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

AMMG – April 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

- Maurizio Grimaldi, professor of neurology/ neuropsychopharmacology and toxicology, NIMH. Now with Natl Inst on Aging, Scientific Review Branch

(12) **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, CH_3, and $COCH_3$.

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PNAS

Proceedings of the National Academy of Sciences of the United States of America

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

Medical Sciences

Cannabidiol and (−)Δ^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.

Beware! Youn

All W



This may be

by the friendly stranger

"Marihuana"-- a powerf

Murder



WARNI

Dope peddl

put some o

in the o

Address: THE INTER-ST

53 W. Jackson Blvd.

ADULTS ONLY!

The Sweet PILL that MAKES LIFE BITTER!



WOMEN CRY FOR IT - MEN DIE FOR IT!

"REEFER MADNESS"

SEE



YOUTHFUL MARIHUANA VICTIMS



DRUG-CRAZED ABANDON

WHAT ACTUALLY HAPPENS

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**

HHS - NIH

- **Holds a patent for CBD:**
  - **Neuroprotectant, anti-epileptic, 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"**

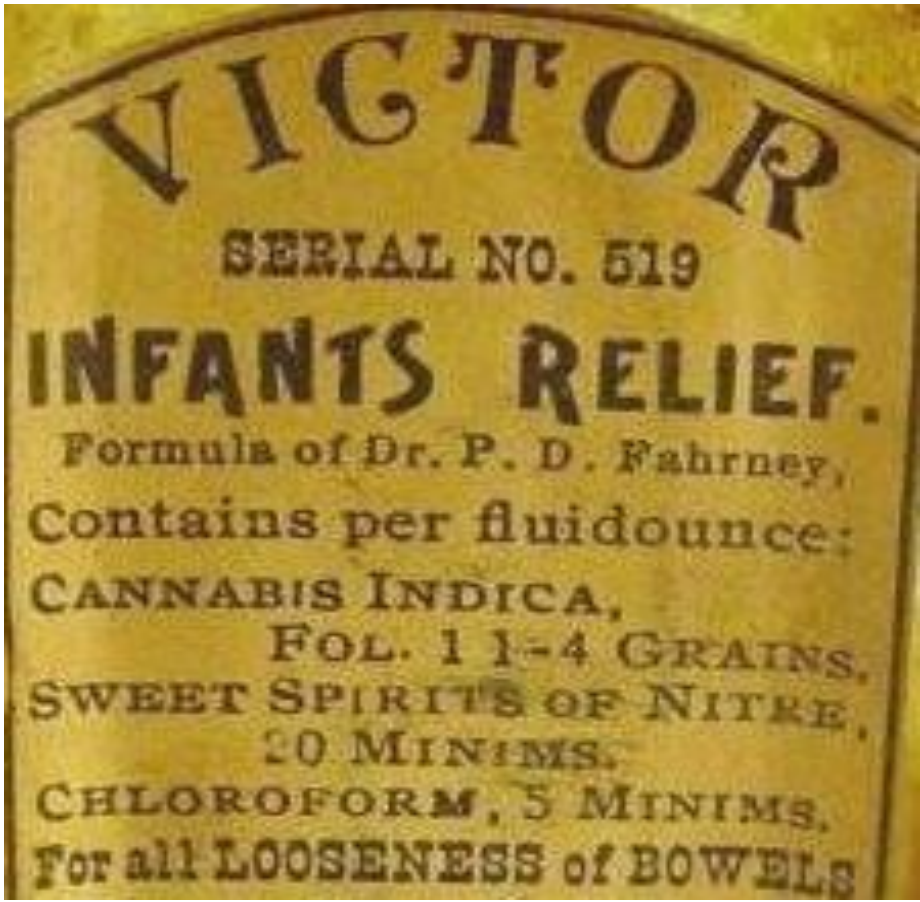

NATIONAL GEOGRAPHIC
WEED
THE NEW SCIENCE OF MARIJUANA
Should Captive Dolphins Be Freed?
Dry Times Are Here for the Aral Sea
Living Goddesses of Nepal
TIME
The Highly Divisive, Curiously Underfunded nd Strangely Promising
orld of Pot Science
CE BARCOTT & MICHAEL SCHERER

History: Cannabis as Medicine

- **2900 BC: Chinese Emperor Fu His - popular medicine that possessed both yin and yang**
- **1450 BC: Book of Exodus (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 *required* 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



AS ACTIVE AS INDIAN CANNABIS

We are marketing a reliable fluid extract of *Cannabis Sativa* 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.

Supplied in pint, ½-pint and 5-pint bottles.

PARKE, DAVIS & COMPANY

HOME OFFICES AND LABORATORIES, DETROIT, MICH.





CANNABIS INDICA

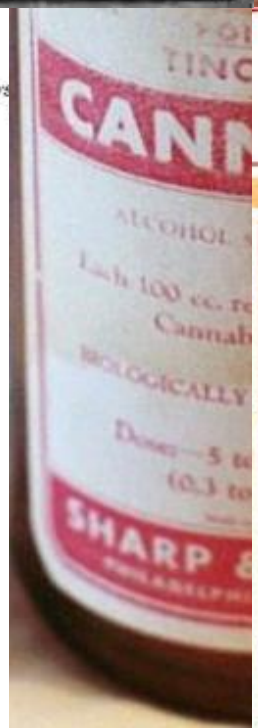
(Catalogue No. 1716)

physiologically; strength is 25 per cent of the U. S. P. solid extract

DOSE—⅓ grain (.043 Gm.)

FROM THE LABORATORY OF
THE WM S. MERRELL COMPANY
CINCINNATI, U.S.A.





One-Fourth Ounce—Solid Extract
CANNABIS AMERICANA
(Cannabis sativa—American grown)
PHYSIOLOGICALLY TESTED
DOSE—1-5 to 1 grain

ELI LILLY & CO.
INDIANAPOLIS
U. S. A.

