The Endocannabinoid System
& The Use of CBD in Substance Abuse

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Outline

- The History/Research of Cannabis in Medicine
- Physiology of the Endocannabinoid System
- CBD and the ECS in Substance Abuse
- Considerations for CBD Products

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“There is nothing more difficult to carry out, nor more doubtful of success, nor more dangerous to handle, than to initiate a new order of things. For the reformer has enemies in all those who profit by the old order”

Niccolò Machiavelli 1469 – 1527
History

- One of the earliest known cultivated plants
- Used and farmed for at least 12,000 years.
- “Co-Evolution”, wild plant no longer exists.
- Only plant cultivated in hunter-gatherer societies (African Pygmy).
- Used medicinally for at least 6,000 years.

32. Malandra, Mass Roots, 10/5/17
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Eli Lilly, Pfizer, Parke Davis, et al. had medical cannabis products.

Cannabis was the third most prescribed medicinal agent for 60 years running prior to its prohibition in 1937.

Parke, Davis with Eli Lilly developed its own indica strain, Cannabis americana. (Indica known to have more medicinal value.)

Only witness who opposed the bill at the hearings for the 1937 Marijuana Tax Act, was a physician, Dr. W.C. Woodward of the AMA.
Cannabis Tidal Wave

- 29 States now have statutes on medical cannabis
- Cannabis use has doubled in last 10 years
- *Forbes* estimates CBD sales $170 million in 2016. Expected to grow 700% to 1000% by the year 2020
- *Hemp Business Journal* estimates $3 billion CBD market by 2021

30. Lindsey, GreenRushDaily: 5/13/2017
31. Stamberger, MedicalMarijuana, Inc: 8/23/2017
89.5% physicians in training felt “not at all prepared” to prescribe medical cannabis.

84.9% report receiving no education in medical school or residency on medical cannabis.

Only 9% of medical schools have any documented content on medical cannabis.

Over 20,000 articles in the basic scientific literature.

Over 3,000 studies in the medical literature.

Phytocannabinoids

Cannabis makes PHYTO-cannabinoids (Over 120 now ID’d from cannabis).

- Interact well with vertebrate eCB receptors
- **THC** (Delta-9 THC)
- **CBD** (Cannabidiol)
- CBC, CBDA, CBG, CBN, THCV, etc…
History of Research

- Dr. Raphael Mechoulam, PhD, Hebrew University, Israel
- Holocaust survivor, Bulgarian, Son of a Physician
- Considered the Father of Cannabinoid Medicine
- Discovered THC in 1964
- Team discovered the first endocannabinoid (AEA) in 1992
- Published over 350 scientific papers.
The Endocannabinoid System (ECS)

Universal body mechanism for homeostatic regulation

System of “signaling lipids,” their receptors, related enzymes

Largest NT system in the body

Present in all vertebrate species

At least 600 million years old


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ECS Comprised of...

**Endocannabinoid (et al)**

**Receptors:**

- CB1 receptors are found on cell surfaces.
- CB2 receptors are mostly in the peripheral organs, especially cells associated with the immune system.

**The Endocannabinoids**

- **2-AG:**

  ![2-AG structure](image)

- **Anandamide:**

  ![Anandamide structure](image)

**Enzymes:**

- **Production:** DAGL, NAPE-PLD
- **Breakdown:** Fatty Acid Amide Hydrolase (FAAH), MAGL

References:

- Bracey. 29 Nov 2002 Vol 298 SCIENCE. 1793-1796
- Mileni. PNAS. Vol 105: 35; 12820-4
- J.M. Andry, MD
Endocannabinoid System (eCB System or ECS):
Diverse mechanisms of Homeostasis

Regulates/Balances:
- Nerve Function (pain levels, anxiety levels, sleep, seizure activity, nerve growth/repair, attention)
- Movement coordination
- Immune system activity
- Inflammation (injury repair, swelling, pain)
- Energy Intake and Storage (appetite/metabolism)
- Cell life-cycles/apoptosis
- Reproduction (hormone levels, implantation)
- Circulatory System (Blood pressure, pulse rate)
- Bone Metabolism (osteoclast activity)
- Mood/Reward signaling (Addiction Implications)

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Endocannabinoid Receptors

CB1 is found mostly in the brain.

CB2 receptors are mostly found within the immune system.

