CBD and the Brain

Michael Lewis, MD, MPH, MBA, FACPM, FACN Colonel (Retired), U.S. Army



Brain Health

Education & Research Institute

a 501(c)(3) nonprofit organization

IHS - February 2018

What do these men have in common?

- •Aiden Hampson, a neuropharmacologist at the Natl Inst for Mental Health (NIMH). Now Health Science Administrator, Natl Inst of Drug Abuse (NIDA), Medications Research Grants Branch
- •Julius Axelrod (1912-2004), Professor Emeritus, NIH, pharmacologist and neuroscientist who shared the 1970 Nobel Prize in Physiology or Medicine for his discovery of the actions of neurotransmitters in regulating the metabolism of the nervous system
- •<u>Maurizio Grimaldi</u>, professor of neurology/ neuropsychopharmacology and toxicology, NIMH. Now with Natl Inst on Aging, Scientific Review Branch

United States Patent

Hampson et al.

(10) Patent No.: US 6,630,507 B1

(45) Date of Patent: Oct. 7, 2003

(54) CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS

(75) Inventors: Aidan J. Hampson, Irvine, CA (US); Julius Axelrod, Rockville, MD (US); Maurizio Grimaldi, Bethesda, MD

(US)

(73) Assignee: The United States of America as represented by the Department of Health and Human Services, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this

patent is extended or adjusted under 35

U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/674,028

(22) PCT Filed: Apr. 21, 1999

(86) PCT No.: PCT/US99/08769

§ 371 (c)(1),

(2), (4) Date: Feb. 2, 2001

(87) PCT Pub. No.: WO99/53917

PCT Pub. Date: Oct. 28, 1999

(57) ABSTRACT

Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia. Nonpsychoactive cannabinoids, such as cannabidoil, are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present invention. A particular disclosed class of cannabinoids useful as neuroprotective antioxidants is formula (I) wherein the R group is independently selected from the group consisting of H, CH₃, and COCH₃.

Proc Natl Acad Sci U S A. 1998 Jul 7; 95(14): 8268–8273. Medical Sciences PMCID: PMC20965

Cannabidiol and $(\neg)\Delta^9$ -tetrahydrocannabinol are neuroprotective antioxidants

A. J. Hampson,*† M. Grimaldi,‡ J. Axelrod,* and D. Wink§

This study reports that CBD and other cannabinoids such as THC are potent antioxidants that protect neurons from glutamate-induced death without cannabinoid receptor activation..... nonpsychoactive CBD was found to prevent both glutamate neurotoxicity and ROS-induced cell death.

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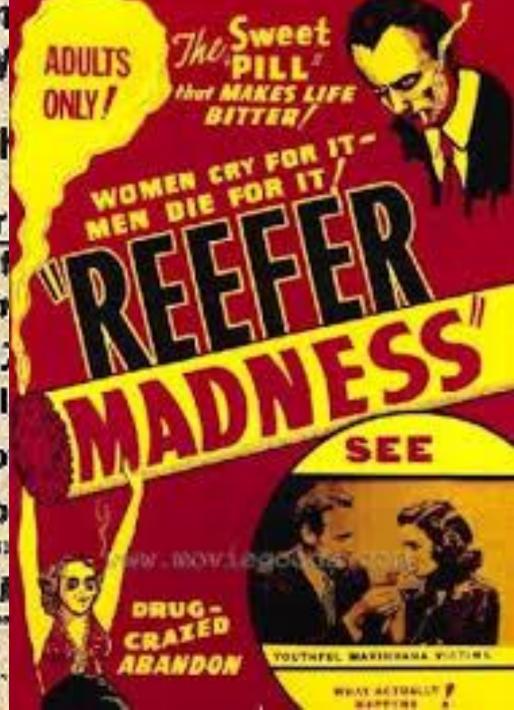
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US Govt: Who's Right about Cannabis?

