucinations.
Forms and Preparations

- Herb 3-22% THC
- Hashish/Hash Oil 40-90% THC
- Synthetic:
  - Dronabinol (Marinol) CIII
  - Nabilone (Cesamet) CII
  - Nabiximols (Sativex)
Epidiolex is a liquid formulation of highly purified CBD extract, as a treatment for various pediatric epilepsy syndromes. In 2013, a total of seven expanded access INDs have been granted by the FDA to independent investigators to allow treatment of approximately 125 pediatric epilepsy patients with Epidiolex.

GW’s lead product, Sativex, is an oral spray which consists of a formulated extract of the cannabis sativa plant that contains the principal cannabinoids delta-9-tetrahydrocannabinol and cannabidiol. Current available in UK and Canada. In clinical trials in the US.

http://www.gwpharm.com/FAQ.aspx
Drug Interactions between Common Illicit Drugs and Prescription Therapies

Wesley LT, et. al. – Auburn University, AL.


Objective: Summarize the clinical literature on interactions between common illicit drugs and prescription therapies.

Findings:
The interactions of illicit drugs with prescription therapies have the ability to potentiate or attenuate the effects of both the illicit agent and/or the prescription therapeutic agent, which can lead to toxic effects or a reduction in the prescription agent’s therapeutic activity.
Cannabis to RX interactions

- Cannabinoid in pregnancy - Marinol category C.
- **Antibiotics** - no direct interaction.
- Cytochrome P450 - competitively inhibit the prescribed RX (e.g. warfarin, theophylline, antiretrovirals, protease inhibitors)
- **General anesthesia** - stop THC 2 weeks before.
- CNS depressants (benzodiazepines, opioids, other sedatives/hypnotics, ETOH) - potentiate the CNS depressant effects.
- Antidepressants, Antipsychotic & Atypical Antipsychotic Medications - depression, anxiety, mania, tachycardia, hypertension.
- Other (Lithium - increased serum lithium levels, Disulfiram (Antabuse) - hypomania, agitation, trouble sleeping, and irritability, Sildenafil - myocardial infarction).
Review of the literature

• 3 minute search of PubMed (research, THC, marijuana, cannabis, medicine, addiction, safety, endocannabinoid) = Results: >5k.

• Largest body of literature
  – Neurological & movement disorders: antispasmodic
  – Wasting syndromes (AIDS): appetite stimulation
  – Cancer: chemotherapy induced nausea/vomiting
  – Addiction & abuse potential, safety
  – Pain

Emerging Clinical Applications For Cannabis & Cannabinoids
A Review of the Recent Scientific Literature, 2000 — 2013
http://norml.org/component/zoo/category/recent-research-on-medical-marijuana
Research

- United States
  - Center for Medicinal Cannabis Research
  - National Center for Natural Products Research (NCNPR) at the University of Mississippi
  - National Institute on Drug Abuse (NIDA)
  - National Institutes of Health (NIH)
- Canada
  - Canadian Institutes of Health Research
- Europe
  - The Medicinal Cannabis Research Foundation (MCRF): a UK registered charity set up to promote and sponsor medicinal cannabis research and to raise public awareness
  - Spain, Germany, Italy
  - ICRS: http://www.cannabinoidsociety.org
  - Sanoti-Aventis, GW Pharmaceuticals, Pfizer
The center will be seen as a model resource for health policy planning by virtue of its close collaboration with federal, state, and academic entities.

To conduct randomized trials to compare the efficacy and safety of various methods of cannabis administration, in patients diagnosed with HIV/AIDS, cancer, seizures or muscle spasms associated with a chronic debilitating condition, or any other serious condition providing sufficient theoretical justification.
Clinical and Psychological Effects of Marijuana in Man

Clinical and Psychological Effects of Marijuana in Man

- Early attempts to investigate marijuana in a formal double-blinded study model.

- Few early studies involving human subjects in US/Internationally.