Image Source: Leafly.com 5/16/2016
Endocannabinoid Receptors

CB1: Brain, spinal cord, connective tissue, reproductive organs, glands, internal organs

CB2: Spleen, tonsils, thymus gland. White blood cells: T-cells, B-cells, macrophages

(GPR55): Involved in bone metabolism and cancer-cell proliferation (CBD is an antagonist)

TRPV1, serotonin, adenosine, GABA, DA, adrenergic receptors

7. Svizenska, Pharmacol Biochem Behav. 2008 Oct; 90(4) 501-11
Endocannabinoids

Most studied endocannabinoids:

1) **Anandamide** (AEA, or arachidonoylethanolamine)

2) **2-AG** (2-arachidonoylglycerol)

Anandamide

- Discovered 1992 at Hebrew University.
- Sanskrit: “ananda” = bliss.
- Produced by NAPE-PLD. Broken down by FAAH.
- Mostly active at CB1 receptors, less so at CB2 receptors.
- Short half-life (<5 min). Broken down in just a few minutes by FAAH enzyme.

Endogenous Cannabinoids - Anandamide

- Pleasure, food intake, reproduction, sleep, pain relief
- Deficiency increases anxiety/stress (Bluett, T Psy (2014))
- Released during ovulation
- oxytocin drives anandamide production
- Required for embryonic uterine implantation
- Produced in meditation, yoga, “runner’s high”
- Necessary for learning: transfer of info from short to long term memory
- Inhibits breast cancer cell growth

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2-AG

- 170 times more 2-AG in the body than anandamide.
- Agonist for both CB1 and CB2 receptors
- Main activator for the CB2 receptor
- Metabolized by MAGL

2-AG Functions

Regulates immune function
Suppresses inflammation
Neuroprotective
Regulates energy balance
Osteoblast proliferation

43. Ofek. J Bone Miner Res. 2011
2-AG Functions

- Suppresses seizure activity.
  

- Regulates the vascular smooth muscle tone:
  - Relaxes blood vessels/lowers blood pressure
  - Effect blocked in many people with heart disease


- Regulates communication from gut flora to the brain
  - Reduces metabolic endotoxemia and systemic inflammation

Endocannabinoid Deficiencies

Dr. Ethan Russo, MD. Neurologist

2004, CECD: Clinical Endocannabinoid Deficiency
- Fibromyalgia Syndrome
- Irritable Bowel Syndrome
- Treatment Resistant Depression/Anxiety
- Migraine Headaches

Health Studies on CBD

- Analgesic (Costa, et al. 2007)
- Neuroprotective antioxidant (greater than ascorbate or tocopherol) (Hampson, et al., 1998)
- Sleep Promotion (Carlini & Cunha, 1981)
- Anti-emetic (Parker, et al., 2002)
- Cytotoxic to breast CA cells (Ligresti, 2006)
- Antagonizes TNFa in RA (Malfait, 2000)
- Agonizes 5HT1A, reducing anxiety (Russo, 2005)
- Anti-depressant action via 5HT1A (Zenalati, et al., 2010)
- Induces apoptosis and reduces angiogenesis in tumors. (Chakravati, et al. 2014)
- Antibacterial. Effective against MRSA (MIC = 0.5-2 microM^-1) (Appendino, et al., 2008)
- Non-opioid responsive cancer pain improvement (Johnson, et al., 2010)
- Reduced development of diabetes (PPAR gamma activity) (Weiss et al., 2006)
- Reduces blood pressure (Jadoon, et al., 2017)
- Cardioprotective. Reduced arrhythmias and infarct size after MI. (Walsh, et al., 2010)
- Reduces inflammation in UC (Filippis, 2011)
- Improved function in Alzheimer’s Disease (Watt, 2017)
- Reduces substance abuse behaviors (Prud’homme, et al., 2015)

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CBD as an ECS Modulator

- Fatty Acid Amide Hydrolase (FAAH): Breaks down anandamide
- Levels of this enzyme can be too high, driving anandamide too low
  - Neuropathic Pain
  - Alzheimer’s Disease
  - Migraine Headache
- CBD BLOCKS FAAH, raising local anandamide levels.
- CBD induces NAPE-PLD, increasing anandamide levels.

20. Dean, Am J of Physiology, 1 April 2017, Vol 312, No. 4
   J.M. Andry, MD
CBD Raises Anandamide by Blocking FAAH

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CBD: Neutral Antagonist/NAM

CBD does nothing on its own, but in the presence of anandamide (or THC), it tunes DOWN the receptor activity.

46. Russo, E. Turned on by Cannabinoids - CB1 Receptor Pharmacology. ProfOfPot, May 17, 2017
Potential Roles for CBD in Substance Abuse

Potential alternative option in conditions where potentially addictive meds are used.