ONE-FOURTH POUND—SOLID EXTRACT

CANNABIS AMERICANA

PHYSIOLOGICALLY TESTED

(Cannabis sativa—American Grown)

Analgesic, Hypnotic, Antispasmodic and powerful Narcotic

DOSE—1-5 to 1 grain

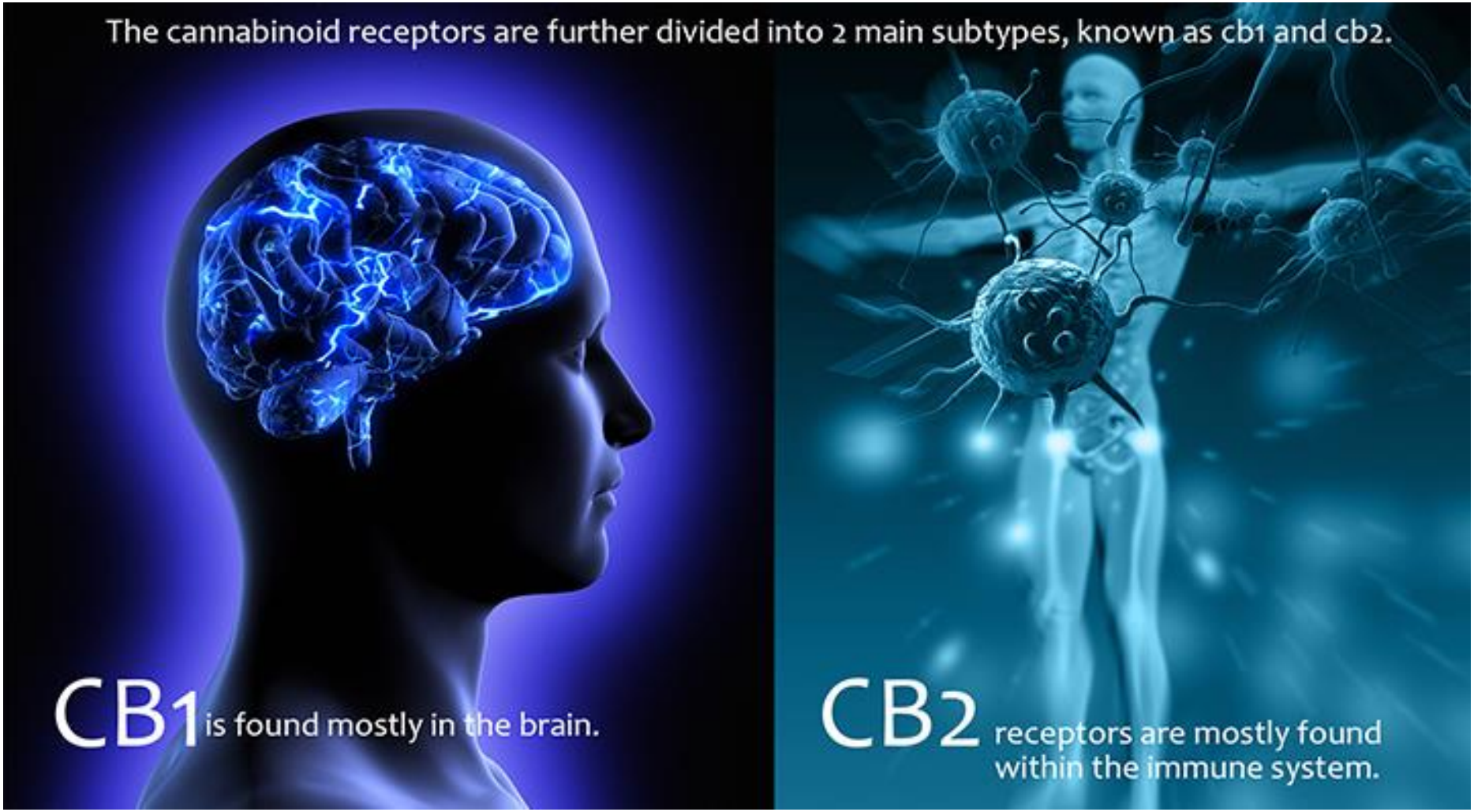
OCT 11 1913

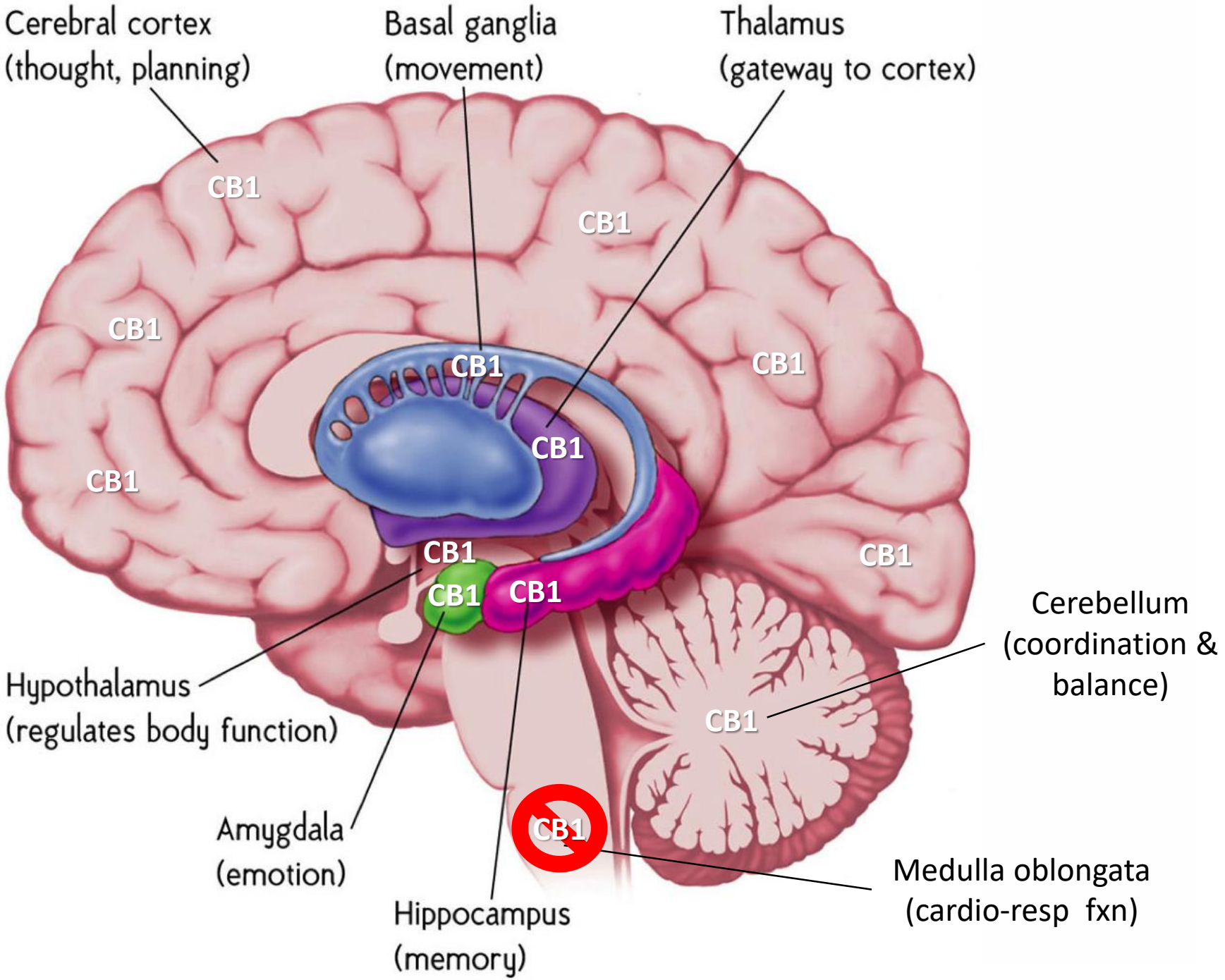
Lilly

ELI LILLY & CO., INDIANAPOLIS, U. S. A.

Guaranteed by Eli Lilly & Co., under Food and Drugs Act, June 30, 1906. Guaranty No. 87.

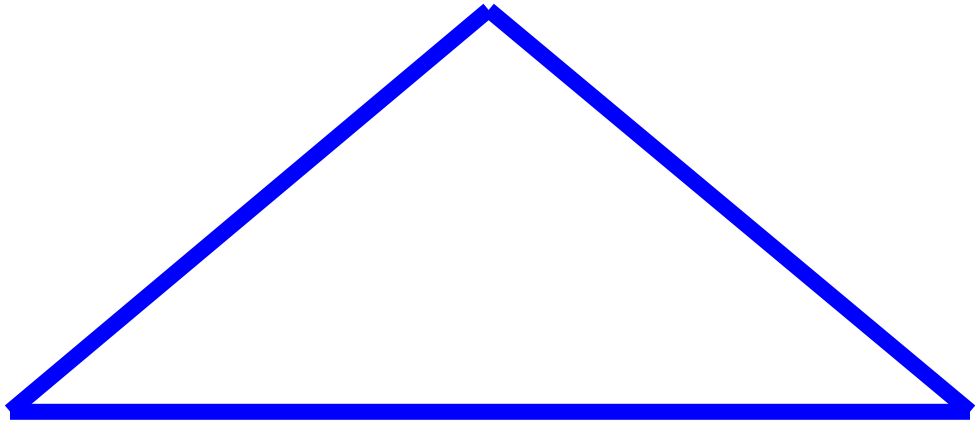
We All Have Cannabinoid Receptors




Cerebral cortex
(thought, planning)
Basal ganglia
(movement)
Thalamus
(gateway to cortex)
CB1
CB1
CB1
CB1
CB1
CB1
CB1
CB1
CB1
CB1
CB1
CB1
CB1
Hypothalamus
(regulates body function)
Amygdala
(emotion)
Hippocampus
(memory)
Cerebellum
(coordination &
balance)
Medulla oblongata
(cardio-resp fxn)