- It is also the first attempt to collect basic clinical and psychological information on the drug by observing its effects on marijuana-naive human subjects in a neutral laboratory setting.
Clinical and Psychological Effects of Marijuana in Man

Design: Single center, randomized, double-blind, placebo controlled.

N = 9 healthy male volunteers, 21-26 y/o, Daily tobacco smokers, marijuana naïve.
N = 8 healthy male volunteers, 21-26 y/o, chronic marijuana smokers.

All subjects smoked 2 standardized cigarettes per session. 
Naïve = placebo, low dose (4.5mg THC), high dose (18mg THC)
Experienced = placebo, high dose (18mg THC)

Randomized subjects 1 of 3 groups, all completing a series of 3 sessions (Naïve subjects required a 4th “practice session”).

- I High Placebo Low
- II Low High Placebo
- III Placebo Low High
Clinical and Psychological Effects of Marijuana in Man

**Physiological Parameters Measured**: heart rate, respiratory rate, pupil size, blood glucose level.

**The Psychological Tests**: Continuous Performance Test (CPT)-5 minutes, The Digit Symbol Substitution Test (DSST)-90 seconds, CPT with strobe light distraction-5 minutes, Self-rating bipolar mood scale-3 minutes, Pursuit rotor-10 minutes.

**Findings**:
- It is feasible and safe to study the effects of marijuana on human volunteers who smoke it in a laboratory.
- Marijuana increases heart rate moderately.
- No change in respiratory rate follows administration of marijuana by inhalation.
- No change in pupil size occurs in short term exposure to marijuana.
- Marijuana treatment produces no change in blood sugar levels.
- Regular users of marijuana do not show the same degree of impairment of performance on the tests as do naive subjects. In some cases, their performance even appears to improve slightly after smoking marijuana.
- In a neutral setting the physiological and psychological effects of a single, inhaled dose of marijuana appear to reach maximum intensity within 30 minutes of inhalation, to be diminished after 1 hour, and to be completely dissipated by 3 hours.
“I think it’s really dumb to grow cotton in Arizona, when growing hemp makes much more sense.”
The authors identified that cannabis use has been associated with a range of acute and chronic mental health problems such as anxiety, depression and neurocognitive alterations and deficits.

The question was to review structural abnormalities in the brain with chronic cannabis use and if there was a differentiation and age and chronicity.
Structural and Functional Imaging Studies in Chronic Cannabis Users: A Systematic Review of Adolescent and Adult Findings

Design:
Systematic review of published papers through August 2012, available scientific databases.

Identified:
one-hundred and forty two studies; 43 met criteria, 8 studies were in adolescent population.

Investigation:
1) Identify structural brain abnormalities fMRI.
2) Identify cognitive alterations (memory, decision making, motor fxn).
3) Age related changes, chronicity in exposure.
Structural and Functional Imaging Studies in Chronic Cannabis Users: A Systematic Review of Adolescent and Adult Findings

Findings:

1) Neuroimaging studies provided evidence of morphological brain alterations in both age populations, particularly in the medial temporal and frontal cortices, as well as cerebellum.

2) Hypothesized a relationship to amount of cannabis exposure, but did not find a direct correlation.

3) Different patterns of brain activity during the performance of several cognitive tasks in both age populations, compared with controls, which again were hypothesized to be related to chronic cannabis exposure.

4) Chronic cannabis use MAY alter brain structure and function in adult and adolescent populations.

5) The authors however point out certain methodological limitations of the work conducted to date and recommend further studies involving larger populations and considering the use of convergent methodology.
Surface maps showing brain regions with greater activation in marijuana users with positive urine for THC (THC+) than those with negative urine toxicology (THC−)
Both marijuana groups activate less within the normal attention network, especially in the dorsal parietal regions, right dorsal and inferior lateral PFC and the medial cerebellum (red regions).