- Pain
- Anxiety
- Sleep

Direct modulation of CNS areas that regulate addiction/reward/craving/dependence behaviors
Phytocannabinoid Actions

Receptor Systems Involved in CBD’s Potential Therapeutic Applications

- **Indirect Interaction**
  - THC

- **Direct Interaction**
  - CBD
  - Cannabinoid: side effects of THC, e.g. anxiety
  - Opioid: pain, addiction
  - Dopamine: addiction, depression
  - Serotonin: addiction, anxiety, depression

9. Blessing Neurotherapeutics. 4 September 2016
Cannabidiol in Pain

- THC can help with pain
- CBD can help with pain: Multiple mechanisms:
  - Raises anandamide tone (Enzyme induction/inhibition)
  - CB1 receptor modulation
  - Vanilloid (TRPV1 Channels) non-noxious desensitization, other TRP actions (TRPV2 mediated CGRP activity)
  - Positive allostertism at alpha glycine receptors
  - Anti-inflammatory effects
  - Sleep improvement (adenosine modulation)
  - Direct action on 5HT-3 receptors


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CBD Actions on Pain

Agonist at TRPV1 (Vanilloid Channels), analogous to capsaicin, without noxious effects (no burning.) Reduces inflammation-induced hyperalgesia.

Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation.

Barbara Costa, Gabriella Giagnoni, Chiara Franke, Anna Elisa Trovato, and Mariapia Colleoni

Author information ► Article notes ► Copyright and License information ►
CBD and Anxiety/Mood

Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of Cannabis sativa.


Abstract
Anxiety and depression are pathologies that affect human beings in many aspects of life, including social life, productivity and health. Cannabidiol (CBD) is a constituent non-psychotomimetic of Cannabis sativa with great psychiatric potential, including uses as an antidepressant-like and anxiolytic-like compound. The aim of this study is to review studies of animal models using CBD as an anxiolytic-like and antidepressant-like compound. Studies involving animal models, performing a variety of experiments on the above-mentioned disorders, such as the forced swimming test (FST), elevated plus maze (EPM) and Vogel conflict test (VCT), suggest that CBD exhibited an anti-anxiety and antidepressant effects in animal models discussed. Experiments with CBD demonstrated non-activation of neuroreceptors CB1 and CB2. Most of the studies demonstrated a good interaction between CBD and the 5-HT1A neuro-receptor.


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CBD Causes Neurogenesis

Some studies show improvement even in alcohol-induced brain atrophy.

The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system

Alline C. Campos, Zaira Ortega, Javier Palazuelos, Manoela V. Fogaça, Daniele C. Aguiar, Javier Díaz-Alonso, Silvia Ortega-Gutiérrez, Henar Vázquez-Villa, Fabricio A. Moreira, Manuel Guzmán ...

International Journal of Neuropsychopharmacology, Volume 16, Issue 6, 1
July 2013, Pages 1407–1419,
https://doi.org/10.1017/S1461145712001502
Published: 01 July 2013  Article history ▼

“findings support that the anxiolytic effect of chronic CBD administration in stressed mice depends on its proneurogenic action in the adult hippocampus by facilitating endocannabinoid-mediated signaling.”
Hypnotic and antiepileptic effects of cannabidiol.

Carlini EA, Cunha JM.

Abstract
Clinical trials with cannabidiol (CBD) in healthy volunteers, insomniacs, and epileptic patients conducted in the authors' laboratory from 1972 up to the present are reviewed. Acute doses of cannabidiol ranging from 10 to 600 mg and chronic administration of 10 mg for 20 days or 3 mg/kg/day for 30 days did not induce psychologic or physical symptoms suggestive of psychotropic or toxic effects; however, several volunteers complained of somnolence. Complementary laboratory tests (EKG, blood pressure, and blood and urine analysis) revealed no sign of toxicity. Doses of 40, 80, and 160 mg cannabidiol were compared to placebo and 5 mg nitrazepam in 15 insomniac volunteers. Subjects receiving 160 mg cannabidiol reported having slept significantly more than those receiving placebo; the volunteers also reported significantly less dream recall; with the three doses of cannabidiol than with placebo. Fifteen patients suffering from secondary generalized epilepsy refractory to known antiepileptic drugs received either 200 to 300 mg cannabidiol daily or placebo for as long as 4.5 months. Seven out of the eight epileptics receiving cannabidiol had improvement of their disease state, whereas only one placebo patient improved.
CBD for Substance Abuse

- Multiple known examples of eCB modulation of CNS areas involved in addiction neurophysiology \(^{22}\).