FDA & DEA

- Schedule I Drug:
 - (a) high potential for abuse;
 - (b) no currently accepted medical use;
 - (c) lack of accepted safety for use of the drug or other substance under medical supervision

<u>HHS - NIH</u>

- Holds a patent for CBD:
 - Neuroprotectant, antiepileptic, anxiolytic
 - "For use in prophylaxis and treatment of disease"
 - "No signs of toxicity or serious side effects have been observed following chronic administration... even when given in large acute doses"

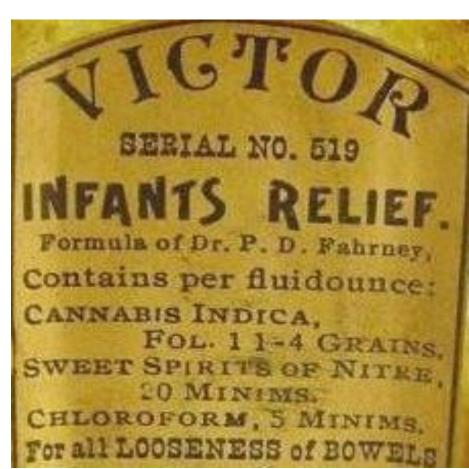


History: Cannabis as Medicine

- 2900 BC: <u>Chinese</u> Emperor Fu His popular medicine that possessed both yin and yang
- 1450 BC: Book of <u>Exodus</u> (30:22-23)
- 1213 BC: Egyptians Use for glaucoma, inflammation
- 1000 BC: Used in India as anesthetic
- 700 BC: Documented use in Persia
- 200 BC: Used in Ancient Greece for inflammation
- 1762: farming of hemp <u>required</u> by law in Virginia
- 1745-1824: grown by Presidents GW, TJ, JM, others
- 1942: USDA film "Hemp for Victory" to support the war effort, encourages growing hemp

History of Cannabis Suggests Safety

- 1850-1942 included in US Pharmacopeia as treatment for neuralgia, alcoholism, opiate addiction, convulsive disorders, several infectious diseases, insanity, among others
- Promoted as analgesic, sedative, antispasmotic, anticonvulsant, and anti-inflammatory
- Manufactured by Eli Lilly,
 Wyeth Park-Davis, Sharp &
 Dohme, and others
- 1937: AMA opposes Tax Act and supports research



Cannabis Americana



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We are marketing a reliable fluid extract of Cannabis Satina from American-grown drug. It has been thoroughly tested by experienced clinicians and pronounced fully equal to the fluid extract obtained from the best Indian Cannabis.

Fluid Extract Cannabis Americana (P. D. & Co.) is physiologically standardized. Practitioners may specify it with perfect assurance of its activity and uniformity. We market it at a price considerably lower than that asked for fluid extract Cannabis Indica.

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One-Fourth Ounce Solid Extract CANNABIS AMERICANA

(Cannabis sativa - American grown)
PHYSIOLOGICALLY TESTED
DOSE -1-5 to 1 grain

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INDIANAPOLIS
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ONE-FOURTH POUND-SOLID EXTRACT

CANNABIS AMERICANA

PHYSIOLOGICALLY TESTED

(Cannabis sativa-American Grown)