Instead, the marijuana users activate more than non-drug users in several small brain regions outside the normal attention network (blue areas for the abstinent subjects and green for the active users).
The study found impaired structural integrity affecting the fibre tracts of the corpus callosum, suggesting the possibility that the structural abnormalities in the brain may underlie cognitive and behavioral consequences of long-term heavy marijuana use.

Another MRI study found that heavy cannabis users had an averaged 12 per cent volume reduction of the hippocampus, and a 7 per cent reduction of the amygdala compared to controls.
Neurochemical Basis of Cannabis Addiction

Maldonado, R., et al. – Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain


Review body of literature that explored the specific involvement of CB1 cannabinoid receptor in the addictive properties of cannabinoids, along with advancing the knowledge based related to the specific contributions of different neurochemical systems in cannabis addiction.

Findings:
1) CB1 cannabinoid receptors are responsible for all the addictive properties of cannabinoids.
2) Involvement of the CB2 receptors undetermined.
3) Dopaminergic, Opioid, & Cannabinoid systems are involved in the NC substrate of addiction.
4) NA, 5HT, GABA, GLU, Ach, Hormones = addiction
Schematic summary of the main neurochemical mechanisms involved in cannabis addiction.
**Diagnostic and Statistical Manual of Mental Disorders (DSM-5)**

**Marijuana** is an intoxicating substance, and it’s abuse and dependence.
- According to DSM-V, marijuana meets the criteria that can cause intoxication, abuse and dependence.
- Since 1960’s the psychoactive properties of its content which has increased as much as 100%.
- Alcohol & Opiates also meet criteria.

**Cannabis Withdrawal** - caused by “cessation of cannabis use that has been heavy and prolonged,” is characterized by at least three of these symptoms:
- irritability, anger or aggression, depressed mood
- nervousness or anxiety, restlessness
- sleep difficulties (insomnia)
- decreased appetite or weight loss
- physical symptoms (stomach pain, shakiness or tremors, sweating, fever, chills, and headache).
## Symptomatic relief in multiple sclerosis (MS) and other neurological effects

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zajicek, J., et al. (2003).</td>
<td>There was no significant benefit on the primary outcome variable, the Ashworth scale for spasticity. On the other hand, numerical rating scale (NRS) measures of spasticity, muscle spasms, pain and sleep, and an objective measure of mobility all showed a significant benefit of both active treatments compared with placebo.</td>
</tr>
<tr>
<td>Novotna et al. (2011).</td>
<td>A highly significant ($p = 0.0002$) benefit in spasticity score (NRS) was reported for Sativex® in comparison with placebo, along with significant improvements in spasm frequency, sleep disturbance and global impression of change. On the basis of the collective results, Sativex® was granted regulatory approval in the UK and Spain for the treatment of MS spasticity in 2010.</td>
</tr>
</tbody>
</table>

# Symptomatic relief of nausea and vomiting

**Study**


**Results**

The introduction of the serotonin 5-HT3 receptor antagonists in the 1990s completely transformed the treatment of severe nausea and vomiting. Cannabinoids are therefore no longer indicated for first-line treatment, and are now generally reserved for patients with non-responsive or breakthrough nausea and vomiting.

# Appetite Stimulation

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beal, J. et al. (1995)</td>
<td>Cannabis stimulates appetite and the same is well established to be the case with THC and other CB1R agonists, in AIDS patients.</td>
</tr>
<tr>
<td></td>
<td>A one-year follow-up trial showed that appetite improvements were well maintained with no increase in dose, and unwanted effects were well tolerated.</td>
</tr>
<tr>
<td>Beal, J. et al. (1997)</td>
<td>THC-containing medicines are also likely to prove helpful for other symptoms commonly experienced by AIDS patients including nausea, pain and insomnia.</td>
</tr>
</tbody>
</table>
The authors presented the following statement that "anti-neoplastic activity of THC and its analogues was first observed in the 1970s, prior to the discoveries of cannabinoid and endocannabinoid receptors".