- Multiple studies show some potential for opiate treatment.
  - Decreased craving
  - Decreased cue-induced relapse after abstinence
  - Attenuation of withdrawal symptoms

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Genetic KO Animal Studies: eCB System and Addiction

- CB1 modulates mesolimbic dopamine transmission in ETOH reward. (57)
- CB1 modulates morphine enhanced extracellular DA concentration in the nucleus accumbens (nAC). (58)
- FAAH KO mice showed greater preference for ETOH intake (similar to the “munchies” for food intake.) (59)
- CB2 agonist decreased cocaine self-administration. (60)
- FAAH inhibitor URB597 (which raises anandamide) reduces THC withdrawal response. (61)
CB1/CB2 KO Mice studies support eCB role in various types of substance dependence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutant mice</th>
<th>Behavioral model</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>CB1R KO</td>
<td>Conditioned place preference</td>
<td>Suppression</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Self-administration in restrained mice</td>
<td>No change</td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawal syndrome</td>
<td>Suppression</td>
<td>[20,11]</td>
</tr>
<tr>
<td>Ethanol</td>
<td>CB1R KO</td>
<td>Conditioned place preference</td>
<td>Attenuation</td>
<td>[12,13]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two-bottle voluntary consumption</td>
<td>Attenuation</td>
<td>[14,15]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawal syndrome</td>
<td>No change</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two-bottle voluntary consumption</td>
<td>Increased</td>
<td>[15,34]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawal syndrome</td>
<td>Decreased</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute withdrawal</td>
<td>No change</td>
<td>[34]</td>
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<tr>
<td>FAAH KO</td>
<td></td>
<td>Conditioned place preference</td>
<td>Suppression</td>
<td>[8,9]</td>
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<td>Self-administration in restrained mice</td>
<td>No change</td>
<td>[11]</td>
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<tr>
<td></td>
<td></td>
<td>Withdrawal syndrome</td>
<td>No change</td>
<td>[8,9]</td>
</tr>
<tr>
<td>Nicotine</td>
<td>CB1R KO</td>
<td>Conditioned place preference</td>
<td>Suppression</td>
<td>[8,9]</td>
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<td>Self-administration in restrained mice</td>
<td>No change</td>
<td>[11]</td>
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<tr>
<td></td>
<td></td>
<td>Withdrawal syndrome</td>
<td>No change</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditioned place preference</td>
<td>Increased</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawal syndrome</td>
<td>Increased</td>
<td>[9]</td>
</tr>
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<td>Cocaine</td>
<td>CB1R KO</td>
<td>Conditioned place preference</td>
<td>No change</td>
<td>[18,12]</td>
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<td></td>
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<td>Self-administration in restrained mice</td>
<td>No change</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Self-administration in freely moving mice</td>
<td>Attenuation</td>
<td>[23*]</td>
</tr>
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<td></td>
<td>CB2R KO</td>
<td>Self-administration in freely moving mice</td>
<td>No change</td>
<td>[28**]</td>
</tr>
<tr>
<td></td>
<td>CB2R overexpression</td>
<td>Conditioned place preference</td>
<td>Attenuation</td>
<td>[29*]</td>
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<tr>
<td>Amphetamine</td>
<td>CB1R KO</td>
<td>Self-administration in restrained mice</td>
<td>No change</td>
<td>[11]</td>
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<td>MDMA</td>
<td>CB1R KO</td>
<td>Conditioned place preference</td>
<td>No change</td>
<td>[25]</td>
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<td></td>
<td></td>
<td>Self-administration in freely moving mice</td>
<td>Suppression</td>
<td>[25]</td>
</tr>
</tbody>
</table>

CBD for Opiate Addiction


Effects of Cannabidiol on Morphine Conditioned Place Preference in Mice.

Markos JR¹, Harris HM¹, Gul W²,³, ElSohly MA²,⁴, Sufka K¹,².

Abstract
This study sought to determine whether the cannabis constituent cannabidiol attenuates the development of morphine reward in the conditioned place preference paradigm. Separate groups of mice received either saline or morphine in combination with one of four doses of cannabidiol using three sets of drug/no-drug conditioning trials. After drug-place conditioning, morphine mice displayed robust place preference that was attenuated by 10 mg/kg cannabidiol. Further, when administered alone, this dose of cannabidiol was void of rewarding and aversive properties. The finding that cannabidiol blocks opioid reward suggests that this compound may be useful in addiction treatment settings.

PMID: 28793355 DOI: 10.1055/s-0043-117838
[Indexed for MEDLINE]
CBD for Opiate Addiction

Clinical Study in human subjects. CBD significantly reduced restarting opiate use after abstinence period. Effect persisted for up to 7 days after a single administration. Suggests utility in prevention of relapse.

(54)
CBD: Opiate Addiction

Human, Placebo-controlled trial

CBD significantly reduced visual cue-induced craving scores in HEROIN dependent subjects. (53)

3 single-dose daily treatments of CBD given. Effects measured at 24 hours after initial administration and persisted 7 days after treatment.
CBD: Opiate Addiction

Same Study; **HEROIN** dependent human subjects.

