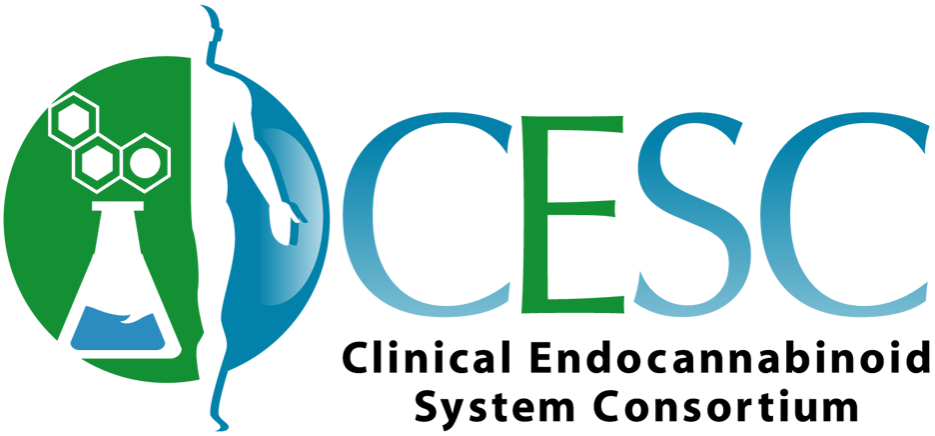
Report on Cannabidiol: Considerations for use in wellness and in treatment of specific illness

December 2018



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Introduction

Cannabidiol (CBD) is a phytocannabinoid. It is one of a group of chemical compounds that are natural constituents of the *Cannabis Sativa* plant. CBD is normally found in the plant in its acid form, Cannabidiolic acid. It is the sibling chemical of THC, as they are both produced from Cannabigerolic acid (CBGA). Although they share similar structure and origin, CBD is different from THC in several ways. The difference of greatest social importance is that CBD produces no psychoactive euphoria or anxiety. These are well known effects of THC. In recent years, CBD has gained popularity with the political unveiling of *Cannabis Sativa*. After 80 years of prohibition, *Cannabis Sativa* is being accepted on a worldwide scale for medicinal and general consumption. As a consequence, investigations into CBD's effects have begun. There is much to learn about CBD. Particularly, studies are necessary on best presentation and dosage per indication. At this point, we know CBD is not causing serious adverse effect. Thus, from a safety standpoint, it is acceptable for general consumption. *In vitro* and *in vivo* animal studies identify a broad spectrum of activity including anti-epileptic, anti-inflammatory, analgesic, anxiolytic, neuroprotective, anti-tumor and sleep inducing effects. Although CBD shows a wide spectrum of activity, its potency is uncertain. This is due to its poor bioavailability and variable metabolism. It is likely through general consumption and observational study that we will learn the most. What's certain is that CBD is now exposed and will be exploited for multiple purposes and in multiple ways.

Plant Classification

- Cannabaceae – Family
  - *Cannabis Sativa*
    - Marijuana – "drug-type", "flower-type"
      - Sativa – long thin leaves
      - Indica – short broad leaves
      - Ruderalis – less than 2 feet tall plant, auto-flowering
    - Hemp – "fiber-type"
  - *Humulus*
    - Hops
  - *Celtis*
    - Hackberries

Cannabis Sativa is the botanical name for a plant with multiple names such as marijuana, hemp, weed, and "Mary Jane". It produces a wide range of cultivars. These cultivars are scientifically categorized into two types, "fiber type" or "flower/drug" type. The distinction is made more evident in that fiber type is generally grown for clothing, food or other industrial uses while flower or drug type has been historically been grown for its THC content. The plant produces oil that contains a class of chemicals known as phytocannabinoids, which include THC and CBD. Recently flower or drug type cultivars have been selected and grown for their higher content of CBD. The phytocannabinoids are originally in their acid form, THCA or CBDA. The acid form converts to THC or CBD through various processes.

Cannabis Sativa

Fiber Type

Flower or "Drug" Type

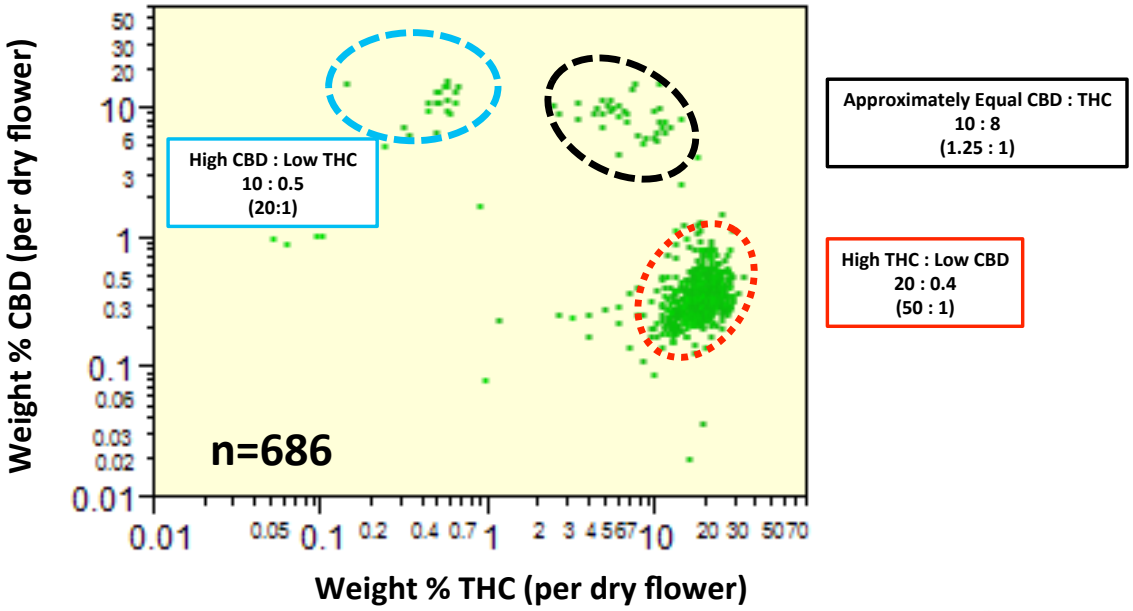
Hemp *def.* THCA + THC < 0.3%

Hemp is defined in the scientific community as **"fiber type"** *Cannabis Sativa*. However, legal authorities have also categorized hemp by the total percentage of potential psychoactive constituents, THC and THCA. Hemp is defined as the sum of THCA+THC in the plant to be less than 0.3%. The total amount of phytocannabinoids found in the fiber type hemp is typically less than 5% as opposed to the flower or drug type, which will produce a much higher percentage of phytocannabinoids by weight. One study concluded that the genetic loci which produce the enzymes that catalyze THC or CBD are not associated with the genetic determination of fiber or flower type[1] Presumably, some fiber type hemp plants may have a higher ratio of THC and others a higher ratio of CBD. If a farmer's intention were to grow fiber type for CBD, they would be prudent to cultivate the appropriate high CBD fiber type cultivar.