Endocannabinoid System (ECS) Triad

Cannabinoid Receptors
CB1, CB2, TRPV1, 5-HT1A

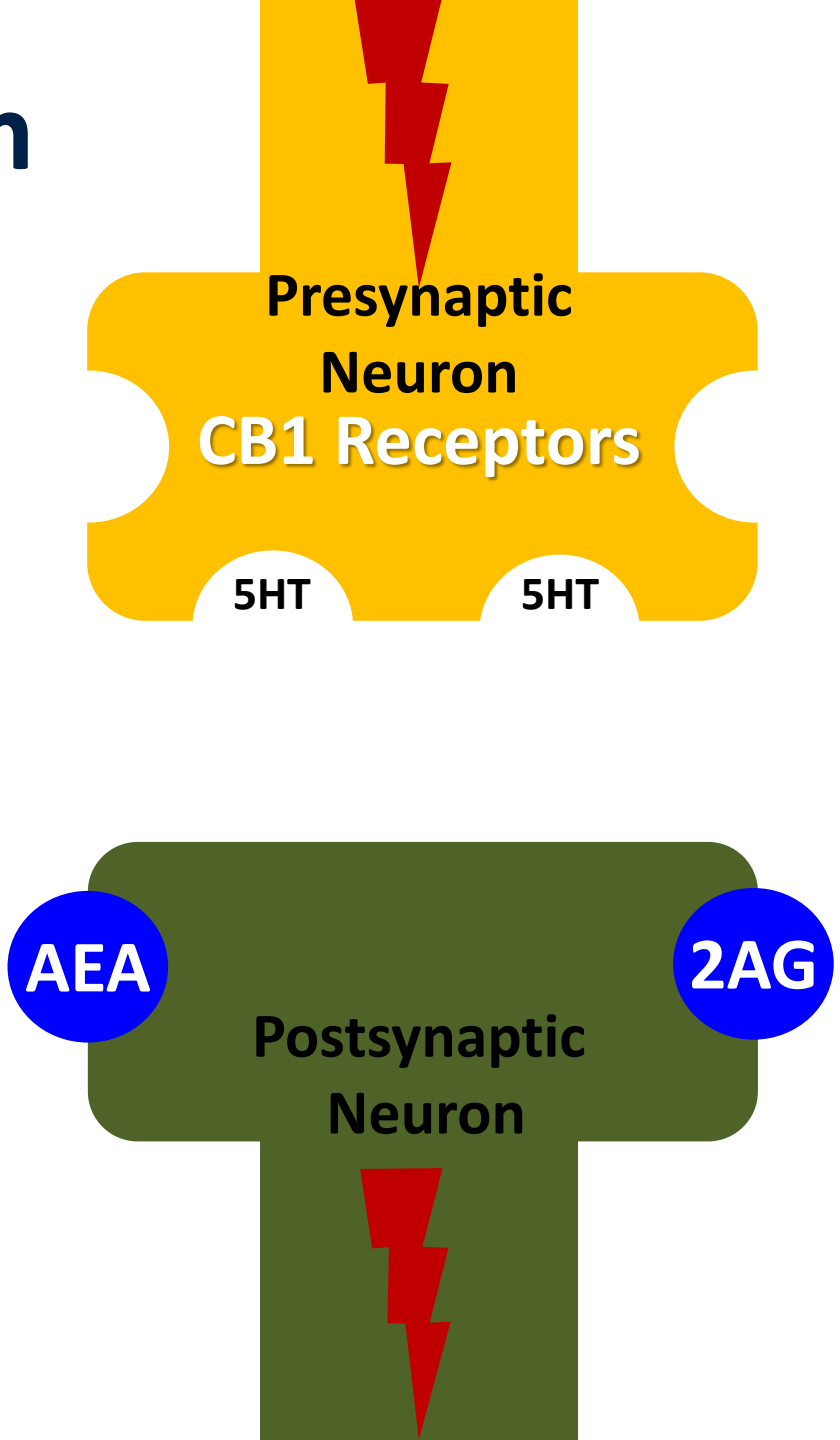


Endogenous Cannabinoids
[Anandamide (AEA) 2-arachidonoylglycerol (2-AG)]

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

Cannabinoid System

- Endocannabinoids released from post-synaptic neuron bind to CB_1 receptors in the pre-synaptic neuron
- Cause reduction in GABA & glutamate
- Stimulates release/ increase in serotonin
- Blocks FAAH enzyme to keep AEA around



Balanced Effects of Endocannabinoids

Ideally, if the ECS is functioning normally, a person might enjoy a normal mental state, without pain, have good digestive function, etc.

Hyperactive/ Too much stimulation

- Metabolic syndrome
- Obesity & over-eating
- Increased inflammation
- Insulin resistance/diabetes
- Mental health instability