Shown video cues for heroin use.

CBD blunted cue-induced anxiety vs neutral cue. (53)

Again, possible implications for supporting abstinence.
THC versus CBD

Marijuana use associated with hypertension being a contributing cause to death 3:1 versus non-users.

THC known to increase sympathetic nervous system tone, increase BP and oxygen demand for tissues.

CBD and CV Health

Where as CBD recently shown to reduce blood pressure by about 6 mm Hg.

Also reduced the Blood Pressure increase that occurs in response to stress.

CBD Safety

“chronic use and high doses up to 1,500 mg/day of CBD are reportedly well tolerated in humans”

In human studies, CBD administration did not induce side effects across a wide range of dosages, including acute and chronic dose regimens, and tolerance to CBD did not develop.


January 2018. World Anti-Doping Agency (WADA) removed CBD from list of prohibited substances, no longer banning use by athletes.

CBD Safety


Table 2. Effects of CBD Administration In Vitro Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Species</th>
<th>Route</th>
<th>Dose</th>
<th>Relevant Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuardi et al. (2001)</td>
<td>[15]</td>
<td>human</td>
<td>oral</td>
<td>1mg/kg bw</td>
<td>no significant effects on heart rate and bodily symptoms</td>
</tr>
<tr>
<td>Costa et al. (1998)</td>
<td>[10]</td>
<td>human</td>
<td>oral</td>
<td>3mg/kg bw; 50 and 150mg/day</td>
<td>no significant effects on neurological and physical examination, blood and urine analysis, electrocardiogram and electropharmacography</td>
</tr>
<tr>
<td>Liguori et al. (2000)</td>
<td>[16]</td>
<td>mouse</td>
<td>intraperitoneal</td>
<td>5mg/kg</td>
<td>lower potency in mouse cells</td>
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<tr>
<td>Mardie et al. (2006)</td>
<td>[14]</td>
<td>mouse</td>
<td>percutaneous</td>
<td>0.5 mg/mouse</td>
<td>no significant effects on non-transformed cells</td>
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<tr>
<td>Boush et al. (2009)</td>
<td>[23]</td>
<td>mouse</td>
<td>intraperitoneal</td>
<td>10mg/kg</td>
<td>no significant effects on weight gain and locomotor activity</td>
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<tr>
<td>Di Marzo et al. (2004)</td>
<td>[24]</td>
<td>mouse</td>
<td>intraperitoneal</td>
<td>10mg/kg</td>
<td>no significant effects on weight gain on blood glucose levels</td>
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<tr>
<td>Wiley et al. (2003)</td>
<td>[23]</td>
<td>mouse</td>
<td>intraperitoneal</td>
<td>0.1mg/kg</td>
<td>no significant effect on weight gain</td>
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<td>Sterpena et al. (2013)</td>
<td>[26]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>20mg/kg</td>
<td>dose-completed MDPH</td>
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<tr>
<td>Varnel et al. (2006)</td>
<td>[29]</td>
<td>mouse</td>
<td>intravenous</td>
<td>1-1.5mg/kg</td>
<td>no significant effects on catalepsy, anticonvulsant and hypotensive</td>
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<tr>
<td>Zuardi et al. (1991)</td>