The graph below shows data from the certificates of analysis of over 600 **flower type** *Cannabis Sativa* plants. When weight of THC and CBD is analyzed in logarithmic scale the values cluster intp three groups. The red circle identifies a cluster of high THC/low CBD plants; the blue circle identifies a high CBD/low THC cluster; and the black circle identifies a clustered one to one ratio. The flowers sampled for this analysis were all of the flower or drug type. Note that the percentage of THC or CBD will reach as high as 20% or more. As well, it is clear that some flower type cultivars produce a higher ration of CBD (blue circle). The decision of which cultivar, fiber type of flower type, is the best source of CBD for manufacturing should follow consideration of manufacturing practices and legality as the end product, CBD, would be the same in either.

1 Sawler J, et al. *The Genetic Structure of Marijuana and Hemp*. PLoS One 2015; 10(8):

Scatterplot: Cannabis Flower Samples – CBD vs THC



CESC
Clinical Endocannabinoid System Consortium

The Endocannabinoid System

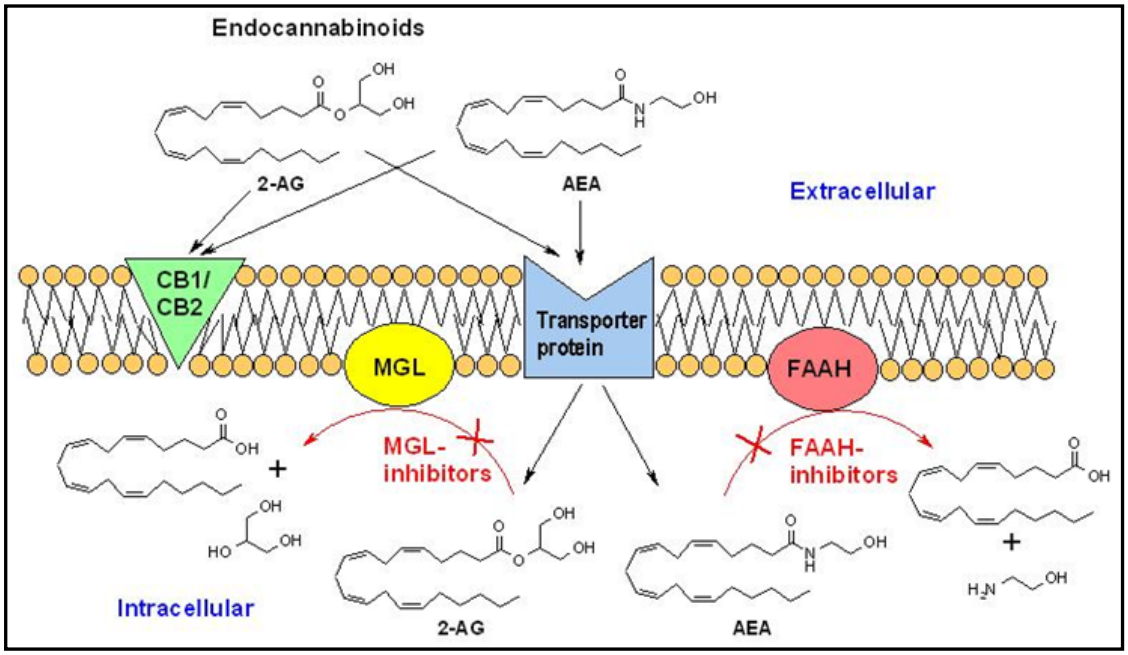
The Endocannabinoid System represents a link between neurological and immunological systems in the human or animal model. It is partially defined by cannabinoid receptors found in the brain, peripheral nerves and immune tissue. Endocannabinoid system receptors are in every organ of the human body. The system was first discovered and named in 1988, by Dr. Raphael Mechoulam. The cannabinoid receptors are G-protein coupled receptors containing seven trans-membrane domains connected by three intracellular loops, three extracellular loops, an extracellular N-terminal tail and an intracellular C- terminal tail. Internal lipophilic molecules called endocannabinoids attach to the receptors and produce specific reactions that influence pain, inflammation, mood, memory, sleep and appetite. There is also evidence that the Endocannabinoid system protects nerves and promotes cancer cell death. Their affinity for THC binding as well as the affinity of endocannabinoids Anandamide (AEA) and 2-Arachidonoylglycerol (2-AG) define the receptors. G-protein coupled receptors are often described as “locks” and the ligands that attach to them, “keys”. These receptor types are well known to be promiscuous. As such, there exists multiple “keys” that fit one “lock” or one “key” that fits many “locks”. One might categorize the ligands (keys) that fit into cannabinoid receptors into three groups; *endocannabinoids*, *phytocannabinoids* and *synthetic cannabinoids*

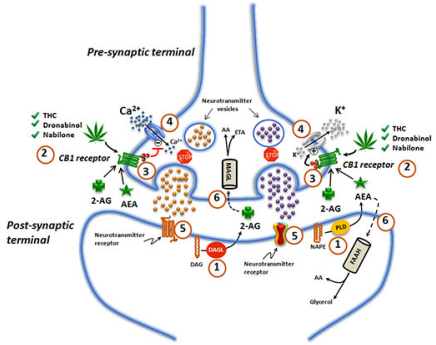
Cannabinoid Receptors

- **CB_1 (CnR1)** – distributed in human brain tissue and currently understood as the densest receptor in the brain. Found peripherally in lower concentrations. Found on enteric nerves, which likely mediate GI effects. Also mediates the brainstem (i.e. control of vomiting.)

- **CB_2 (CnR2)**– mostly found on immune cells in all organ tissue. Involved in anti-inflammatory activity

Endocannabinoids - internally produced cannabinoid molecules that bind to CB_1 and CB_2 cannabinoid receptors





Endocannabinoids set off a series of intracellular reactions feed back to the extracellular space and establish a "tone" that can be depicted as the **idle to a car engine.** As such, **THC** is like **fuel** to the engine and **CBD** is like **oil** to the engine.