Analgesic, Hypnotic, Antispasmodic and powerful Narcotic

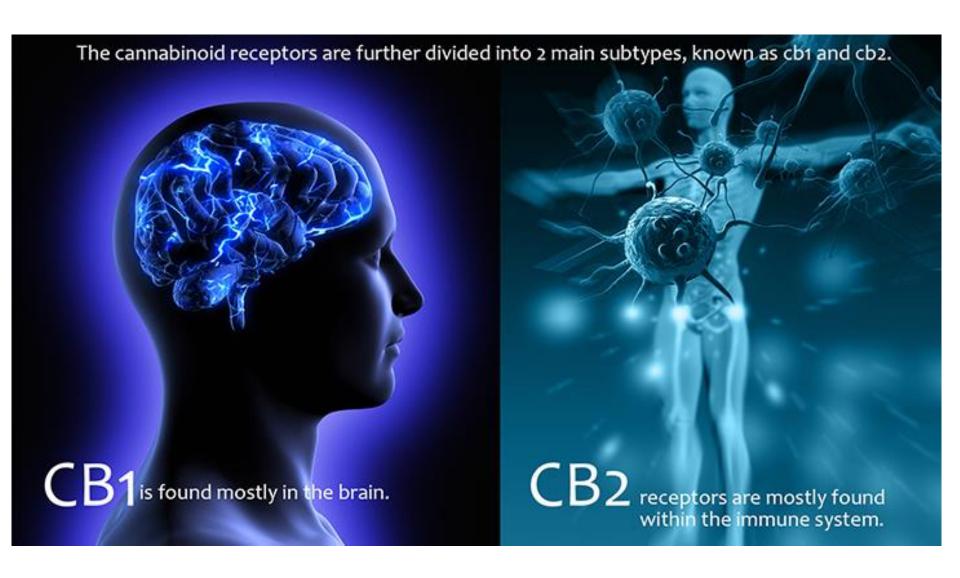
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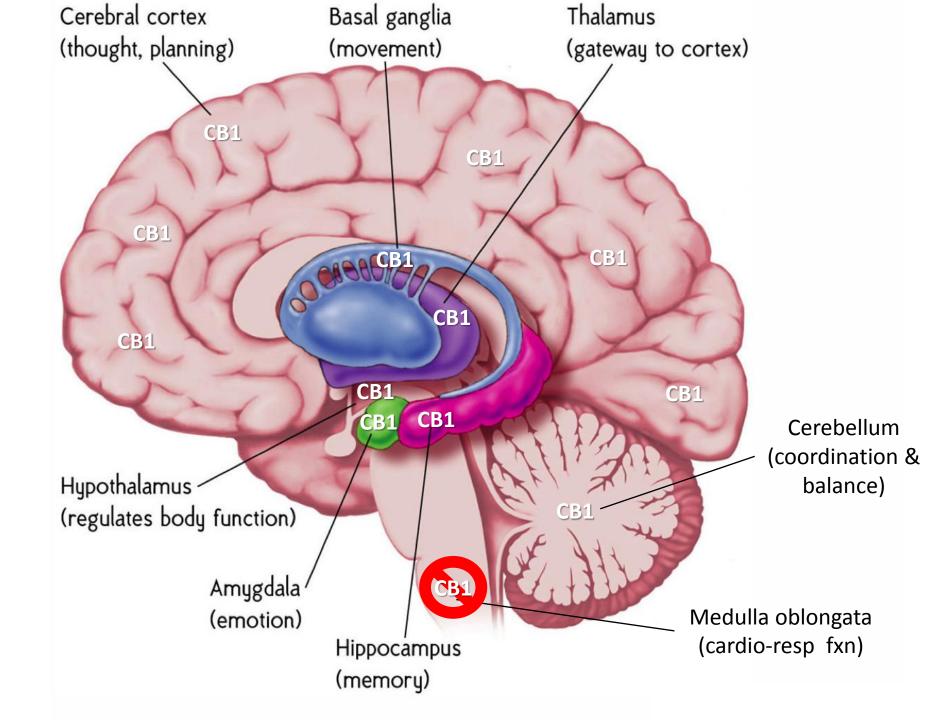
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We All Have Cannabinoid Receptors





Endocannabinoid System (ECS) Triad

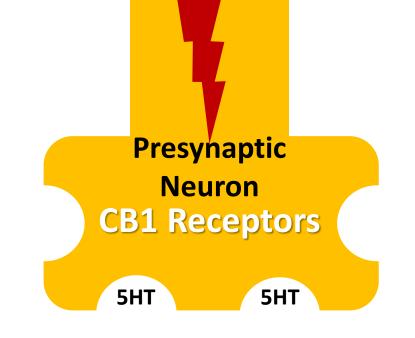
Cannabinoid Receptors CB1, CB2, TRPV1, 5-HT1A

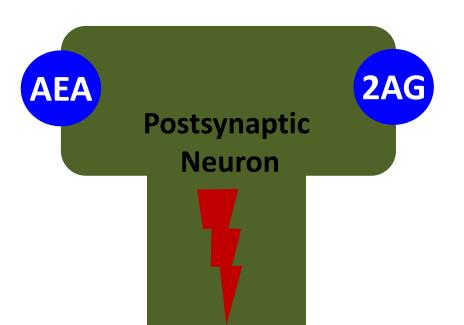
Endogenous
Cannabinoids
[Anandamide (AEA)
2-arachidonoylglycerol (2-AG)]

Regulatory Metabolic/
Catabolic Enzymes
[fatty acid amide hydrolase
(FAAH), monoacylglycerol lipase
(MAGL), and others]

Endocannabinoid System

- Endocannabinoids
 released from post synaptic neuron bind to
 CB₁ receptors in the
 pre-synaptic neuron
- Cause reduction in GABA & glutamate release
- Cause increase in serotonin





Balanced Effects of Endocannabinoids

- Migraines
- Chronic pain
- Production of Fibromyalgia oddeally, if the ECS is functioning normally, a person might enjoy a normal mental state, without pain, have good digestive function, etc.
- Wetabolic syndrome
- Obesity & over-eating
- Increased inflammation
- Insulin resistance/diabetes
- Mental health instability