<td>[30]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>3-10mg/kg</td>
<td>no significant effect on catalepsy</td>
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<tr>
<td>Farahani et al. (1997)</td>
<td>[31]</td>
<td>mouse</td>
<td>oral</td>
<td>3.13-10mg/kg</td>
<td>no significant effects on catalepsy</td>
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<tr>
<td>Pertwee et al. (1972)</td>
<td>[32]</td>
<td>mouse</td>
<td>oral</td>
<td>3.13-10mg/kg</td>
<td>no significant effects on catalepsy</td>
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<tr>
<td>Zuardi et al. (2010)</td>
<td>[33]</td>
<td>mouse</td>
<td>intraperitoneal</td>
<td>3-10mg/kg</td>
<td>did not induce motor changes</td>
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<tr>
<td>Guadagnoli et al. (1995)</td>
<td>[36]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>2-5mg/kg</td>
<td>did not induce motor changes</td>
</tr>
<tr>
<td>de Filippis et al. (2008)</td>
<td>[37]</td>
<td>mouse</td>
<td>intraperitoneal</td>
<td>10mg/kg</td>
<td>no significant effects on gastro-intestinal symptoms</td>
</tr>
<tr>
<td>Haskin et al. (2007)</td>
<td>[38]</td>
<td>mouse</td>
<td>intraperitoneal</td>
<td>3mg/kg</td>
<td>no significant effects on blood pH, PCO2, PCO2, hemoglobin, K+ and Na levels, glucose, blood pressure, heart rate and blood temperature</td>
</tr>
<tr>
<td>Huh et al. (1988)</td>
<td>[39]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>16.6-30mg/kg</td>
<td>no significant effects on mental activity and on sleep deprivation</td>
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<td>Harrison et al. (2001)</td>
<td>[40]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>20mg/kg</td>
<td>no significant effects on PCO2, PCO2, glucose, blood pressure and mental temprerature</td>
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<tr>
<td>Rozini et al. (1994)</td>
<td>[41]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>10mg/kg</td>
<td>no significant effects on blood pressure and heart rate</td>
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<tr>
<td>Chouraqui et al. (1979)</td>
<td>[42]</td>
<td>mouse</td>
<td>oral</td>
<td>6-30mg/kg</td>
<td>no significant effects on gastro-intestinal motility</td>
</tr>
<tr>
<td>Huh et al. (1988)</td>
<td>[43]</td>
<td>mouse</td>
<td>intraperitoneal</td>
<td>3mg/kg</td>
<td>no significant effects on blood pH, PCO2, PCO2, hemoglobin, K+ and Na levels and mental temperature</td>
</tr>
<tr>
<td>Dallal et al. (2007)</td>
<td>[44]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>60mg/kg</td>
<td>no significant effects on anorexia, generalized ataxia, xerostomia, dry mouth, sensory disturbances and hyperactivity</td>
</tr>
<tr>
<td>Derenon et al. (2007)</td>
<td>[45]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>1.0 and 50mg/kg</td>
<td>did not induce motor changes</td>
</tr>
<tr>
<td>McGovern et al. (2004)</td>
<td>[46]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>0.003-0.5mg/kg; 1-2.5mg/kg</td>
<td>no significant effects on blood pressure, arterial blood gas analysis, pH, respiratory response and respiratory system toxicity</td>
</tr>
</tbody>
</table>