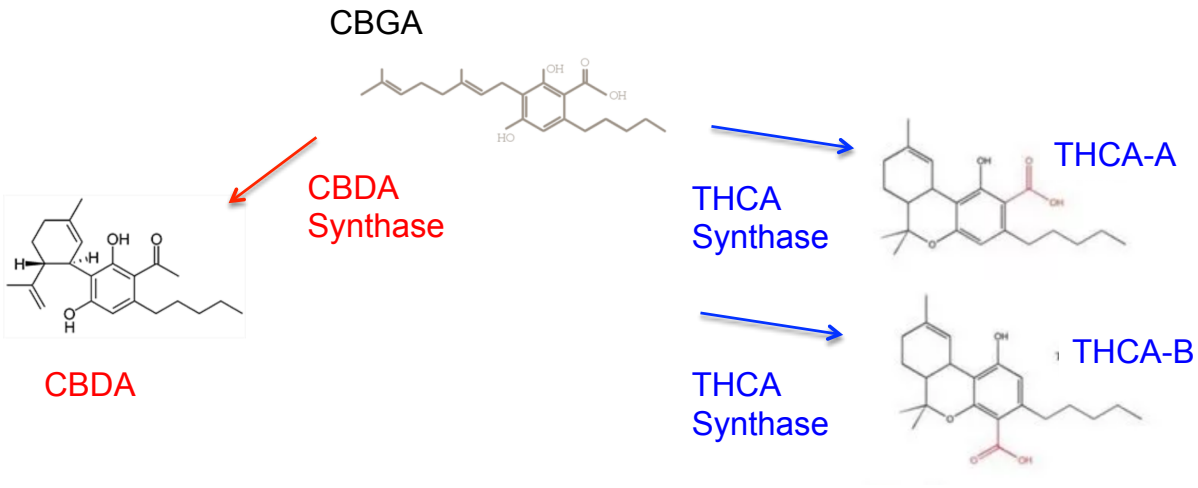
Molecular Reactions of the Endocannabinoid System in a nerve cell

1. Endocannabinoids (AEA, 2-AG) are manufactured in the post synaptic terminal – Phospholipase D and Diacyl glycerol lipase
2. Endocannabinoids are transported across post-synaptic membrane and diffuse in retrograde fashion toward pre-synaptic membrane to attach to CB1 receptor
3. Activation of CB1 receptor causes release of G proteins, inhibits adenylyl cyclase, decrease cAMP and activity of protein kinase A
4. Release of G protein (activation of CB1 receptor) causes opening of K+ Channels (hyperpolarization) and a closing of Ca+ Channels. Results in arresting the release of GABA, Glutamate, 5HT, acetylcholine, norepinephrine, dopamine, D-aspartate, cholecystokinin
5. These neurotransmitters, once released, will bind to post synaptic receptors and trigger the influx of AEA and 2-AG and the metabolism by FAAH and MAGL

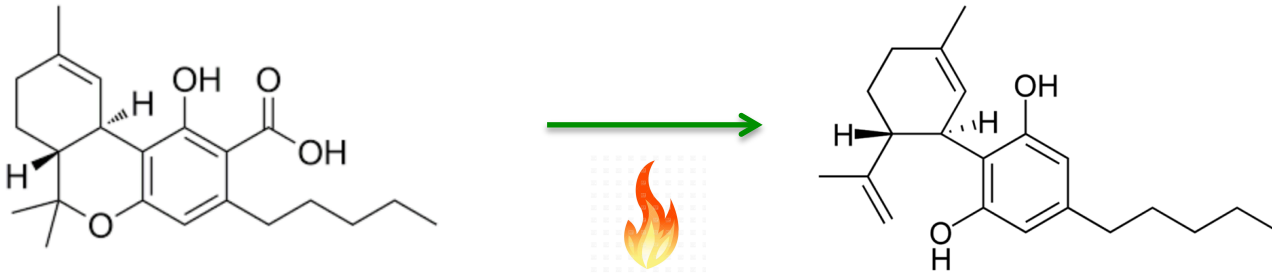
Phytocannabinoids

Cannabis Sativa contains 489 distinct compounds distributed over 18 chemical classes including more than 70 phytocannabinoids

- Phytocannabinoids are produced in the plant through an *enzymatic reaction*



Cannabigerolic acid (CBGA) is the precursor molecule to either THCA or CBDA. The Cannabis sativa plant genetically produces either enzyme THCA synthase (blue) or CBDA synthase (red) that with maturity catalyzes CBGA to either THCA or CBDA. Once the fiber type of flower type plant is harvested, CBDA can be converted with heat to CBD through a process called **decarboxylation**



Cannabidiol (CBD)

Description

Appearance: colorless crystalline solid
Insoluble in water; soluble in ethanol and DMSO
Molecular Formula: $C_{21}H_{30}O_2$
Molecular Weight: 314.469 g/mole
Melting Point: 62-63°C
Boiling Point: 160-180°C

In most clinical studies, CBD is administered orally as either a capsule, or as an oral oil-based solution (e.g. olive or sesame oil). Due to its lipophilic nature, it is typically incorporated in an oil base. It is also presented in forms to be inhaled, taken sublingually, intravenously or administered through intranasal routes.

Mechanisms of Action

CBD has sixty-five known molecular targets. These targets are all potential mechanisms of action. The actual mechanism of action is likely grouped through inter-related activity initiated from multiple molecular targets. As such, the synergy of multiple biochemical pathways is likely causing the effect of CBD. Although CBD performs as a concert of multiple actions, the nature of science is to deconstruct and understand the activity of each molecular target individually. Listed in the table below are a selected few molecular targets and evidence of the effect of CBD on each.

Receptor	Serotonin 5HT1A	Vanilloid TRPV1	Adenosine A2a	GPR55	PPAR γ	FAAH Inhibition
Agonist	✔	✔	✔		✔	
Antagonist				✔		
Receptor Independent						✔
Regulates	Anxiety Sleep Appetite	Pain Inflammation Body temperature Blood flow	Neuro-protective Movement Inflammation	Seizures Cancer Bone Density	Neuro-protective inflammation	Anandamide

Not CB_1 or CB_2 - Research has demonstrated *poor* affinity of cannabidiol (CBD) to either CB_1 or CB_2 receptors. [2] There is also evidence that CBD is not psycho active and reduces the psycho-activity of THC.[3] This effect is generally attributed to the low CBD affinity to CB_1 receptors.