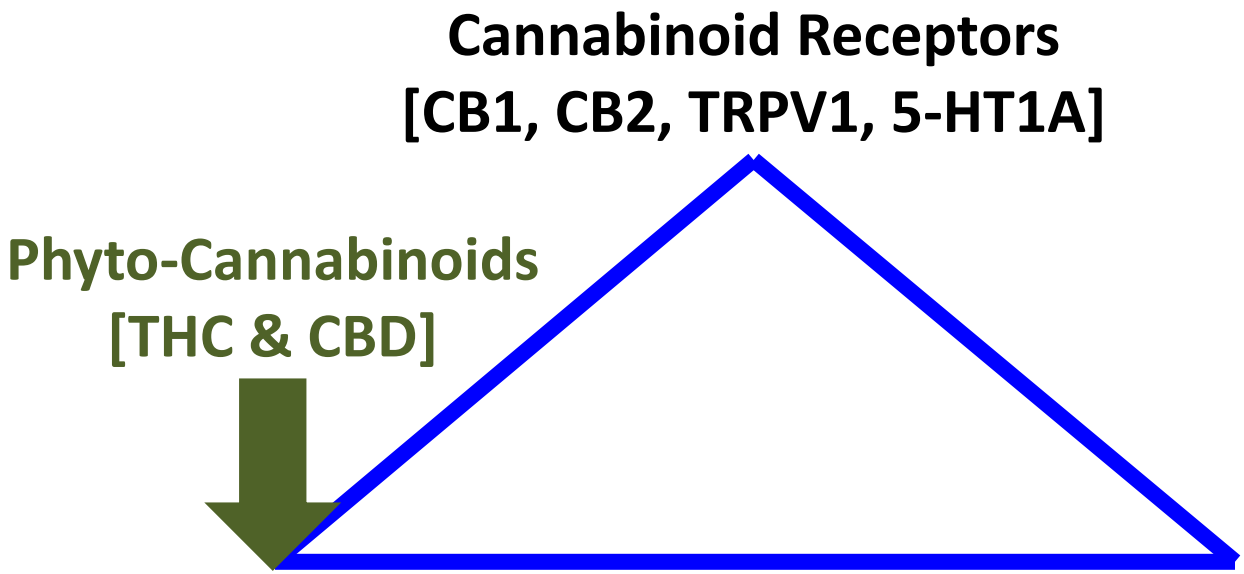
Clinical Endocannabinoid Deficiency

- Migraines
- Chronic pain
- Fibromyalgia
- IBS
- Depression
- PTSD

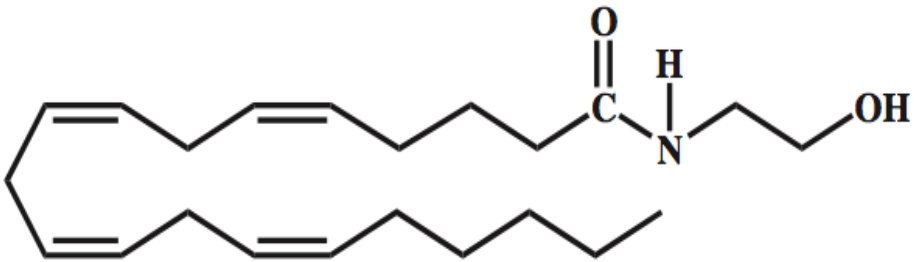
Endocannabinoid Tone

- **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***

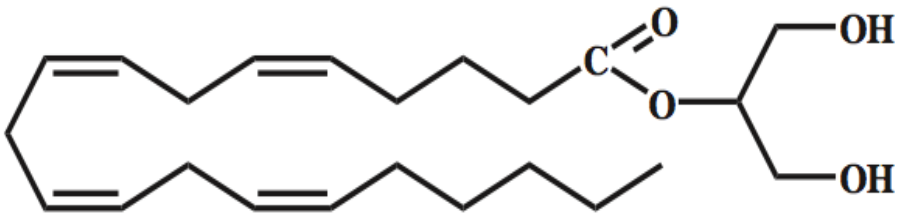