Table 3. Effects of CBD Administration In Vivo Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Species</th>
<th>Route</th>
<th>Dose</th>
<th>Relevant Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham et al. (1973)</td>
<td>[35]</td>
<td>rat</td>
<td>intravenous</td>
<td>1mg/kg</td>
<td>no significant effects on cardiovascular and respiratory parameters</td>
</tr>
<tr>
<td>Aronne et al. (2008)</td>
<td>[31]</td>
<td>rat</td>
<td>intravenous</td>
<td>0.1mg/kg</td>
<td>no significant effects on blood pH, PCO2, PCO2, heart rate, blood pressure, hemodynamics and respiratory parameters</td>
</tr>
<tr>
<td>Heyer et al. (1983)</td>
<td>[59]</td>
<td>rat</td>
<td>intraperitoneal</td>
<td>0.75-2.5mg/kg</td>
<td>no effect delayed muscle tone to sample task performance</td>
</tr>
<tr>
<td>Hellman et al. (1973)</td>
<td>[61]</td>
<td>human</td>
<td>oral</td>
<td>26-100mg</td>
<td>no significant side effect</td>
</tr>
<tr>
<td>Hellman et al. (1973)</td>
<td>[61]</td>
<td>human</td>
<td>oral</td>
<td>5-30mg</td>
<td>no significant side effect</td>
</tr>
<tr>
<td>Kuriel et al. (1973)</td>
<td>[62]</td>
<td>human</td>
<td>oral</td>
<td>15-60mg</td>
<td>no significant effects on heart rate, psychological reaction and on time to production line performance</td>
</tr>
<tr>
<td>Bergamaschi et al. (2011)</td>
<td>[65]</td>
<td>human</td>
<td>oral</td>
<td>600mg</td>
<td>no significant effects on heart rate, blood pressure, skin condensation, bodily symptoms and psychological measurements</td>
</tr>
<tr>
<td>Crippa et al. (2011)</td>
<td>[66]</td>
<td>human</td>
<td>oral</td>
<td>400mg</td>
<td>no significant effects on subjective and psychological measurements</td>
</tr>
<tr>
<td>Crippa et al. (2011)</td>
<td>[67]</td>
<td>human</td>
<td>oral</td>
<td>300-600mg/day</td>
<td>no significant side effect</td>
</tr>
<tr>
<td>Fauser et al. (2009)</td>
<td>[68]</td>
<td>human</td>
<td>oral</td>
<td>600mg</td>
<td>no significant effects on heart rate, blood pressure, task performance and psychological measurements</td>
</tr>
<tr>
<td>Fauser et al. (2009)</td>
<td>[69]</td>
<td>human</td>
<td>oral</td>
<td>600mg</td>
<td>no significant side effect</td>
</tr>
<tr>
<td>Bhattacharya et al. (2009)</td>
<td>[70]</td>
<td>human</td>
<td>oral</td>
<td>600mg</td>
<td>no significant effects on verbal learning task and psychotic symptoms</td>
</tr>
<tr>
<td>Bergamaschi et al. (2011)</td>
<td>[71]</td>
<td>human</td>
<td>oral</td>
<td>600mg</td>
<td>no significant effects on intoxication, sedation, psychotic symptoms and motor activity task</td>
</tr>
<tr>
<td>Crippa et al. (2004)</td>
<td>[72]</td>
<td>human</td>
<td>oral</td>
<td>400mg</td>
<td>no significant effects psychological measurements</td>
</tr>
<tr>
<td>Zuardi et al. (1995)</td>
<td>[73]</td>
<td>human</td>
<td>oral</td>
<td>300mg</td>
<td>no significant effects on heart rate, blood pressure, psychometric performance, bodily symptoms and psychological measurements</td>
</tr>
<tr>
<td>Conner et al. (1979)</td>
<td>[74]</td>
<td>human</td>
<td>oral</td>
<td>200mg</td>
<td>no significant improvements in motor and mental performance</td>
</tr>
<tr>
<td>Hashik et al. (2011)</td>
<td>[75]</td>
<td>human</td>
<td>oral</td>
<td>600mg</td>
<td>no significant effects on heart rate, blood pressure and behavior measurements</td>
</tr>
<tr>
<td>Bhattacharya et al. (2010)</td>
<td>[76]</td>
<td>human</td>
<td>oral</td>
<td>600mg</td>
<td>no significant effects on heart rate and blood pressure</td>
</tr>
<tr>
<td>Hashik et al. (2011)</td>
<td>[77]</td>
<td>human</td>
<td>oral</td>
<td>300 and 600mg</td>
<td>no significant side effect</td>
</tr>
<tr>
<td>Mincle et al. (1973)</td>
<td>[78]</td>
<td>human</td>
<td>oral</td>
<td>10mg</td>
<td>no significant change in neurological, clinical, psychiatric, blood and urine examinations</td>
</tr>
<tr>
<td>Conner et al. (1979)</td>
<td>[79]</td>
<td>human</td>
<td>oral</td>
<td>10mg/kg/day</td>
<td>no significant side effect</td>
</tr>
<tr>
<td>Zuardi et al. (1995)</td>
<td>[80]</td>
<td>human</td>
<td>oral</td>
<td>1.5mg/kg/day</td>
<td>no significant side effect</td>
</tr>
<tr>
<td>Zuardi et al. (2009)</td>
<td>[81]</td>
<td>human</td>
<td>oral</td>
<td>40-120mg/kg/day</td>
<td>no significant side effect</td>
</tr>
<tr>
<td>Zuardi et al. (2010)</td>
<td>[82]</td>
<td>human</td>
<td>oral</td>
<td>600-1,200mg/kg/day</td>
<td>no significant side effect</td>
</tr>
<tr>
<td>Lowery et al. (2007)</td>
<td>[83]</td>
<td>human</td>
<td>oral</td>
<td>500mg/kg/day</td>
<td>less side effect than amilpride</td>
</tr>
<tr>
<td>Zuardi et al. (2009)</td>
<td>[84]</td>
<td>human</td>
<td>oral</td>
<td>150-400mg/kg/day</td>
<td>no significant side effect</td>
</tr>
</tbody>
</table>
**NOT** just CBD…