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[2] Pertwee, R G et al, The diverse CB_1 and CB_2 receptor pharmacology of three plant cannabinoids: Δ^9 tetrahydrocannabinol, cannabidiol and Δ^9 tetrahydrocannabivarin. Br. J of Pharmacology 2008 Jan; 153(2); 199-215

[3] Casajuana Kogel, et al, Psychoactive constituents of cannabis and their clinical

5HT1A – This receptor is well known as a serotonin receptor. Animal models of stress show attenuation of acute and delayed stress responses by CBD and its activity on the 5HT1A receptor.[4] Animal studies such as the forced swimming test (FST), the elevated plus maze (EPM), and the Vogel conflict test (VCT) demonstrated both an anti-anxiety and anti-depressant effect of CBD.[5]

$TRPV_1$ – Transient Receptor Potential (TRP) are characterized as cell membrane pores that when activated by ligand allow the influx of ions into cells. They exist as multiple subtypes including Ankyrin (TRPA) and Vanilloid (TRPV). Capsaicin acts a ligand to the TRPV1 receptor and activates the receptor to transmit the pain associated with chili pepper. Regular use of capsaicin desensitizes the receptor and reduces pain. CBD has affinity for the TRPV1 receptor and has demonstrated a reduction of pain in an animal pain model.[6]

Adenosine A2a – Adenosine receptors are involved in coronary blood floor and cardiac muscle oxygen consumption. Adenosine is internally produced as well as synthetically produced as a medication that slows an overly rapid heart rate. Adenosine receptors are also found to release dopamine and glutamate neurotransmitters in the forebrain creating a sedative like affect. Caffeine antagonizes the adenosine receptor resulting in increases in heart rate and a stimulant effect. CBD's affinity for the adenosine receptor likely contributes to CBD's sedative like effects. It has also been demonstrated that CBD produces an anti-inflammatory effect and neuro-protective effect via Adenosine receptors.[7]

GPR55 – GPR55 is a recently discovered (1999) G-coupled receptor that was proposed as cannabinoid receptor CB_3 due to the affinity of multiple endocannabinoids and phytocannabinoids to its receptor. GPR55 is found throughout the central nervous system and proposed to be involved in pain, cancer, and drug addiction.[8] CBD antagonizes the effect of THC on this receptor similar to CB_1 and CB_2. Current known mechanisms of action through the GPR55 receptor only highlight the complexity of the endocannabinoid system and have not resulted in clear clinical applications.

$PPAR_\gamma$ – The peroxisome proliferator-activated receptor is involved in lipid storage and glucose metabolism. CBD, in particular, shows moderate affinity for the receptor.[9] As well, CBD has demonstrated reduction of β- Amyloid deposits in mice and an anti-

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[4] Restell, L B et al, 5-HT_{1A} receptors are involved in the cannabidiol-induced attenuation of behavioral and cardiovascular responses to acute restraint stress in rats. Br. J of Pharmacology 2009 Jan; 156(1); 181-88

[5] De Mello Schier AR et al, Anti-depressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of Cannabis sativa. CNS Neurol Disord Drug Targets: 2014; 13(6); 953-60

[6] Costa B et al, Vanilloid $TRPV_1$ receptor mediates the anti-hyperalgesic effect of the non-psychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. Br. J of Pharmacology 2004 Sep; 143(2); 247-50

[7] Bih, C I et al, Molecular Targets of Cannabidiol in Neurological Disorders, Neurotherapeutics 2015 Oct; 12(4); 699-730

[8] Ryberg E et al, The orphan receptor GPR55 is a novel cannabinoid receptor. Br. J of Pharmacology 2007 Dec; 152(7); 1092-101

[9] Sun Y et al, Cannabinoids: A New Group of Agonists of PPARs, PPAR Research 2007 Nov 15;

inflammatory effect in the gut both mediated by PPAR. [10] This effect may have clinical significance in Alzheimer's and Inflammatory Bowel Diseases

FAAH Inhibition – Fatty Acid Amide Hydrolase is an intracellular enzyme that breaks down the endocannabinoid anandamide. It has been noted that CBD effects FAAH, but in conflicting ways. One study on cells *in vitro* identified an inhibition of FAAH and thus an increase in Anandamide.[11] Another study demonstrated an *in vivo* and *in vitro* increase in FAAH at similar concentrations. [12]

Conclusion:

Mechanism of action of CBD is multi-focal and its potency depends on the intended therapeutic indication. The molecular target that best represents an indication can be selected to ascertain the potency of a specific CBD formulation. For example, if reduction of pain is the desired indication, CBD affinity at either of the TRP receptors might represent a good model for CBD potency against pain. In this instance, the potency of CBD containing products would be defined through receptor bioassay. CBD's broad spectrum of activity might make it an ideal agent for general wellness formulas.

Pharmacodynamics and Pharmacokinetics

First Pass Effect

Ingested CBD products go through a normal digestive process. This includes a first pass effect through the liver prior to CBD and its metabolites circulating through the blood stream. The liver contains a group of enzymes called Cytochrome P450 that metabolize CBD. Specifically, subtypes CYP2C19 and CYP3A4 enzymes; and UGT1A7, UGT1A9, and UGT2B7 isoforms metabolize CBD.

Metabolites

6-OH-CBD
7-OH-CBD
7-COOH-CBD
CBD 7-oic acid

½ life

Intravenous - 18-33 hours
Inhaled - 27-35 hours
Oral - 2-5 days

Bioavailability

Oral – 6%
Inhaled - 31%

Maximum Concentration

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[10] De Felippis et al, Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. PLoS One 6; 2011, e28159

[11] De Petrocellis et al, Effect of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br. J of Pharmacology 2011; 163; 1479-1494

[12] Massi P et al, 5-Lipoxygenase and anandamide hydrolase (FAAH) mediate the anti-tumor activity of cannabidiol, and non-psychoactive cannabinoid. J Neurochemistry 2008; 104;

Time to maximum (TMax) concentration in blood plasma after oral ingestion = 2-5 hours
High calorie/high fat meals increase max concentration by 5-fold and AUC by 4-fold

Indications and Usage

Overview of diseases for which CBD may have therapeutic benefits[13]

Disease	Effects
Alzheimer's Disease	Anti-inflammatory, antioxidant, anti-apoptotic in *in vitro* and *in vivo* models of β amyloid evoked neuroinflammatory and neurodegenerative processes
Parkinson's Disease	Attenuation of dopaminergic impairment *in vivo*; neuroprotection; improvement of psychiatric rating and reduction of agitation, nightmare and aggressive behavior in patients
Multiple Sclerosis	Improvement of experimental autoimmune encephalomyelitis in mice, anti-inflammatory and immunomodulatory properties
Huntington's Disease	Neuroprotective and anti-oxidant in mice transgenic models, no clinical improvement in patients
Hypoxia-ischemia injury	Short-term neuroprotective effects; inhibition of excitotoxicity, oxidative stress and inflammation *in vivo* and in rat models
Pain	Analgesic effect in patients with neuropathic pain resistant to other treatments
Psychosis	Attenuation of the behavioral and glial changes in animal models of schizophrenia; anti-psychotic properties on ketamine induced symptoms
Anxiety	Reduction of muscular tension, restlessness, fatigue, problems in concentration; improvement in social interaction in rodent models of anxiety and stress; reduced social anxiety in patients
Depression	Anti-depressant effect in genetic rodent model of depression
Cancer	Anti-proliferative and anti-invasive effect in a large range of cancer types; induction of autophagy mediated cancer cell death; chemopreventive effects
Nausea	Suppression of nausea and conditioned gasping in rats
Inflammatory Disease	Anti-inflammatory properties in several *in vitro* and *in vivo* models; inhibition of inflammatory cytokines and pathways
Rheumatoid Arthritis	Inhibition of TNFα in an animal model
Inflammatory bowel and Crohn's Disease	Inhibition of macrophage recruitment and TNFα secretion *in vivo* and *ex vivo*; reduction in disease activity in Crohn's patients