Nature and the Endocannabinoid System



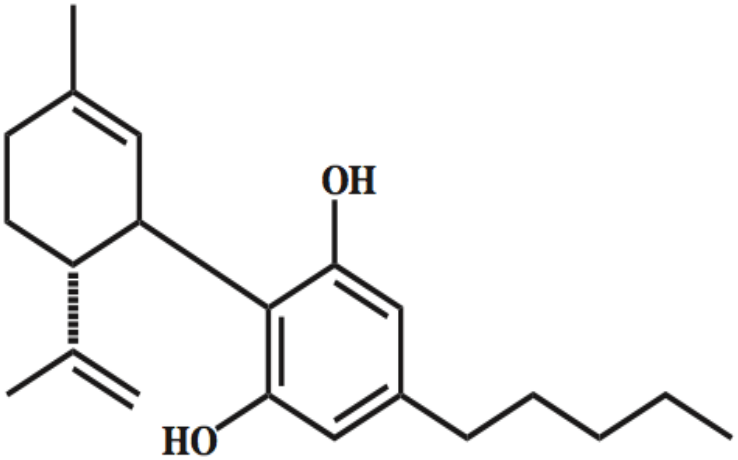
Endocannabinoids



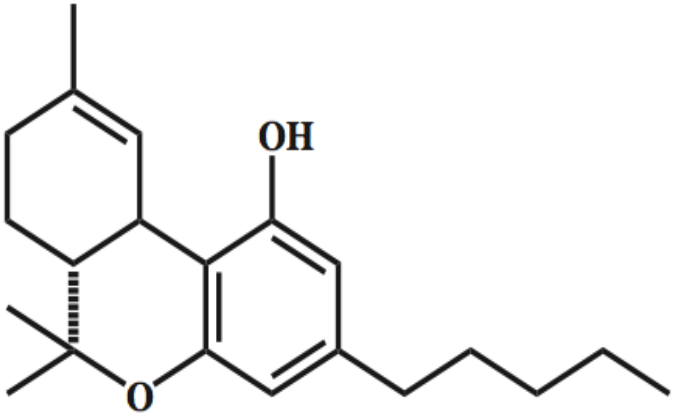
Arachidonoyl ethanolamide (anandamide)(AEA)



2-arachidonoyl glycerol (2-AG)

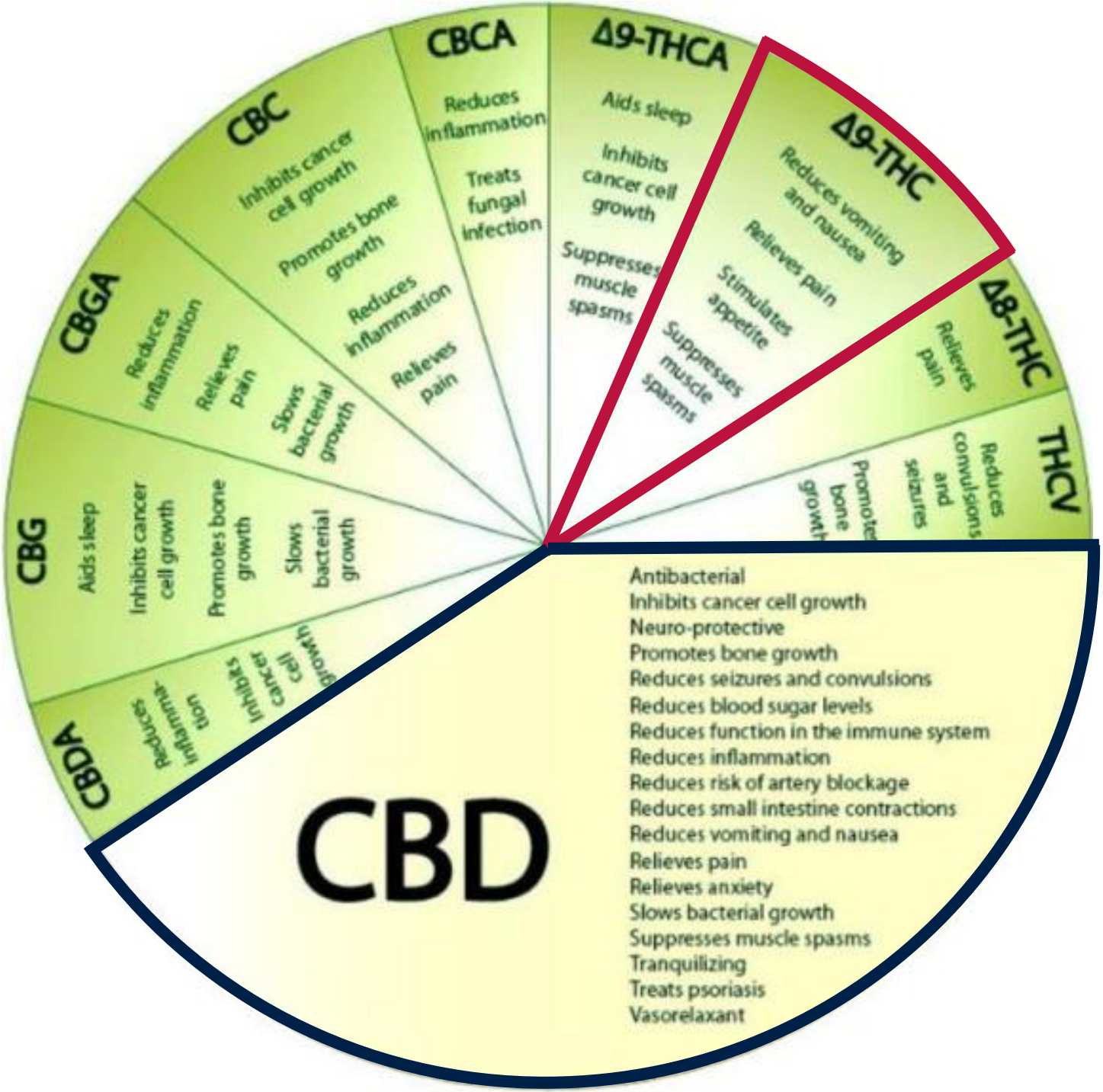


Cannabidiol (CBD)



Δ^9-tetrahydrocannabinol (Δ^9-THC)