PTSD

Clinical Endocannabinoid Deficiency

Endocannabinoid Tone

- Most important physiologic system involved in establishing and maintaining human health
- Various lifestyle factors including diet and aerobic activity affect the overall ECS function or 'endocannabinoid tone'
- Keeps internal bodily functions stable and controls how we think, feel, and react



Influence of Cannabinoid System

- Modulate neurotransmitter release in a manner that prevents excessive neuronal activity (thus calming and decreasing anxiety)
- Reduces pain and inflammation
- Regulates movement and posture control
- Regulates sensory perception, memory, and cognitive function



Published in final edited form as:

FEBS J. 2013 May; 280(9): 1918–1943. doi:10.1111/febs.12260.

Modulating the endocannabinoid system in human health and disease: successes and failures

Pál Pacher and George Kunos

Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland, USA

Abstract

The discovery of the endocannabinoid system (ECS; comprising of G-protein coupled cannabinoid 1 and 2 receptors, their endogenous lipid ligands or endocannabinoids, and synthetic and metabolizing enzymes, triggered an avalanche of experimental studies that have implicated the ECS in a growing number of physiological/pathological functions. They also suggested that modulating ECS activity holds therapeutic promise for a broad range of diseases, including neurodegenerative, cardiovascular and inflammatory disorders, obesity/metabolic syndrome, cachexia, chemotherapy-induced nausea and vomiting, tissue injury and pain, among others. However, clinical trials with globally acting CB₁ antagonists in obesity/metabolic syndrome, and other studies with peripherally restricted CB_{1/2} agonists and inhibitors of the endocannabinoid metabolizing enzyme in pain introduced unexpected complexities, and suggested that better understanding of the pathophysiological role of the ECS is required in order to devise clinically successful treatment strategies, which will be critically reviewed in this brief synopsis.

Nature and the Endocannabinoid System

Cannabinoid Receptors [CB1, CB2, TRPV1, 5-HT1A]

Phyto-Cannabinoids [THC & CBD]

Endogenous
Cannabinoids
[Anandamide (AEA)
2-arachidonoylglycerol (2-AG)]

Regulatory Metabolic/
Catabolic Enzymes
[fatty acid amide hydrolase
(FAAH), monoacylglycerol lipase
(MAGL), and others]

Endocannabinoids

Arachidonoyl ethanolamide (anandamide)(AEA)

2-arachidonoyl glycerol (2-AG)

Cannabidiol (CBD)

OH

OH

OA9-tetrahydrocannabinol (
$$\Delta$$
9-THC)

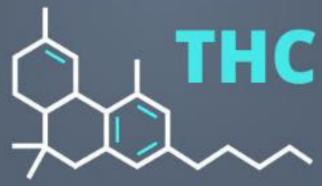
Phytocannabinoids



Cannabinoids in the Body

80+

cannabinoid compounds are found in cannabis plants



(Delta-9-tetrahydrocannabinol)



Psychoactive



Creates the characteristic marijuana "high"



Can relieve pain and inflammation



(Cannabidiol)



Non-psychoactive



Can reduce negative psychoactive effects of THC



Responsible for many of the medical benefits of cannabis

Analgesic

Relieves pain and inflammation

Relaxation

Creates sense of relaxation and well-being

Drowsiness

Induces sleep

Euphoria

Creates "high"