13. Pisanti S et al. Cannabidiol: State of the art and new challenges for therapeutic

Cardiovascular Disease	Reduced infarct size through anti-oxidant and anti-inflammatory properties *in vitro* and *in vivo*
Diabetic Complications	Attenuation of fibrosis and myocardial dysfunction
Infection	Activity against methicillin-resistant *Staphylococcus aureus*
Drug Addiction	Pre-clinical evidence that has therapeutic effect on alcohol, opiate, cocaine and psychostimulant addiction; clinical evidence that it may be beneficial in cannabis and tobacco addiction[14]

Presentation, Dosage and Administration

CBD has been isolated to its pure form as a crystalline powder. It can also present in the dried cannabis flower at up to 20% by weight. The oil of a high percentage CBD flower can be extracted by various methods and placed in capsules or blended with another liquid. CBD has been incorporated into beverages and food products. As well, it is presented in topical lotions or salves. A wide range of oral CBD doses has been reported in the literature. Most studied doses range from 100 - 800mg/day.[15]

Experimental Study in healthy humans

N	CBD dose	Outcome
9	100 mg oral	No effect[16]
5	30 mg intravenous	No effect
10	200 mg oral	No effect[17]
11	300 mg oral	Sedation and decreased cortisol level[18]
11	600 mg oral	Sedation and decreased cortisol level
10	300 mg oral	Reduced anxiety in speech test[19]
10	400 mg oral	Reduced anxiety and increased sedation[20]
15	600 mg oral	Reduced anxiety[21]

Clinical Study in patient populations

N	CBD dose	Diagnosis	Outcome
15	700 mg	Huntington's Disease	No changes in chorea movement

[14] Prud'homme M et al, Cannabidiol as an intervention for addictive behaviors: as systematic review of the evidence. Substance Abuse: Research and Treatment 2015; 9; 33

[15] Fasinu P S et al, Current Status and Prospects for Cannabidiol Preparations as New Therapeutic Targets. Pharmacotherapy 2016; 36(7); 781-96

[16] Hollister LE, Cannabidiol and cannabinol in man. Experientia 1973; 29, 825-6

[17] Consroe P et al, Interaction of cannabidiol and alcohol in humans. Psychopharmacology 1979; 66; 45-50

[18] Zuardi AW et al, Effects of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers. Braz. J. Med. Biol. Res. 1993; 26; 213-17

[19] Zuardi AW et al, Effects of ipsapirone and cannabidiol on human experimental anxiety. Journal of Psychopharmacology 1993; 7; 82-88

[20] Crippa JA et al, Effect of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology 2004; 29; 4127-426

[21] Zhornitsky et al, Cannabidiol in Humans: The Quest for Therapeutic Targets

15	40 mg	Insomnia	Increased dream recall[22]
	80 mg	Insomnia	Increased dream recall
	160 mg	Insomnia	Increased dream recall and sleep duration
8	200-300 mg	Epilepsy	Reduced seizures[23]
10	400 mg	Social Anxiety Disorder	Reduced anxiety[24]
12	600 mg	Social Anxiety Disorder	Reduced anxiety[25]
21	600 mg	Schizophrenia	Improved symptoms[26]
3	1280 mg	Schizophrenia	No effect[27]
2	1280 mg	Bipolar Disorder	No effect[28]

Conclusion:

Ingested CBD has low bioavailability (6%). Studies with CBD have been performed at higher doses of CBD then are generally presented in the market place. In developing a product, manufacturers should investigate formulas that improve bioavailability. As well, they should consider multiple routes of administration.

Adverse Effects

A comprehensive review of 132 studies by Bermaschi et al concludes that chronic use of CBD and doses up to 1500 mg per day are well tolerated by humans.[29] Of note, catalepsy was not induced; heart rate, blood pressure and body temperature were not altered. As well, there is no evidence of psychological and psychomotor dysfunction and no internal cellular toxicity. Despite the apparent safety of CBD, the safety profile of cannabis continues to be controversial due to variability in study methodology.[30] Below is a table listing multiple clinical trials and noting their adverse effects.

Patient	CBD Dose/Day	Duration	Adverse Effects
Healthy Volunteers	10 mg	12 days	No Serious Adverse Effects[31]
Healthy Volunteers	3 mg/kg	30 days	No Serious Adverse Effects

[22] Carlini EA et al, Hypnotic and anti-epileptic effects of cannabidiol. Journal of Clinical Pharmacology 1981; 21; 417S-427S

[23] Cunha JM et al, Chronic administration of cannabidiol to healthy volunteers and epileptic patients. 1980; 21; 175-185

[24] Crippa JA et al, Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized anxiety disorder: A preliminary report. *Journal of Psychopharmacology* 2011; 25, 121-130

[25] Bergamaschi MM et al, Cannabidiol reduces the anxiety induced by simulated public speaking in treatment naïve social phobia patients. *Neuropsychopharmacology* 2011; 36; 1219-1226

[26] Leweke FM et al, Antipsychotic effects of cannabidiol. Eur Psychiatry 2009; 24; S207

[27] Zuardi AW et al, Cannabidiol monotherapy for treatment resistant schizophrenia. *Journal of Psychopharmacology* 2006; 20; 683-6

[28] Zuardi AW et al, Cannabidiol was ineffective for manic episode of bi-polar affective disorder. *Journal of Psychopharmacology* 2010; 24; 135-7

[29] Bergmaschi MM et al, Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Current Drug Safety 2011*; 6(4); 1-13

[30] Iffland K et al, An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. Cannabis and Cannabinoid Research 2017; 21; 139-154

[31] Mincis M et al, Chronic administration of cannabidiol in man: A pilot study. *AMB Rev. Assoc*