Phytocannabinoids

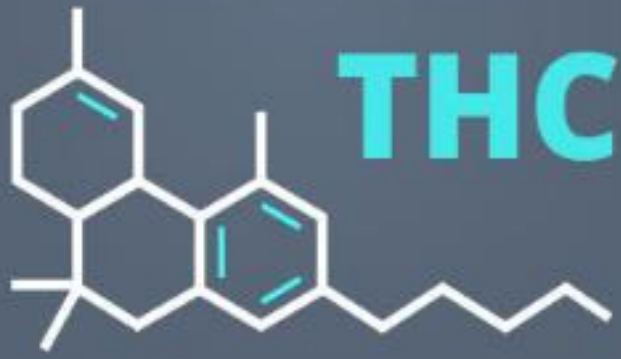

CBDA
Reduces inflammation
Inhibits cancer cell growth
CBG
Aids sleep
Inhibits cancer cell growth
Promotes bone growth
Slows bacterial growth
CBGA
Reduces inflammation
Relieves pain
Slows bacterial growth
CBC
Inhibits cancer cell growth
Promotes bone growth
Reduces inflammation
Relieves pain
CBCA
Reduces inflammation
Treats fungal infection
Δ9-THCA
Aids sleep
Inhibits cancer cell growth
Suppresses muscle spasms
Δ9-THC
Reduces vomiting and nausea
Relieves pain
Stimulates appetite
Suppresses muscle spasms
Δ8-THC
Relieves pain
THCV
Reduces convulsions and seizures
CBD
Antibacterial
Inhibits cancer cell growth
Neuro-protective
Promotes bone growth
Reduces seizures and convulsions
Reduces blood sugar levels
Reduces function in the immune system
Reduces inflammation
Reduces risk of artery blockage
Reduces small intestine contractions
Reduces vomiting and nausea
Relieves pain
Relieves anxiety
Slows bacterial growth
Suppresses muscle spasms
Tranquilizing
Treats psoriasis
Vasorelaxant

Cannabinoids in the Body



80+ cannabinoid compounds are found in cannabis plants

THC



(Delta-9-tetrahydrocannabinol)

- Psychoactive
- Creates the characteristic marijuana "high"
- Can relieve pain and inflammation

CBD



(Cannabidiol)

- Non-psychoactive
- Can reduce negative psychoactive effects of THC
- Responsible for many of the medical benefits of cannabis

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

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

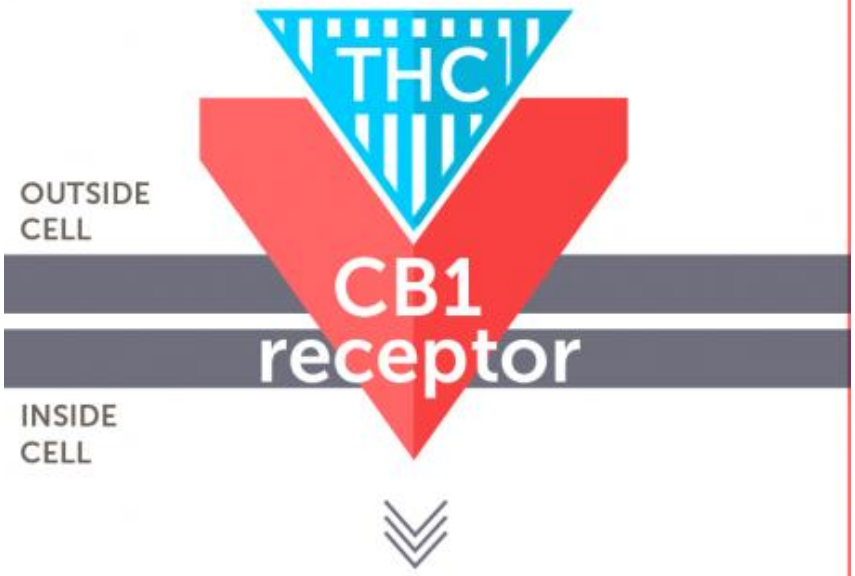
What is Difference Between THC & CBD?

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



Common Effects:

- euphoria
- relaxation
- anxiety
- short term memory impairment

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

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

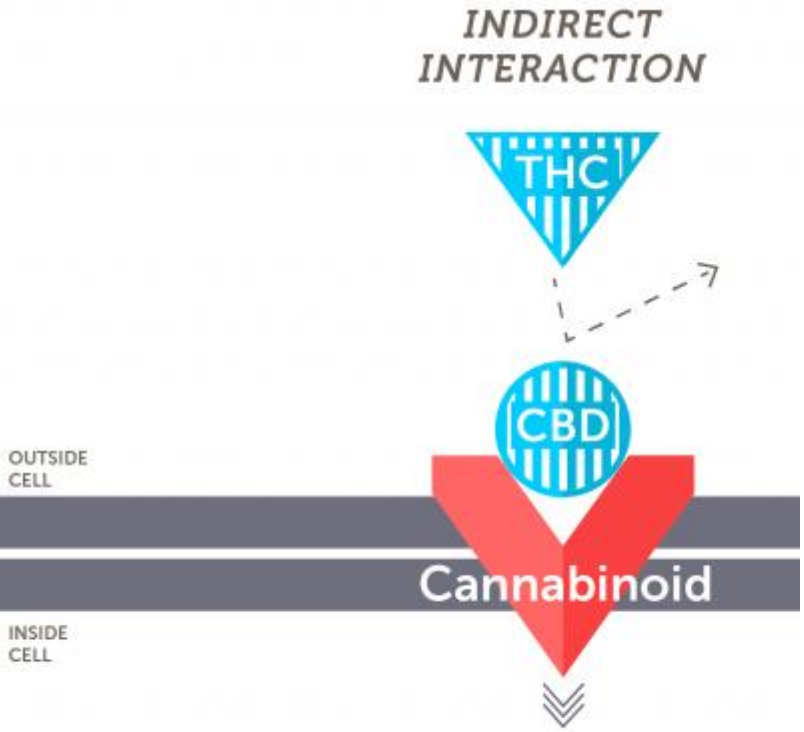
Thinking/ Remembering	Physical
Difficulty thinking clearly	Headache Fuzzy or blurry vision
Feeling slowed down	Nausea or vomiting (early on) Dizziness
Difficulty concentrating	Sensitivity to noise or light Balance problems
Difficulty remembering new information	Feeling tired, having no energy



