Tetrahydrocannabinol ("THC")

Tetrahydrocannabinol ("THC, THC, Delt-9, Marijuana") is one of the two most extensively studied phyto-cannabinoids found in the Cannabis Sativa plant ("cannabis").

- THC is a naturally occurring phyto-cannabinoid constituent of cannabis
- THC is being used today in medicine for a variety of physical & mental health conditions
- THC is psychoactive & is the phyto-cannabinoid that makes people "high"
- THC can affect one's decision making & impairs ability to drive/operate heavy machinery
- Medicinal THC is legal in 39 states - South Carolina is not one of them

THC Therapies:

US healthcare started to incorporate THC therapies 30+ years ago & in 1996 AZ & CA were the first pass medical THC legislation. THC has been touted to support a wide variety of health issues, but strongest evidence is for its effectiveness in treating chronic pain, inflammation, anxiety, & addiction.

Medical THC is most widely used for chronic pain management & inflammation, especially when other therapies are exhausted. Therapeutic examples include the management of chronic conditions such as multiple sclerosis, Parkinson's, IBS, Crohn's, cancer, fibromyalgia, endometriosis, & others where the final common pathway is chronic pain.

According to Harvard Med School (www.health.harvard.edu) it is safer than opiates as one cannot overdose & it is far less addictive. Whether in states where THC is legal or illegal, combined data from studies suggests patients are replacing opioids with THC despite THC is not FDA approved.

How Does THC Work:

THC works in the body through the Endocannabinoid System ("ECS"). ECS was discovered in the 90's when researchers set out to study a series of plant-like molecules produced by the human body.

ECS is an important physiological system that is involved in almost every aspect of our moment-to-moment functioning. ECS plays a major role in "balancing" many important functions such as memory, processing, sleep, temp control, pain control, inflammatory & immune responses, as well as eating.

ECS involves three core components: cannabinoids, receptors, & enzymes.

1. Endocannabinoids & Phyto-Cannabinoids:

Cannabinoids are naturally occurring chemical compounds produced by the human body as well as found in specific plants. Cannabinoids are segmented in two main categories:

- Endocannabinoids, also called endogenous cannabinoids, are molecules made by your body
- Phyto-cannabinoids are molecules found in the Cannabis Sativa plant

Examples of endogenous cannabinoids (endocannabinoids) include n-arachidonoyl dopamine (NADA), 2-arachidonoylglycerol (2-AG), anandamide (AEA), & virodhamine (OAE).

The most well-known examples of phyto-cannabinoids are tetrahydrocannabinol (THC) & cannabidiol (CBD). There are 100+ known phyto-cannabinoids, with 100's more expected to be identified over time.

Both cannabinoids operate differently compared to other neurotransmitters like serotonin or dopamine. Endocannabinoids are not synthesized in advance & stored; rather, produced on demand as needed. Phyto-cannabinoids, when introduced in the body, supplement endocannabinoids.

Endocannabinoids & phyto-cannabinoids are the "fuel" that helps keep internal functions within the body running smoothly. This "fuel" is delivered through the ECS via endocannabinoid receptors.

2. Endocannabinoid Receptors:

Endocannabinoid receptors are found throughout your body. Endocannabinoids bind to these receptors to signal the ECS to take action. There are two main endocannabinoid receptors:

- CB1 receptors, which are mostly found in the central nervous system
- CB2 receptors, which are mostly found in your peripheral nervous system

Receptors are activated by the examples of endocannabinoids listed above. Using phyto-cannabinoids, such as THC, in addition to naturally occurring endocannabinoids help boost receptor activity.

When receptors are activated, endocannabinoids & phyto-cannabinoids bind to either receptor listed above. When receptors are activated specific enzymes in the body are key to the binding process.