Parkinson's Disease	150 mg-400 mg	4 weeks	No Serious Adverse Effects including cognitive and motor effects[32]
Schizophrenia	200 mg - 800 mg	28 days	No Serious Adverse Effects[33]
Bipolar Disorder	600 mg - 1200 mg	24 days	No Serious Adverse Effects
Epilepsy	200 mg - 300 mg	135 days	No Serious Adverse Effects
Epilepsy	10-25 mg/kg	3 month	No Serious Adverse Effects – reduced appetite/weight loss, increased appetite/weight gain, tiredness
Epilepsy	10-25 mg/kg	1 year	Tiredness 21%, Diarrhea 17%, Reduced appetite 16% – Status Epilepticus (n=10), Diarrhea (n=3), Weight Loss (n=2), Elevated liver transaminase (n=1)
Epilepsy	25-50 mg/kg	1 year	Somnolence 25%, Decreased appetite 19%, Diarrhea 19%
Parkinson's Disease	75 and 300 mg	6 weeks	No Serious Adverse Effects[34]
Huntington's Disease	10 mg/kg versus placebo	6 weeks	No Serious Adverse Effects in either group[35]
Leukemia with transplant of hematopoietic cells	300 mg/kg	37 days	No Serious Adverse Effects[36]
Type 2 Diabetes – non-insulin treated	200 mg versus placebo	13 weeks	No Serious Adverse Effects

Conclusion:

Cannabidiol displays no serious adverse effects throughout a wide range of doses and in studies up to one-year duration. Clinical studies on epilepsy reveal somnolence, diarrhea, and weight loss at doses of 10 mg/kg - 50 mg/kg. As well, one patient had an increase in liver transaminases and ten patients experienced status epilepticus. It is uncertain whether these adverse effects were due to cannabidiol. Likely, the events are due to the originating diagnosis. The epilepsy studies were open label. Additionally confounding the data is the understanding that patients were taking up to 3 other anti-epileptic medications during the trial.

Drug Interactions

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[32] Zuardi AW et al, Cannabidiol for the treatment of psychosis in Parkinson's disease. *J of Psychopharmacology* 2009; 3; 979-983

[33] Leweke et al, Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2012; 2; e94

[34] Chagas MHN et al, Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double blind trial. *J of Psychopharmcology* 2014; 28; 1088-98

[35] Consroe P et al, Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Beh* 1991; 40; 701-708

[36] Yeshurun M et al, Cannabidiol for the prevention of graft-versus-host disease after allogeneic hematopoietic cell transplantation results of a phase II study. *Biol Blood Marrow*

The liver through a first pass effect metabolizes drugs via a family of enzymes called Cytochrome P450. There is evidence that CBD both induces and inhibits Cytochrome P450 enzymes thereby affecting the concentration and bioavailability of concomitantly administered medications. However, the studies were performed with supra-physiological concentrations in order to demonstrate the inhibitory effect. It is likely that very little inhibitory action occurs, as very large doses of CBD would be required to achieve the simulated *in vitro* effects. Other studies have demonstrated that CBD influences its own metabolism when it is repeatedly administrated. Thus, over time, CBD stimulates the production of mRNA, which is responsible for the synthesis of multiple Cytochrome P450 enzymes and metabolism of itself. *In vitro* studies have demonstrated that CBD inhibits Cytochrome P450 subtypes CYP1A2, CYP2B6, CYP2C9, CYP2D6 and CYP3A4. CBD inhibits CYP2C9. CYP2C9 metabolizes omeprazole, risperidone, warfarin and diclofenac and thus the use of CBD would presumably increase plasma concentration of these medications. CBD also induces CYP1A1, which is responsible for degradation of carcinogenic substances such as benzopyrene. This may be an additional mechanism by which CBD produces an anti-cancer effect. Medications can influence Cytochrome P450 subtypes and thus influence the metabolism of CBD. Anti-fungal drugs ketoconazole and itraconazole, anti-viral ritonavir and antibiotic clarithromycin inhibit subtype CYP3A4 and thus increase plasma concentrations of CBD. Anti-epileptic drugs phenytoin and carbamazepine induce CYP3A4 and thus reduce plasma concentration of ingested CBD. CBD is not alone, as sixty percent of prescribed drugs are metabolized via enzymatic subtype CYP3A4. Evidently the metabolism of CBD and other medications is complex. The recommended clinical approach is to monitor drug levels or their therapeutic effects and adverse effects in order to avoid unwanted outcomes. As well, the consumer should understand that the dose might have varying effects based on the individual's distribution of metabolic enzyme subtypes.

Use in Specific Populations

Pain

Pain was identified as the chief complaint in 52.2% for emergency department visits in one study.[37] As well, approximately thirty percent of family practice visits are for pain.[38] A cross sectional study of CBD users by Dr. Jamie Corroon reported that over sixty percent use CBD for pain.[39] However, very few double blind, placebo controlled clinical trials for pain have been performed with CBD alone. Most have been performed with a combination of CBD and THC or THC alone. CBD's multiple mechanisms of action make it an ideal consideration for treatment of pain. In particular, its activity on $TRPA_1$ and $TRPV_1$ receptors may be the main mechanisms of action on pain. As well, the associated activity on the Adenosine $A2_a$ and $PPAR_\gamma$ receptors reduces inflammation, which contributes to pain. Finally, its anxiolytic effect via 5HT1A receptors might improve mood during pain. Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[40] It involves multiple disciplines, which include neurology and mental health. It's complexity calls for a complex solution. CBD may very well be that solution.

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[37] Cordell WH et al, The high prevalence of pain in emergency medical care. *American Journal of Emergency Medicine* 2002 May; 20(3); 165-169

[38] Hasselstrom J et al, Prevalence of pain in general practice. *European Journal of Pain* 2002; 6(5); 375-385

[39] Corroon J et al, A Cross-Sectional Study of CBD Users. *Cannabis and Cannabinoid Research* 2018; 3(1); 152-161

Stress

Anecdotal claims of CBD improving stress are common. Two molecular targets, the 5HT1A receptor and FAAH inhibition, identify potential mechanisms of action. Clinical trials on CBD show benefit in acute situations, such as social anxiety when provoked to make speech or fear extinction when confronted with fearful situations.[41] However, there are no clinical studies yet on regular CBD use for chronic anxiety disorders. This includes long-term studies on the affect of CBD on the anxiogenic properties of THC. Nevertheless, there is enough evidence to suggest that regular CBD use should likely have a stress reducing effect on certain populations.

Insomnia

Generally, medical cannabis users use CBD during the day because it doesn't create a psychoactive effect or induce somnolence, yet it still addresses pain and stress. As well, in low doses it tends not to appear to induce somnolence. Clinical study in patient populations with insomnia did not observe an increase sleep duration at doses of 40 mg or 80 mg, but did observe an increase at a dose of 160 mg. As well, it may be that lower doses are effective in patients with stress or anxiety, which results in improved sleep.