Appetite Stimulant

Creates urge to eat

EFFECTS



Anti-depressant

Combats anxiety and depression

Anti-convulsant

Suppresses seizure activity

Anti-oxidant

Combats neurodegenerative diseases

Anti-psychotic

Combats psychosis

Neuro-protective

May protect neurons in the brain

Anti-emetic

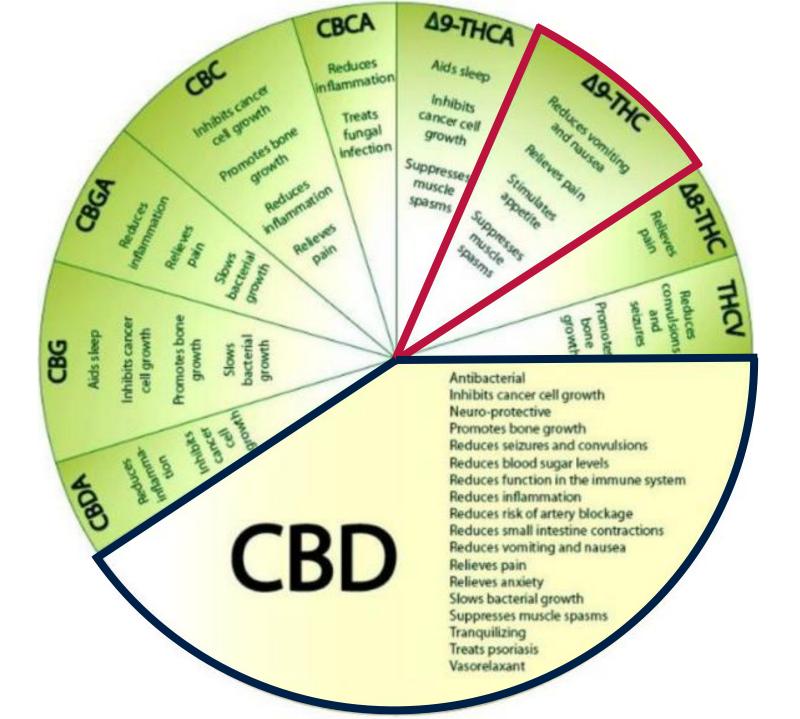
Reduces nausea and vomiting

Anti-inflammatory

Combats inflammation and pain

Anti-tumoral

Combats tumor and cancer cells



What is Difference Between THC & CBD?

Tetrahydrocannabinol (THC)

- Psychoactive or "high"
- Mimics anandamide
- Anxiogenic
- Paranoia potential
- Stimulates appetite
- Sleep inducing

Cannabidiol (CBD)

- Non-psychoactive
- Counters THC effects
- Anxiolytic
- Anti-psychotic
- Decreases appetite
- Promotes wakefulness

ACTION	THC	CBD
Cannabis' main mind altering ingredient	X	
Increases appetite	X	(-)
Reduces nausea	X	
Decreases pain / analgesic	X	X
Muscle control / anti-spasmodic & anti-tremor	X	
Reduces inflammation		X
Reduces seizures / epilepsy / anti-convulsant		X
Suppresses muscle spasm	X	X
Anti-anxiety		X
Lowers intraocular pressure for glaucoma	X	X
Slows bacterial growth		X

Side Effects

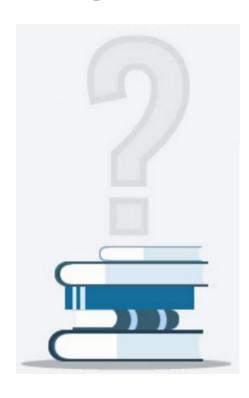
THC



Anxiety and paranoia are well-known potential side effects

May have acute and long-term adverse effects on parts of brain for learning and memory

CBD



Immediate and long-term side effects appear to be minimal

CBD: Preclinical and Clinical Evidence

Anti-Seizure Effects: Elimination or decreased frequency of seizures

Neuroprotective and Anti-Inflammatory Effects:

Alzheimer's, stroke, glutamate toxicity, multiple sclerosis, Parkinson's disease, and neurodegeneration caused by alcohol abuse

Analgesic Effects: Efficacy on central and peripheral neuropathic pain, rheumatoid arthritis, and cancer pain

Anti-Tumor Effects: Antioxidant/anti-inflammatory effects

Anti-Psychotic Effects: May mitigate, particularly induced by THC

Efficacy for Treating Substance Use Disorders: Reduced rewarding effects of morphine and reduced cue-induced heroin seeking

Anti-Anxiety, Stress Reduction Effects: Reducing behavioral and physiological measures of stress and anxiety



Common Effects:

- euphoria
- relaxation
- anxiety
- short term memory impairment

CBD has powerful anti-anxiety properties

- Panic disorder
- Obsessive Compulsive Disorder (OCD)
- Social phobia
- Post-Traumatic Stress Disorder (PTSD)
- Generalized Anxiety Disorder (GAD)
- Mild to moderate depression



Symptoms Following Brain Injury

Thinking/ Remembering	Physical	
Difficulty thinking clearly	Headache Fuzzy or blurry vision	
Feeling slowed down	Nausea or vomiting (early on) Dizziness	
Difficulty concentrating	Sensitivity to noise or light Balance problems	
Difficulty remembering new information	Feeling tired, having no energy	