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

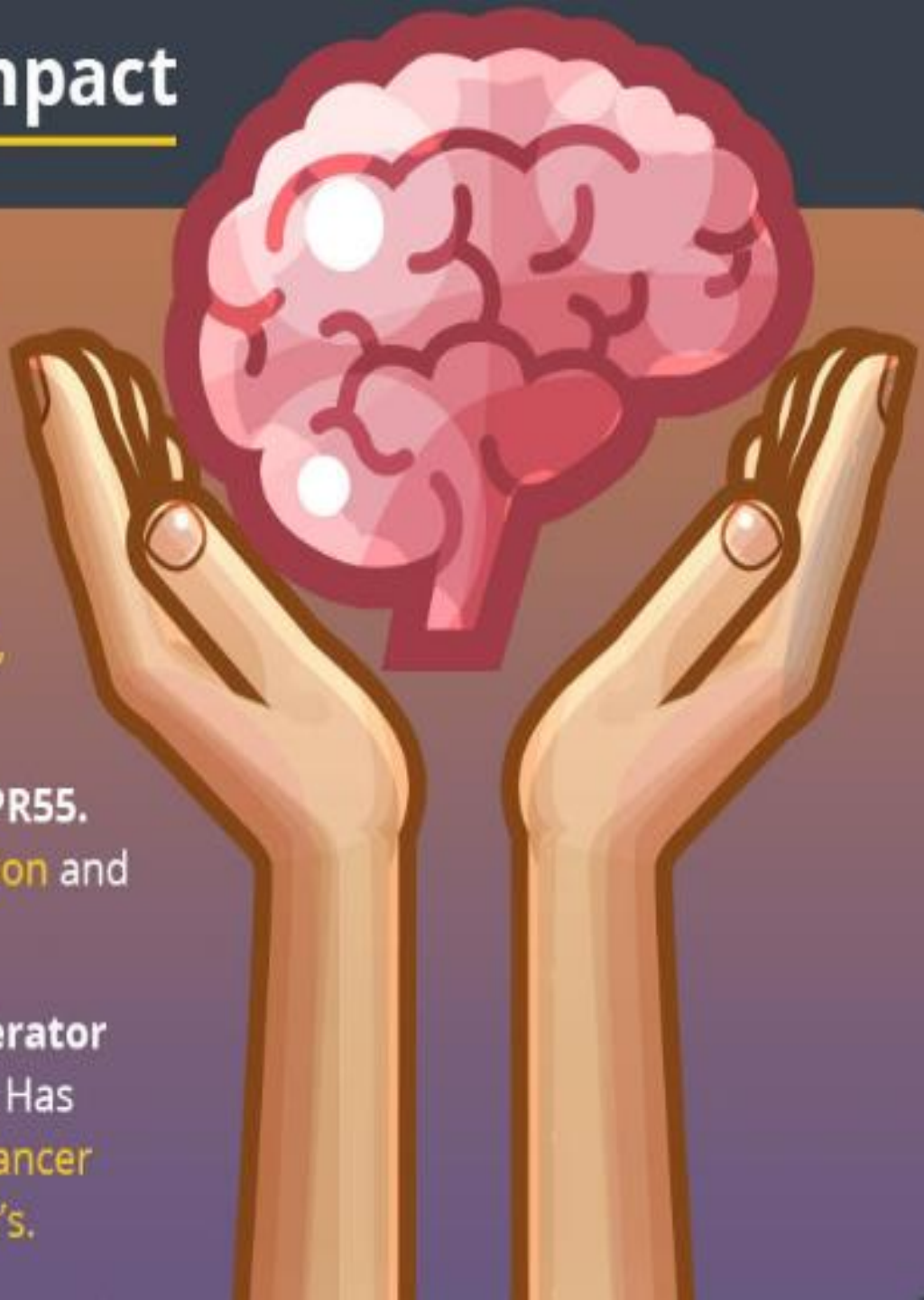
CBD's Therapeutic Impact

Activates 5-HT1A serotonin 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 - Schizophrenia

- RCT compared CBD v. antipsychotic in 33 patients over 4 weeks. Both: highly significant improvements. CBD had better improvement of negative symptoms and superior safety profile, lacking amisulpride's extrapyramidal symptoms, weight gain, and elevated prolactin.
- In fMRI studies, CBD alters limbic and neocortical function that show abnormalities in schizophrenia.
- In healthy subjects, effects of THC correlated significantly on fMRI with attenuation of striatal activation during a verbal memory task, whereas CBD augments striatal activation in the same task.

Devinsky, et al. Epilepsia 55(6): 791–802

Anxiety disorders

- CBD reduced anxiety in simulated public-speaking task
- Social anxiety d/o CBD had anxiolytic effect. SPECT analysis showed alterations in blood flow in para/limbic brain areas
- Anxiolytic effect 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, opposite of that seen following THC treatment

Devinsky, et al. Epilepsia 55(6): 791–802

Addictive Behavior

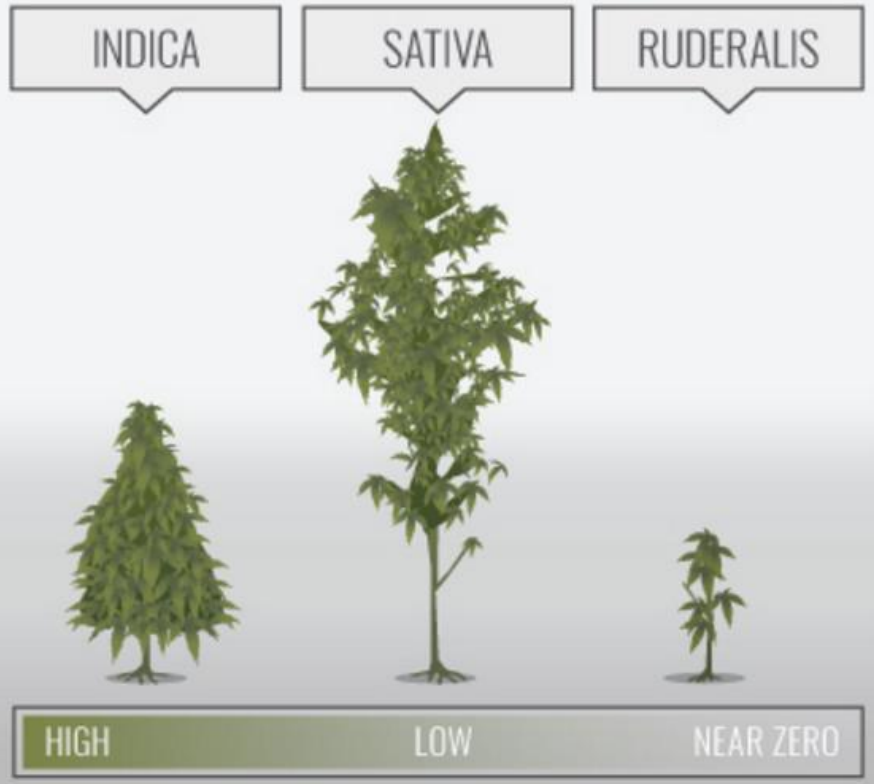
- Animal models of heroin/stimulant dependence show that CBD reduces drug-seeking behavior
  - Cocaine/amphetamine in rats, THC and CBD potentiated the extinction of stimulant-dependence behavior without altering learning or memory retrieval
  - CBD inhibits heroin-seeking behaviors and normalized drug-induced 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 in 94 cannabis users
- CBD therapeutic for cannabis withdrawal, nicotine dependence