Wellness

On April 23, 2018, Allison Aubrey of NPR's morning addition discusses the CBD as growing in popularity due to its non-psychoactive effect combined with some observations that it reduces anxiety and pain. On July 17, 2018, Nicole Catanese describes CBD as a "hot topic" and an "emerging wellness trend" in US Weekly. Finally, Alex Williams of the New York Times chimes in with his October 27, 2018 article titled, "Why is CBD everywhere?" The American Institute of Stress reports three quarters of the population experiencing either physical or emotional symptoms from stress and one third of the population experiences extreme stress. Low doses of CBD (2.5 mg to 25 mg) are presented in the market in beverages, foods, as a pain relieving ointment and in skin care products. The combination of an anti-anxiety, anti-inflammatory and pain reliever with fairly benign safety profile makes CBD a popular consideration for general well being.

Polypharmacy in the Elderly

Polypharmacy is a known concern in the elderly. It is defined as the use of more prescribed drugs than are medically necessary. One study indicates that over 50% of older adults take one or more medicines that are not necessary.[42] The burden of taking multiple medicines has been associated with greater health care costs, an increased risk of adverse events, drug interactions, medication non-compliance and multiple geriatric syndromes. The elderly population is subject to increased falls, more hospitalizations and cognitive impairment with polypharmacy. CBD improves pain, inflammation, mood and sleep. As such, it is a potential substitute for multiple medications. In a June 2018 article, the AARP stated that baby boomers are fueling the popularity of CBD. In October 2018, Alex Williams of the New York Times explains that celebrities like Willie Nelson have promoted and invested in the use of CBD. As well, Dr. Sunjay Gupta, former surgeon general recently endorsed CBD on "The Dr. Oz Show". CBD seems to be a natural solution to the polypharmacy issues in the elderly. However, CBD manufacturers still need to surmount the hurdle of batch-to-batch consistency and physicians lack sufficient clinical studies to support CBD as the solution for over prescribed medication.

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[41] Blessing E et al, Cannabidiol as a Potential Treatment for Anxiety Disorders. *Neurotherapeutics* 2015 Oct; 12(4); 825-836

[42] Maher RL et al, Clinical Consequences of Polypharmacy in the Elderly. *Expert Opinion Drug*

Epilepsy

The first FDA approved CBD medication, Epidiolex, a GW Pharmaceuticals product was approved for Epilepsy. Epidiolex was approved for Dravet's Syndrome and Lennox-Gastaut Syndrome, rare conditions of intractable seizures in the pediatric population. A 2018 review in the British Medical Journal of 555 participants with epilepsy reported that over fifty percent experienced a reduction in seizures.[43] The participants were mostly pediatric and conclusions were made that a broader age range should be studied.

Autism

Autism or Autism Spectrum Disorder (ASD) refers to a broad range of conditions characterized by difficulty with social skills, repetitive behaviors, and communication. There are no current approved medicines for Autism. Medication prescribed ranges from anti-depressants to sedatives. Dr. Adi Aran at the Shaare Zedek Medical Center in Jerusalem, Israel performed a retrospective feasibility study on cannabis derived CBD.[44] The study identified sixty children with ages ranging from 5 to 17 years old with the diagnosis of ASD. The children received doses of 20:1 CBD to THC cannabis extract ranging up to 10 mg/kg of CBD. Sixty-one percent of the parents reported lessened behavioral outbreaks after their child received a dose of CBD. Thirty-nine percent of the children showed reduction in anxiety and forty-seven percent had improved communication. Based on these results, the authors have launched a double blind placebo controlled cross over trial with 120 participants.

Abuse and Dependence

At present, there are no case reports of abuse or dependence relating to the use of pure CBD. There are also no published statistics on non-medical use of pure CBD. There is unsanctioned medical use of CBD based products. These are produced from high CBD content plants and distributed in a variety of forms, including oils and capsules. These products are sold online or in stores as unapproved treatments for a variety of disorders including epilepsy, cancer, AIDS/HIV, anxiety, arthritis, pain, and posttraumatic stress disorder (PTSD). Additionally, CBD is being used in skin and beauty products such as shampoos and skin creams.

Summary

- **Cannabidiol (CBD) is a natural constituent of the Cannabis sativa plant. Cannabis sativa has multiple cultivar types of which some are available for legal purchase and sale.**

- **The Endocannabinoid system is a biochemical system that links neurological and immunological activity in humans and animals. CBD is defined by its activity and inactivity on the Endocannabinoid system. CBD also acts on multiple molecular targets outside the Endocannabinoid system.**

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[43] Stockings E, Zagic D, Campbell G, *et al* Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *J Neurol Neurosurg Psychiatry* 2018; 89**;** 741-753

[44] Aran A et al. Cannabidiol based medical cannabis in children with autism – a retrospective

- **CBD and the Endocannabinoid system influence all organs. Thus, CBD is potential therapy for multiple indications, including those that involve pain, inflammation, mood, and sleep.**

- **CBD is currently marketed in multiple forms at low doses. Clinical studies with positive outcome have been documented at much higher doses than are generally available in the market place. It is recommended to focus product development efforts on increasing dose and/or improving bioavailability.**

- **CBD reveals no serious adverse effects at high doses and is unlikely to at lower doses. The higher doses demonstrated mild to moderate effects including, drowsiness, diarrhea, weight loss, and one patient who was taking anti-seizure medication demonstrated elevated liver enzymes in plasma**

- **CBD shows no potential for abuse and may have therapeutic uses in addiction behavior**

Addendum

Coupling Cannabidiol with Opiates - An Effort to Improve Chronic Pain and Reduce Serious Adverse Effects from Chronic Opiate Use.

Cannabidiol (CBD) shows tremendous promise as pharmaceutical treatment for chronic pain alone. Coupled with opiates, CBD would improve chronic pain management and reduce the serious adverse effects of chronic opiate use. Investigations into the benefit of CBD alone or coupled with opiates have been scant and limited in deference to a focus on THC. Current evidence indicates that CBD coupled with opiates may be a better option than THC. Unlike THC, CBD does not induce psycho-activity. As well, CBD has a mechanism of action distinct from THC. THC's mechanism of action has similarities to opiates. Although this allows for synergy, it may also induce cross-tolerance and increase addiction potential.

Management of chronic pain is complex and thus requires a multi-modal approach. In addition to pharmaceutical use, psychological treatment and physical therapy is often considered. Nerve block via injection of analgesics and potent anti-inflammatory agents may be used when pain is refractory. As well, spinal cord stimulators may be surgically implanted to send electrical signals to the spinal cord and hyperpolarize an affected nerve. Non-opiate medication such as gabapentin is an early choice in the pharmaceutical approach to neuropathic pain. On the other hand, non-steroidal anti-inflammatory drugs are not ideal for chronic pain due to the adverse effects that occur with chronic use. In current medical practice, opiates are frequently prescribed. However, they are also of great concern due to tolerance and their addictive potential. In 2016, deaths from opiates (including prescription and illegal opiates) grew five times higher than 1999.[45]

There is ample preclinical evidence that Cannabidiol (CBD) has anti-inflammatory, analgesia, and anxiolytic properties. As well, there is clinical evidence that CBD improves social anxiety disorder. At this point, there are no published clinical studies demonstrating the efficacy of CBD alone on chronic pain. Cannabis Sativa used as medicine has grown as a popular movement and not through the traditional scientific process. MediCann, a medical cannabis specialty practice, was established in 2004 in order to observe and evaluate the popular movement of cannabis use. In 2011, MediCann published a study identifying pain as the primary reason for Cannabis use.[46] Today, there is significant consideration and study in the scientific community of the constituents of Cannabis for chronic pain. However, early attention and study has been on THC as the major active ingredient to treat chronic pain. THC is the psychoactive component of Cannabis Sativa. The Endocannabinoid System and cannabinoid receptors CB_1 (CnR_1) and CB_2 (CnR_2) are defined by THC's affinity. Despite (or perhaps due to) legal prohibition, THC is the most studied constituent of the plant.