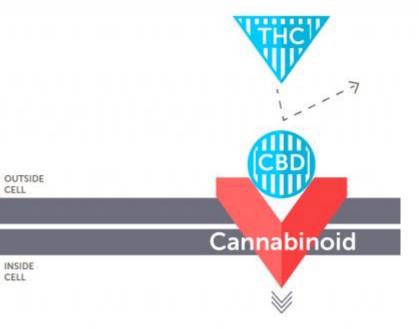


F Emotional/ Mood	Sleep
Irritability	Sleeping more than usual
Sadness	Sleep less than usual
More emotional	Trouble falling asleep
Nervousness or anxiety	

How CBD Treats Anxiety (Mechanisms)

- Blocks FAAH enzyme from breaking down anandamide increasing its levels in the brain
- Serotonin 5-HT1A receptor (partial agonist)
 - CBD (but not THC) binds to receptor, but only stimulates partially
 - Displaces agonists in dose-dependent manner
 - Results in increased serotonin, dopamine
- Hippocampal neurogenesis
 - Stimulation of CB1/CB2 receptor sites upregulates endocannabinoid signaling leading to growth





AILMENTS CBD MAY DECREASE:

 side effects of THC, e.g. anxiety CBD's Therapeutic Impact

Activates 5-HT1A serotonin



Activates 5-HT1A serotonin receptor. Helps with anxiety, addiction, appetite, sleep, nausea, vomiting.



Binds to TRPV1 receptors.

Moderates pain, inflammation, body temperature



Blocks G protein receptor GPR55.

May decrease bone reabsorption and the spread of cancer cells.



Activates peroxisome proliferator activated receptors (PPARs). Has been shown to produce anti-cancer effect and help with Alzheimer's.

CBD as an Antidepressant

- Study results demonstrate that CBD exerts fast and maintained antidepressant-like effects
- CBD significantly enhanced serotonin and glutamate levels
- CBD could represent a novel fast antidepressant drug, via enhancing both serotonergic and glutamate cortical signaling through a 5-HT1A receptor-dependent mechanism

Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT1A receptors. Linge et al. Neuropharmacology. 2016 Apr;103:16-26.



Cannabinoids for Psychiatric Sx

- CBD is emerging as potential treatment for:
 - Psychosis
 - Anxiety disorders
 - Addictive behavior

Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Devinsky, et al. Epilepsia 55(6): 791–802



Psychosis

- Current antipsychotics block dopamine D2 receptors (D2R), a mechanism that doesn't treat the underlying cause or neurochemical disorder
- Acute schizophrenia RCT compared CBD and a standard antipsychotic in 33 patients over 4 weeks. Both groups showed highly significant improvements. CBD had better improvement of negative symptoms and a significantly superior safety profile, lacking amisulpride's extrapyramidal symptoms, weight gain, and elevated serum prolactin.
- In fMRI studies, CBD alters brain function in the limbic and neocortical areas that show abnormalities in schizophrenia. In healthy subjects, the acute psychotomimetic effects of Δ^9 -THC correlated significantly with attenuation of striatal activation during a verbal memory task, whereas CBD augments striatal activation in the same task.

Anxiety disorders

- CBD reduces anxiety in a simulated public-speaking task
- A more recent study in patients with social anxiety disorder confirmed an anxiolytic effect of CBD, and SPECT analysis showed that this was associated with alterations in blood flow in limbic and paralimbic brain areas
- A significant anxiolytic effect has also been demonstrated during emotional processing following exposure to neutral, mildly fearful, and intensely fearful visual cues
- fMRI revealed that this effect correlated with decreased left amygdala activity, an effect opposite of that seen following THC treatment

Addictive Behavior

- Animal models of heroin- and stimulant-dependence show that CBD reduces drug-seeking behavior
 - In a study using cocaine and amphetaminein rats, THC and CBD potentiated the extinction of stimulant-dependence behavior without altering learning or memory retrieval
 - CBD inhibits heroin-seeking behaviors and normalized drug-induced changes within the nucleus accumbens for up to 2 weeks suggesting long-term impact relevant to drug relapse
- Smokers of higher CBD:THC showed lower attentional bias to drug stimuli and lower self-rated liking of cannabis stimuli in 94 cannabis users
- CBD therapeutic for cannabis withdrawal and nicotine dependence



Safety of CBD

The alterations in thinking and perception caused by THC are not observed with CBD. The different pharmacological properties of CBD give it a different safety profile from THC.