“Entourage Effect” (w/ or w/o THC)

- Multiple Cannabinoids
- Dozens of Terpenes
- Flavonoids
- Omega FAs (ALA)
- Vitamins: A, B1, B2, B3, B6, B12, C, E, folic acid
- Minerals: Mg, K, Fe
CBD/Terpene Synergy


<table>
<thead>
<tr>
<th>Terpenoid</th>
<th>Structure</th>
<th>Commonly encountered in</th>
<th>Pharmacological activity (References)</th>
<th>Synergistic cannabinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limonene</td>
<td><img src="image" alt="Limonene Structure" /></td>
<td>Lemon</td>
<td>Potent AD/Inmunosuppressant by inhalation (Kanus et al., 1995); Analgesic (Canfora-finola and Costa, 2002; Puketi et al., 2004) via 5-HT1a (Komiya et al., 2001); Apoptosis of breast cancer cells (Vaghan et al., 2008); Active against acne bacteria (Kim et al., 2008); Dermatomelody (Zargaryan et al., 2001; Singh et al., 2010); Cardiovascular reflex (Hirata, 2010)</td>
<td>CBD</td>
</tr>
<tr>
<td>α-Pinene</td>
<td><img src="image" alt="α-Pinene Structure" /></td>
<td>Pine</td>
<td>Anti-inflammatory via PGE-1 (Gil et al., 1999); Bronchodilatory in humans (Kalk et al., 1991); Acetylcholinesterase inhibitor, aiding memory (Ferry et al., 2000)</td>
<td>THC, CBD</td>
</tr>
<tr>
<td>β-Myrcene</td>
<td><img src="image" alt="β-Myrcene Structure" /></td>
<td>Hop</td>
<td>Blocks inflammation via PGE-2 (Correia et al., 1991); Analgesic, antagonized by naltrexone (Van et al., 1990); Sedating, muscle relaxant, hypotonic (De Vale et al., 2002)</td>
<td>THC</td>
</tr>
<tr>
<td>Linalool</td>
<td><img src="image" alt="Linalool Structure" /></td>
<td>Lavender</td>
<td>Anti-anxiety (Russi, 2001); Sedative on in vivo in mice (Buchbauer et al., 1993); Local anesthetic (de Gre et al., 2000)</td>
<td>CBD, THC</td>
</tr>
<tr>
<td>β-Caryophyllene</td>
<td><img src="image" alt="β-Caryophyllene Structure" /></td>
<td>Pepper</td>
<td>Anti-malarial (Campbell et al., 1997)</td>
<td>THC, CBD</td>
</tr>
<tr>
<td>Caryophyllene Oxide</td>
<td><img src="image" alt="Caryophyllene Oxide Structure" /></td>
<td></td>
<td>Selective CB2 agonist (‘900-sm’ (Gotsch et al., 2008); Treatment of peptic ulcer (Karas et al., 2007); Treatment of addiction (Li et al., 2010)</td>
<td>CBD</td>
</tr>
<tr>
<td>Nerolidol</td>
<td><img src="image" alt="Nerolidol Structure" /></td>
<td>Lemon balm</td>
<td>Sedative (Bisset et al., 1972)</td>
<td>THC, CBN</td>
</tr>
<tr>
<td>Phytol</td>
<td><img src="image" alt="Phytol Structure" /></td>
<td>Orange</td>
<td>Potent antioxidant (Jepson et al., 1999); Anti-inflammatory activity (Mola et al., 2005)</td>
<td>?</td>
</tr>
</tbody>
</table>

Representative plants containing each terpenoid are displayed as examples to promote recognition, but many species contain them in varying concentrations.

- 5-HT1A, 5-hydroxytryptamine (serotonine); 5-HT, anti-depressant; 5-HT1A, anti-inflammatory; CB1/CB2, cannabinoid receptor 1 or 2; GABA, gamma amino butyric acid; PGE-1/PGE-2, prostaglandin E-1/prostaglandin E-2; 5SADH, succinic semialdehyde dehydrogenase.

J.M. Andry, MD
CBD/Hemp Products: Our 4 Requirements

1. **Full Spectrum Hemp Oil versus CBD-isolates:**
   1. **Entourage Effect:** “Preclinical and clinical data indicate that cannabinoids administered together are more effective at ameliorating neuropathic pain than the use of a single agent.” (47 Comelli).
   2. Terpene and phytocannabinoid content across different strains can vary and can impact efficacy. (50 Baron).

2. **Organically Sourced:** Hemp is a bio-accumulator, concentrates compounds from soil, especially heavy metals and is used for bio-remediation of contaminated soilbeds in many parts of the world, especially in Asia. Recommend only USDA Certified Organic Sourcing (which requires the soil that the hemp is grown in is certified organic as well.)

3. **Absorption Enhanced:** Most CBD oils very poorly absorbed orally (approximately 3-6%) (62).
   Solution: **WATER-COMPATIBLE NANOEMULSIONS**
   
   1) Gives many times greater absorption (up to over 85% with some formulations.) Much more cost effective. Must consider absorption when considering price of product.
   2) Also confers rapid onset. VERY IMPORTANT for something you expect to FEEL. EXTREMELY IMPORTANT FOR THOSE WITH ADDICTION. (5-15 minutes vs 1-2 Hours.)

4. **Low THC content.** Extracts up to 0.3% legal, but higher risk for positive UDS testing. Extracts with THC reduced to levels below 0.0% and 0.00% are available.
   a. Less risk to patient (employment or provider-opiate contract obligations).
   b. Less professional liability for provider.

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Thank you!!!

Be kind whenever possible.

It is always possible.

-Dalai Lama

J.M. Andry, MD