3. Enzymes

Enzymes are responsible for breaking down endocannabinoids & phyto-cannabinoids during the binding process. There are two main enzymes responsible for this:

- Fatty acid amide hydrolase (FAAH), which breaks down anandamide (AEA)
- Fatty acid binding proteins (FABP), which bind to anandamide & transport the enzyme outside the synapse to be broken down & metabolized by the FAAH

The effects that result from the binding process depends on where the receptor is located within the body & which endocannabinoid or phyto-cannabinoid it binds to.

THC within the Endocannabinoid System

THC mediates its biological effects through binding to CB1 & CB2 receptors. Because cannabinoid receptors are in so many parts of the brain & body, the effects of THC are wide-ranging.

AEA is considered the "bliss molecule" & plays an important role in the generation of pleasure & motivation. THC is similar in structure & mimics AEA. During the binding process, increased concentration of THC & AEA is the direct action that creates a positive effect on the ECS.

Being a partial rather than a full agonist of CB1, THC demonstrates lower cytotoxicity compared with synthetics and consequently has a better safety profile.

How to Take THC:

THC forms include topicals, oils, extracts, capsules, patches, vapes, & smokables. Topical & smokable are the most fast acting way to use THC & should be used at healthcare professional's direction.

Where to Get THC:

South Carolina patients are currently purchasing THC from illegal sources or traveling to a State where THC is sold legally (however, transporting THC back to South Carolina is illegal).

Adverse Reactions/Side Effects:

According to the Mayo Clinic (www.mayoclinic.org), medical THC use is generally considered safe; however, different strains have different amounts of THC making dosing marijuana difficult.

THC use directly affects the brain, specifically the parts of the brain responsible for memory, learning, attention, decision-making, coordination, emotion, & reaction time. Infants, children, & teens (who still have developing brains) are especially susceptible to the adverse effects of THC.

THC impairs attention, judgement & coordination. Side effects are mild to moderate & resolve quickly - but severe side effects can occur. Common side effects are dizziness, fatigue, light- headedness, drowsiness, & nausea. More severe side effects can cause high blood pressure or other cardiovascular issues. If used frequently, THC might increase risk of depression or worsen depression symptoms.

If a patient has a mental health condition, THC use may worsen manic symptoms in people who have bipolar disorder & risk of psychosis in people who have schizophrenia.

THC has a depressant effect. As a result, THC in combination with anesthesia or other drugs used during or after surgery might cause an additive effect. Stop THC use two weeks before planned surgery.

Interactions:

Possible interactions include:

- Anticoagulants & anti-platelet drugs - THC may reduce blood clotting or increase risk of bleeding
- CNS depressants - THC may increase sedative effect of these drugs
- Protease inhibitors - When used with antiviral drugs, THC might reduce effectiveness
- Selective serotonin reuptake inhibitors - Mixing THC with these may increase risk of mania

Tetrahydrocannabinol ("THC") Research

THC has & continues to be studied for its role in addressing symptoms of many health conditions. Ongoing research is helping to clarify the specific way that THC impacts the Endocannabinoid System & what these interactions mean in terms of the overall influence on our health & wellness.

Some of the most established data comes from pre-clinical studies of autoimmune diseases, specifically rheumatoid arthritis & multiple sclerosis. Other common studies center on oncologic patients as palliative medicines due to their analgesic & anti-emetic effects. Funding has precipitously increased for studies focused on whether or not THC therapies are replacing opioid-based pain medication & conventional pain medications.

Federal law makes THC illegal & this has severely limited research funding. Research funding in the US, Canada, & the UK has totaled $1.56B from 2000 to 2018. Overwhelming majority of $'s spent required trials to study harms of THC. Over $1B came from US National Institute on Drug Abuse, which earmarked disproportionate amount of $'s to research THC's negative effects rather than its positive therapies.

This is changing as universities are allowed to perform studies where THC has been legalized at the state level. Below are examples of autoimmune disease & PTSD related studies. Subsequent page covers opioid-based studies.