Additionally they had identified that the more in-depth research on the subject was not pursued until the 1990s. Today cannabinoids present two well-established endocannabinoids: anandamide and 2-arachidonolyglycerol (2-AG).

The aim of the study was to review the available literature to discover the anti-tumor effects of cannabinoids on gliomas.
Systemic Review of the Literature on Clinical and Experimental Trials on the Antitumor Effects of Cannabinoids in Gliomas

Design:
Systematic review of the available literature through December 2012, searching the databases of the Cochrane Controlled Trials Register Group, PUBMED, LILACS and EMBASE.

Identified:
From >2000 initially identified articles, 35 fulfilled the inclusion criteria for this review.

Conclusions:
1) In all studies included, cannabinoids were shown to exert anti-tumor activity.
2) Anti-tumor evidence included: reduction in tumor size, antiangiogenic, anti metastatic effects.
3) Normal cells used as controls were not effected.
4) In vivo, the safety factor in cannabinoid administration was well established.
5) Cannabinoids are promising compounds in the treatment of gliomas.
The Endocannabinoid System, Cannabinoids, and Pain


Aim of the authors was to provide the reader with the foundational basic and clinical science linking the endocannabinoid system and the phytocannabinoids with their potentially therapeutic role in the management of chronic pain.

It may now be concluded that cannabinoids play a role in endogenous (homeostatic) modulation of nociception, and that exogenous cannabinoids potentially offer some degree of analgesia in various pain states.
The Endocannabinoid System, Cannabinoids, and Pain

Design:
Systematic review of the available scientific and medical literature through 2013.

Identified:
Studies with key words: cannabinoids, cannabinoid receptors, chronic pain, endocannabinoid system, and phytocannabinoids.
<table>
<thead>
<tr>
<th>Type of Pain and Condition (if described)</th>
<th>Number of Subjects</th>
<th>Cannabinoid Type, Preparation</th>
<th>Dosage and Route</th>
<th>Treatment Duration</th>
<th>Study Design</th>
<th>Results</th>
<th>Author, Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>50</td>
<td>Marijuana</td>
<td>3.56% THC, smoked 3 tid</td>
<td>5d</td>
<td>RCT</td>
<td>Significant pain reduction in active treatment group</td>
<td>Abrams et al.⁶⁷</td>
</tr>
<tr>
<td>Chronic NP pain</td>
<td>34</td>
<td>THC+CBD 1:1</td>
<td>Oral mucosal, variable dose</td>
<td>12 wks</td>
<td>RCT</td>
<td>Positive pain relief (not otherwise specified)</td>
<td>Notcutt et al.⁶⁸</td>
</tr>
<tr>
<td>Chronic NP pain</td>
<td>21</td>
<td>CT-3 (THC analogue)</td>
<td>Oral, 20 mg bid × 4d, then 40 mg bid × 3d</td>
<td>7d</td>
<td>RCT cross-over</td>
<td>Significant decrease in hyperalgesia, allodynia, and VAS pain intensity scores</td>
<td>Karst et al.⁶⁹</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>630</td>
<td>THC cannabis extract</td>
<td>Oral, variable dose</td>
<td>15 wks, with 52 wks continuation</td>
<td>RCT</td>
<td>Statistically significant reduction in pain scores and clinically meaningful sense of improvement</td>
<td>Zajicek et al.⁷⁰</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>24</td>
<td>Dronabinol</td>
<td>Oral, 10 mg</td>
<td>3 wks</td>
<td>RCT cross-over</td>
<td>Significant pain reduction with active treatment</td>
<td>Svendsen et al.⁷¹</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>137</td>
<td>THC+CBD 1:1 (Sativex™)</td>
<td>Oral mucosal, variable dose</td>
<td>10 wks controlled trial followed by 52 wks open label</td>
<td>RCT and open label</td>
<td>Significant pain reduction with active treatment; continued pain relief in about half of long-term use patients</td>
<td>Wade et al.⁷²</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>66</td>
<td>THC+CBD 1:1 (Sativex™)</td>
<td>Oral mucosal, variable dose</td>
<td>4 wks</td>
<td>RCT</td>
<td>Significant pain reduction with active treatment</td>
<td>Rog et al.⁷³</td>
</tr>
<tr>
<td>Chronic NP pain conditions</td>
<td>24 total: MS-18; BPI-1 SCI-4; PLP-1</td>
<td>THC+CBD 1:1 (Sativex™)</td>
<td>Oral mucosal, variable dose</td>
<td>2 wks</td>
<td>RCT cross-over</td>
<td>Significant pain reduction with active treatment</td>
<td>Wade et al.⁷⁴</td>
</tr>
<tr>
<td>Brachial plexus injury</td>
<td>48</td>
<td>THC+CBD 1:1 (Sativex™) vs THC vs placebo spray</td>
<td>Oral mucosal, variable dose</td>
<td>3 × 2-week treatment periods</td>
<td>RCT cross-over</td>
<td>Significant pain reduction with both active treatments</td>
<td>Berman et al.⁷⁵</td>
</tr>
<tr>
<td>Peripheral NP pain</td>
<td>125</td>
<td>THC+CBD 1:1 (Sativex™)</td>
<td>Oral mucosal, variable dose</td>
<td>5 wks controlled trial followed by 52 wks extension</td>
<td>RCT</td>
<td>Significant pain reduction with active treatment</td>
<td>Nurmiakko et al.⁷⁶</td>
</tr>
<tr>
<td>Inflammatory Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>58</td>
<td>THC+CBD 1:1 (Sativex™)</td>
<td>Oral mucosal, variable dose</td>
<td>5 wks</td>
<td>RCT</td>
<td>Significant pain reduction in active treatment group both at rest and with movement</td>
<td>Blake et al.⁷⁷</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Not specified</td>
<td>HU-210 (synthetic CB₁ and CB₂ agonst)</td>
<td>Oral</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Significant pain reduction</td>
<td>Michalski et al.⁷⁸</td>
</tr>
</tbody>
</table>
Conclusions:

1) The phytocannabinoids have efficacy in the treatment of various chronic pain conditions with greatest promise as a therapeutic adjunct in treating peripheral and central neuropathic pain, and inflammation-mediated chronic pain.

2) The smoked route of administration and the psychoactive activity of THC with associated concerns about abuse and long-term cognitive adverse effects continue to pose a serious barrier to acceptance and use.

3) A formidable barrier to oral bioavailability resides in the pharmacokinetics of naturally occurring and synthetic cannabinoids. Phytocannabinoids are metabolized rapidly in the liver, undergoing extensive hepatic first pass metabolism.

4) The future of cannabinoid use in chronic pain relies on the development of orally administered, highly bioavailable, non-psychoactive phytocannabinoid products.
Cannabinoid–Opioid Interaction in Chronic Pain


Study Design and Results

• Twenty-one individuals with chronic pain, who took twice-daily doses of sustained-release morphine or oxycodone, were enrolled in the study and admitted for a five-day inpatient stay.

• Participants were asked to inhale vaporized cannabis (marijuana) in the evening of day one, three times a day on days two through four, and in the morning of day five. Blood sampling was performed at 12-hour intervals on days one and five. Chronic pain levels were assessed daily.

• Investigators found that there was no significant change in the area under the plasma concentration–time curves for either morphine or oxycodone after exposure to cannabis. In fact, the morphine levels were slightly lower with cannabis.

• What is really interesting is that despite opioid levels being the same or lower with cannabis, patients experienced greater pain relief, reporting an average of 27 percent less pain.

• The researchers concluded, “that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.”
Final Thoughts

- Endocannabinoid system vital regulation many body systems.
- Effects of exogenous cannabinoids.
- CBD v/s THC safety, efficacy, addiction.
- Stigma, legality.
- Education/counseling.
- Drug to drug interactions.
- Keep abreast of the literature.
Stanford Division Pain Medicine

Thank You