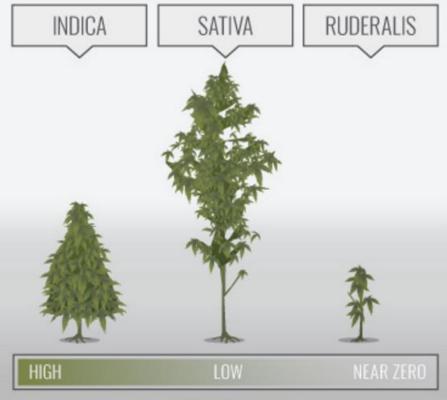
A review of 25 studies on the safety and efficacy of CBD did not identify significant side effects across a wide range of dosages, including acute and chronic dose regimens, using various modes of administration.

Nora D. Volkow, Director, National Institute on Drug Abuse
Testimony on June 24, 2015, to Senate Caucus on International Narcotics Control

THC is found in cannabis plants.

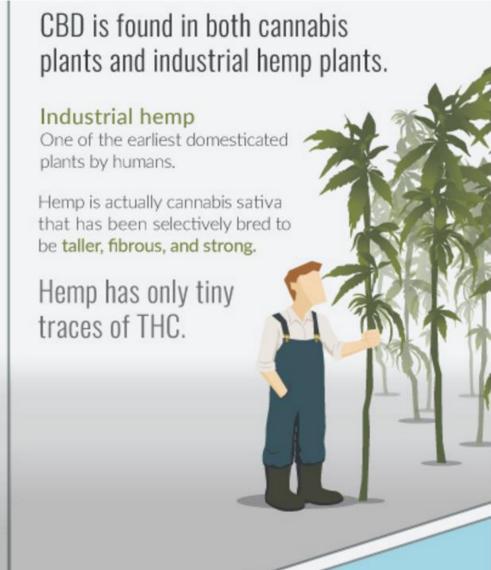
Cannabis

A flowering plant with three species:



THC/CBD RATIO

Ratios highly variable based on individual strains.



Cannabis sativa



- THC content 5-30%
- Cultivated for THC from budding flowers
- Grown under controlled conditions
- Classified as illegal drug
- Use: Recreational/ medical drug

<u>Hemp</u>

- THC content < 0.3%
- Cultivated like bamboo: tall, thick, fast growing
- Grown outside >20 ft
- Classified as food, legal to import into U.S.
- Use: Foods, oils, textiles, rope, fabrics

Comparing Hemp to Medical Cannabis

Agricultural Hemp

- Grown outdoors
- Sequesters CO2
- Environmentally Helpful
- Requires 80% less water
- Energy provided by the sun
- No pesticides required
- Textbook Sustainability

Medical Cannabis

- Enormous Carbon Foot Print
- Environmentally Harmful
- Wasteful Water Demands
- Huge Strain on Power Grid
- Consequences of Fungicides,
 Pesticides and Fertilizers
- Unsustainable



My Clinical Experience with Hemp CBD

- Clinical practice focused on helping people recover from TBI/concussions
- Very effective for anxiety and depression
- Overdoing it is possible creating anxiety
- Concentrated 15mg gelcaps once/twice a day and as needed throughout the day
- One oral dose usually sufficient
- Vaping is a great way to get CBD as needed











The story of Bobby

Lewis MD, Ghassemi P, Hibbeln JR. Therapeutic use of omega-3s in severe head trauma. Am J of Emergency Med, e-publ, Aug 2012

American Journal of Emergency Medicine (2012) xx, xxx-xxx



The American Journal of Emergency Medicine

www.elsevier.com/locate/ajem

Case Report

Therapeutic use of omega-3 fatty acids in severe head trauma[☆]

Abstract

Traumatic brain injury (TBI) has long been recognized as the leading cause of traumatic death and disability. Tremendous advances in surgical and intensive care unit management of the primary injury, including maintaining adequate oxygenation, controlling intracranial pressure, and ensuring proper cerebral perfusion pressure, have resulted in reduced mortality. However, the secondary injury phase of TBI is a prolonged pathogenic process characterized by neuroinflammation, excitatory amino acids, free radicals, and ion

was intentionally treated with substantial amounts of omega-3 fatty acids (n-3FA) to provide the nutritional foundation for the brain to begin the healing process following severe TBI.