Examples of Completed Studies:

CCRC: The Analgesic Effect of Vaporized Cannabis on Neuropathic Pain

Sponsor: University of California, Davis
Responsible Party: University of California, Davis
Collaborators:
Center for Medicinal Cannabis Research
VA Northern California Health Care System
Primary Trial ID - 200614658
Secondary IDs – C06-DA-119
ClinicalTrials.gov ID - NCT01037088
Published: National Library of Medicine
Publish Date: January 31, 2018
DOI: 10.1016/j.jpain.2012.10.009

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	44 participants
Interventional Model:	Crossover Assignment
Allocation:	Randomized
Study Parameters:	Double-blind, placebo-controlled, crossover study evaluating the analgesic efficacy of vaporized THC in subjects, the majority of whom were experiencing neuropathic pain despite traditional treatment. Patients with central and peripheral neuropathic pain underwent a standardized procedure for inhaling of medium-dose (3.53% THC by weight), low-dose (1.29% THC by weight), or placebo THC with the primary outcome being visual analog scale pain intensity. Psychoactive side effects and neuropsychological performance were also evaluated.
Official Title:	CCRC: The Analgesic Effect of Vaporized Cannabis on Neuropathic Pain
Actual Study Start Date :	December 2009
Actual Primary Completion Date :	November 2012
Actual Study Completion Date :	November 2012

Initial Results:

Mixed-effects regression models demonstrated an analgesic response to vaporized cannabis.

Cannabis NNT scores were comparable to those of traditional neuropathic pain medications.

Cannabis has analgesic efficacy with the low dose being as effective a pain reliever as the medium dose.

Psychoactive effects were minimal and well tolerated

Conclusion:

Vaporized cannabis, even at low doses, may present an effective option for patients with treatment-resistant neuropathic pain.

Placebo-Controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans With Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)

Sponsor: Multidisciplinary Association for Psychedelic Studies
Responsible Party: Multidisciplinary Association for Psychedelic Studies
Collaborator: Scottsdale Research Institute
Primary Trial ID - 33730032
Secondary IDs – MJP-1
ClinicalTrials.gov ID - NCT02759185
Published: National Library of Medicine
Publish Date: September 16, 2021
DOI: 10.1371/journal.pone.0246990

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	76 participants
Interventional Model:	Cohort
Allocation:	Randomized
Study Parameters:	Pilot study gathered preliminary evidence of the safety & efficacy of four potencies of smoked cannabis to manage chronic, treatment-resistant PTSD among veterans. Study will produce preliminary evidence to help elucidate the potential effects of THC, CBD, or a combination of both constituents to reduce PTSD symptoms. Primary objective to compare three active concentrations of 1.8g of smoked cannabis & placebo per day on PTSD symptom severity measured by CAPS-5 severity scores.
Official Title:	Placebo-Controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans With Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)
Actual Study Start Date :	January 2, 2017
Actual Primary Completion Date :	January 2019
Actual Study Completion Date :	January 2019

Initial Results:

This double-blind, cross-over study found that all treatment groups, including placebo, showed good tolerability & significant improvements in PTSD symptoms during three weeks of treatment.

Conclusion:

This preliminary trial shows the need for additional well-controlled and adequately powered studies with cannabis suitable for FDA drug development.

Examples of THC & Opioid-Based Studies:

In recent years, under increasing pressure the emergent problem of opiate dependency, THC research has started to provide evidence & ongoing trials showing THC therapies are replacing opioid-based pain medication & other similar conventional pain medications.

In the US, various studies were performed in states that had medical cannabis legislation passed within 3-year period or more. In comparing these studies, existing literature displays similar conclusions despite the lack of controlled clinical trials.

Similarly, recent analyses of prescription data from Medicare Part D enrollees in states with medical access to THC suggest a significant reduction in prescribing conventional pain medications.