Opiates alleviate pain via their affinity for three specific receptors in the central nervous system identified as mu, delta and kappa opiate receptors. These receptors influence dopamine and glutamate neurotransmission. Similar to cannabinoid receptors, opiate receptors are G-coupled protein receptor types. As well, both opiate and cannabinoid receptors are found in similar regions of the central nervous system.[47] Due to a similar mechanisms of action, THC coupled with opiates was considered early on as a novel pharmaceutical approach to pain therapy.[48] In contrast to opiate receptors, there are few cannabinoid receptors in the respiratory drive center of the brain stem. The result of coupling THC with an opiate in pharmaceutical formulation should be pain relief at lower opiate doses and thus less chance of overdose.

Early in Cannabis drug development, a binding study on opiate receptors in rats demonstrated the same effect of THC and CBD.[49] Observations of naloxone, an opiate receptor antagonist and 3H-DAMGO, an opiate agonist, demonstrated the same dissociative activity by both THC and CBD. The authors concluded that CBD is an allosteric modulator of both mu and delta receptors. In light of the evidence on both THC and CBD, GW pharmaceuticals produced a sublingual spray, Sativex, containing an equal amount of each. They spray was studied and approved in Canada and UK for central neuropathic pain in multiple sclerosis and cancer pain. Sativex is efficacious because of its multi-modal effects upon various nociceptive pathways, its adjunctive anxiolytic side benefit, its successful safety profile and the advantages of prescription in combination with opioid therapy.[50] Sativex contains plant derived THC and CBD. Despite the success of Sativex, it has yet to be approved in the United States. FDA has approved synthetic THC-like dronabinol. Dronabinol was first approved in 1995 for nausea and vomiting associated with cancer chemotherapy. However, plant derived THC products continue to be identified by the Controlled Substances Act as Schedule I, of no medicinal value and with potential

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[46] Nunberg, H et al. Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice. *Journal of Drug Policy* 2011 Feb; 4(1); 1

[47] Befort, K. Interactions of the opioid and cannabinoid systems in reward: Insights from knockout studies. *Frontiers in Pharmacology* 2015 Feb 5; 6; 6

[48] Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sciences* 2004 Jan 30; 74(11); 1317-24

[49] Kathmann M et al. Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. Naunyn-Schmiedebergs Archive of Pharmacology 2006 Feb; 372(5); 354-61

[50] Russo E B. Cannabinoids in the management of difficult to treat pain. *Therapeutics and*

for abuse. One can only assume that the DEA and the pretzel logic of the Controlled Substances Act have slowed the approval of plant derived THC products like Sativex.

In 2009, Elikottil reviewed studies and discussed the potential of phytocannabinoids (plant derived), endocannabinoids and synthetic cannabinoids (dronabinol) as analgesic agents.[51] The study focused on ligand activity on CB_1 and CB_2 receptors of which THC has affinity for both. Another review discusses the mechanism of action of both opioid receptors (mu delta and kappa) and cannabinoid receptors (CB_1 and CB_2).[52] The receptor classes share similar activity, including pain relief and addiction. Cannabinoid receptor agonists release endorphins. As well opiates (specifically morphine) release endocannabinoids. Cross-tolerance and synergy occurs when both are activated. These mechanisms are what make coupling THC and opiates attractive for the treatment of chronic pain. As well, it may be THC containing products have yet to be approved for chronic pain. In contrast to THC, CBD has poor activity on CB_1 and CB_2 receptors. However, CBD has multiple molecular targets outside of these cannabinoid receptors. The potential for pain relief with CBD remains without increasing tolerance and potential addiction. Although the coupling of THC with opiates shows promise, eliminating THC and coupling opiates with CBD alone may have a better side effect profile and be more readily approved by the FDA and DEA. In addition to chronic pain, CBD may have benefit in opiate addiction.[53] CBD seems to reduce the potential of morphine addiction via its activity on the 5HT1A receptor. Overall, CBD was found to have an impact on the intoxication and relapse phase of opioid addiction. Until now, there are no published clinical studies investigating the coupling of CBD with opiates for pain.

In 2011, Abrams et al took advantage of a grant from NIDA to publish a study on the clinical effects of vaporized and inhaled Cannabis flower in conjunction with oral morphine and oxycodone.[54] The Cannabis flower contained 3.6% THC by weight. The CBD content of the flower was not defined. The study was not blinded and no placebo was used. Twenty-one patients with chronic pain ingested sustained release morphine or oxycodone twice per day and inhaled vaporized Cannabis flower. Blood tests revealed that the inhaled Cannabis flower did not affect the level of opiates. As expected, there was significant improvement in pain when Cannabis flower was inhaled. The prospective study was ground breaking early clinical evidence of what has been suggested by early preclinical studies. Currently, the University of Utah is conducting a clinical study on different doses of CBD and THC for pain. As well, Albert Einstein College of Medicine and Montefiore Health System is performing an18 month study on CBD and opiate use in HIV patients with chronic pain.

Conclusion:

The mechanism of action of both THC and CBD indicate potential therapeutic benefit when coupled with opiates. Until recently, clinical studies on CBD for pain seem to have been delayed in favor of THC. Along with its pain reducing potential,

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[51] Elikottil J et al. The Analgesic Potential of Cannabinoids. Journal of Opioid Management 2009 Nov-Dec; 5(6); 341-357

[52] Bushlin I et al. Cannabinoid-opioid interactions during neuropathic pain and analgesia. Current Opinions in Pharmacology 2010 Feb; 10(1); 80

[53] Prud'homme M et al. Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence

[54] Abrams D et al. Cannabinoid-opioid interaction in chronic pain. *Clinical Pharmacology*

CBD is non-psychoactive and may even counteract the addictive potential of opiates and THC. Ongoing long-term studies are now comparing CBD to THC as chronic pain medicine. CBD may soon replace THC as the more commonly used phytocannabinoid in pain therapy.