In March 2010, a teenager sustained a severe TBI in a motor vehicle accident. After prolonged extrication, he was resuscitated at the scene and flown to a Level I Trauma Center. His Glasgow Coma Scale score was 3. Computerized tomography revealed panhemispheric right subdural and small temporal epidural hematomas and a 3-mm midline shift (Fig. 1). The patient underwent emergency craniotomy and intracranial pressure monitor placement. The patient was rated at Rancho Los Amigos Cognitive Scale Level I, and the attending neurosurgeon's impression was that the injury was likely lethal.



Fish oil helped save our son

r∆11k ✓ Recommend 887

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113

in Share

92 **Q** +1

By Stephanie Smith, CNN

updated 1:40 PM EDT, Mon October 22, 2012



Update on Bobby

- Started on hemp-derived CBD oil June 2015
- Phone call two weeks later....
 - No longer depressed
 - Stopped taking SSRI's
 - Anxiety levels completely vanished
 - Asked a girl for her phone number
 - Set goal to walk without assistance
- 10 months later, an email...



Bobby Ghassemi

Apr 29





to me 🔻

Dr. Lewis,

Thank you so much for giving me CBD oil. It drastically changed my life, I cannot begin to describe it with words. Thanks to CBD oil, I'm feeling much more comfortable in my own skin, I'm being more social, I'm making BIG noticeable changes. I'm doing stand-up comedy now, I have my own place, I got a raise at my job, and I'm feeling VERY optimistic about the future! A friend I made when I was doing improv comedy told me, and I've also been told repeatedly this, that I have a great personality and a great ZEST for life!!!

I can't wait to see what adventures up next in life

All the best, Bobby Ghassemi aka DJ Sh8oon



Other Patient Feedback: 4.5yrs post-TBI

 I'm feeling really good overall. I feel like I'm able to move easier which has been the most noticeable change for me thus far. Most importantly, I started the CBD oil Saturday morning. I can't begin to tell you how life changing this little pill has been for me. I am actually relaxed and not anxious. However, I'm so much more focused than I have been and get a lot done.



Patient Feedback: Anxiety

...introduced me to the benefits of CBD oil –
those who know me know I am a skeptic and
not easily convinced... My personal results
have been truly life-changing – reduced
anxiety, less aches on the tennis court,
overall sense of calm – but most importantly,
no side effects that pharmaceuticals cause.



Practical Notes on Using CBD

- Rule #1: low doses start low and gradually 个
- High doses may overwhelm CB1 receptors and ↑spaciness and anxiety
- Very safe: no receptors in Respiratory & C-V nuclei
- Positive interaction with the Limbic system: stress, anxiety, fear, emotions
- Good quality CBD in measured doses is important
- Possibly synergistic with The Omega-3 Protocol



Summary: Cannabis/CBD

- Cannabis has a long tradition in the healing arts
- The Endocannabinoid system plays a central role in most biological systems
- Is well tolerated and has a calming effect
- Could become a useful tool for a range of psychiatric disorders in the future including those as a result of TBI



The American people are the ultimate owners of U.S. Patent 6,630,507 B1 [Cannabinoids as Antioxidants and Neuroprotectants] that the USG holds for us

READ THIS BOOK:

"The Medicinal Powers Of Cannabis"

By John Hicks, MD

Available At GreenHealthCube.com

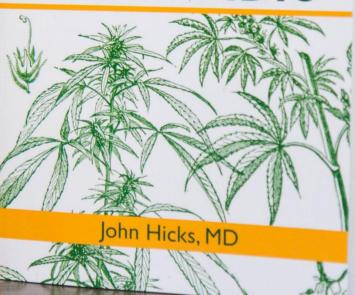
Using a Natural Herb to Heal Arthritis, Nausea, Pain, and Other Ailments

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If you've been diagnosed with a concussion or other head injury,

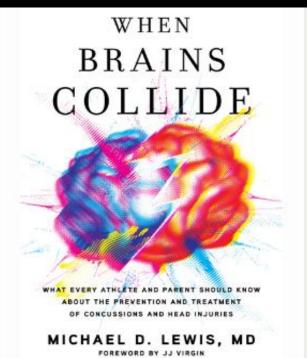
CLICK HERE TO READ THE

Omega-B Protocol

www.brainhealtheducation.org/newsletter



Latest Brain Health News and Information





GOED Exchange 2014

Dr. Lewis' presentation at GOED Exchange 2014 on the innovative uses for Omega-3s for concussions and TBI.