- In Florida – 2020 FSU College of Medicine study reported 60.9% of participants used pain medications prior to using medical THC, **93.3% of these participants reported a change in pain medication after medical THC** (DOI: https://doi.org/10.1080/10826084.2022.2107673)
- In Delaware – 2020 Delaware Dept. of Health study displayed a 10% decrease in Rx rates for long-acting opioids & a **20% decrease in the prescribing rates for high-dose opioids** (DOI:10.7759/cureus.20240)
- *In New Hampshire* – 2019 Dartmouth-Hitchcock Medical Center study demonstrated **reduced daily opiate use**, as well as fewer hospital admissions & **fewer emergency department visits**. *(DOI: https://doi.org/10.1016/j.cgh.2019.01.018)*
- Multiple States – 2018 U. or Georgia analysis of Medicare Part D records from 2010 through 2015 found prescriptions filled for all **opioids decreased by 2.11 million daily doses per year** from an average of 23.08 million daily doses per year when a state instituted any medical cannabis law (medical or recreational). Prescriptions for **all opioids decreased by 3.742 million daily doses per year when medical THC dispensaries opened**. (DOI: 10.1001/jamainternmed.2018.0266)
- *In New Mexico* – 2017 University of New Mexico, Department of Psychology study found statistically significant **47% reduction in daily opioid use** compared to an increase in the comparison group. *(DOI: https://doi.org/10.1371/journal.pone.0187795)*
- *In Michigan* – 2016 U. of Michigan study found **64% reduction in opioid use** as well as an improved quality of life. *(DOI: https://doi.org/10.1016/j.jpain.2016.03.002)*
- In Canada – 2014 study lead by U. of Victoria & Centre for Addictions Research found **63% substitute for prescription drugs, 30% for opioids**, 16% benzodiazepines, & 12% antidepressants. *(DOI: https://doi.org/10.1016/j.drugpo.2017.01.011)*

While many studies have shown medical cannabis can help patients decrease their opioid usage, some have found no material evidence.

- In Australia – 2018 Australian National Health & Medical Research Council study from participants with cannabis use presented **no evidence of a reduction in prescription opiate use**. (DOI: https://doi.org/10.1016/S2468-2667(18)30110-5)

Medical Cannabis Patients Report Improvements in Health Functioning and Reductions in Opiate Use

Sponsor: Emerald Coast Research
Responsible Party: Carolyn E. Pritchett, PhD
Collaborator: Florida State University College of Medicine
Published: Taylor & Francis Group
Publish Date: 27 Sep 2022
DOI: 10.1080/10826084.2022.2107673

Study Type :	**Survey**
Actual Enrollment :	2,209 participants
Observational Model:	Cross-sectional survey (patient reported)
Allocation:	Dosage & method of delivery varied due to physician recommendation. Patient use varied greatly among the respondents. The majority reported using medical cannabis daily. Reported use of all OBPM was below 7.5% of patients after beginning medical cannabis use
Study Parameters:	Aims of study were to (1) characterize the demographics & use patterns of participants who had physician-approved medical cannabis access, (2) provide information on patient perceptions of changes in health functioning after initiation of medical cannabis use & (3) examine participant perceptions of the effects of medical cannabis access on their use of opioid-based pain medication
Actual Study Start Date :	August 2015
Actual Primary Completion Date :	October 2018

Results:

- 90.59% reported medical cannabis was helpful when dealing with their medical condition
- 68.72% reported at least one side effect
- 88.67% reported improved quality of life
- 60.98% reported using pain medications prior to medical cannabis
- 93.36% of these reported a change in pain medication after medical cannabis
- At time of the study, Florida reported opioid prescriptions rates slightly higher than the US avg & it was lowest rate reported in Florida since 2006

Conclusions:

Use of opiate based pain medication may be reduced, or even ceased, in patients with chronic pain.

Initiation of medical cannabis laws could lead to public health changes through the potential opioid-sparing effects of medical cannabis without worsening health functioning.