Devinsky, et al. Epilepsia 55(6): 791–802

Brain Health
Education and Research Institute

THC is found in cannabis plants.

Cannabis
A flowering plant with three species:



THC/CBD RATIO

Ratios highly variable based on individual strains.

CBD is found in both cannabis plants and industrial hemp plants.

Industrial hemp
One of the earliest domesticated plants by humans.

Hemp is actually cannabis sativa that has been selectively bred to be **taller, fibrous, and strong.**

Hemp has only tiny traces of THC.



Cannabis *sativa*

Marijuana

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

Hemp

- 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

ELSEVIER

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.

www.cnn.com/2012/10/19/health/fish-oil-brain-injuries

Fish oil helped save our son

11k Recommend | 887 Tweet | 113 Share | 92 +1

By **Stephanie Smith**, CNN
updated 1:40 PM EDT, Mon October 22, 2012



Bobby Ghassemi was just 17 years old when he was in a horrific car accident.

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

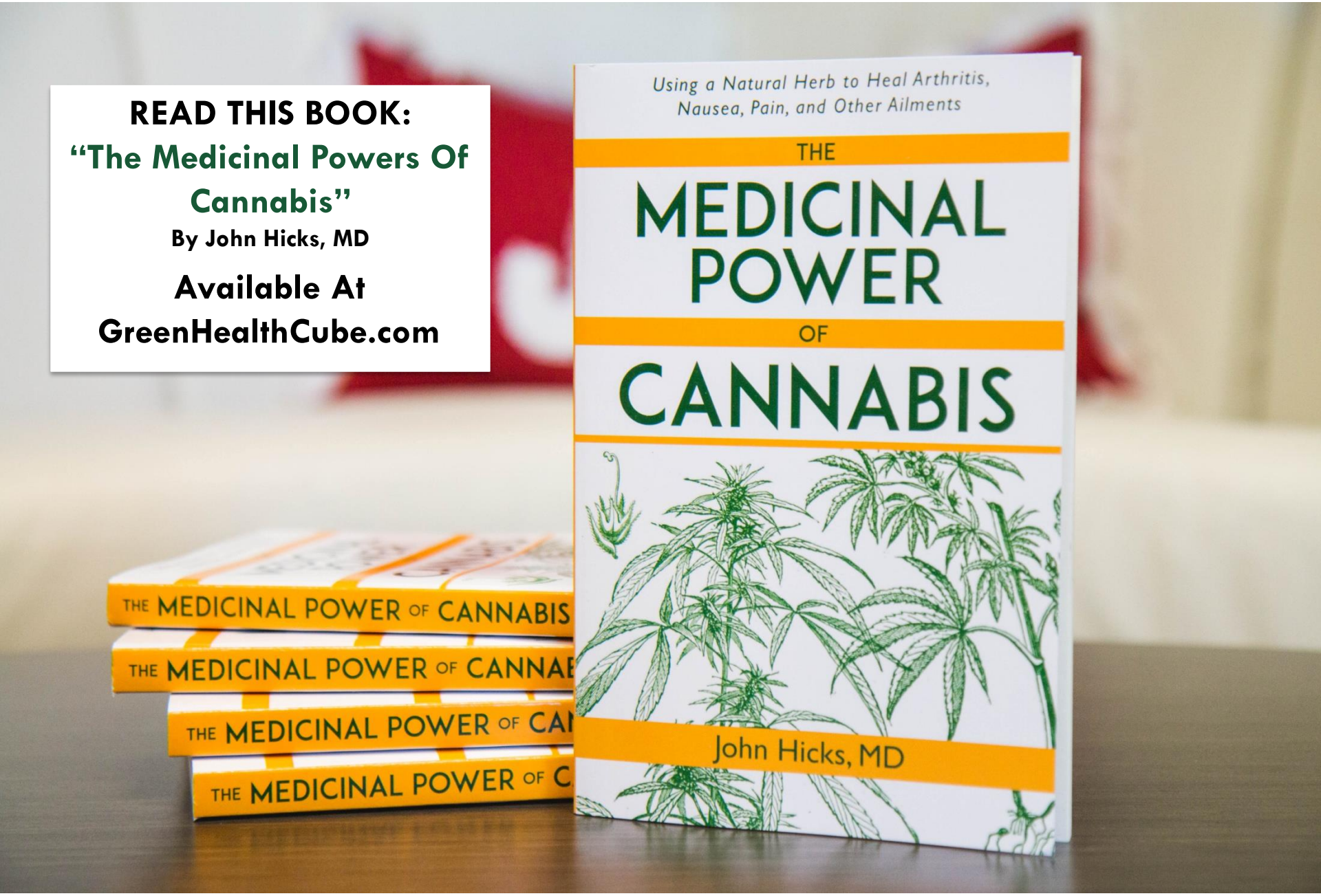
- **…introduced me to the benefits of CBD oil – those who know me know I am a skeptic and not easily convinced… My personal results have been truly life-changing – reduced anxiety, less aches on the tennis court, overall sense of calm – but most importantly, no side effects that pharmaceuticals cause.**

Practical Notes on Using CBD

- **Rule #1: low doses – start low and gradually ↑**
- **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**
- **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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By John Hicks, MD
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Using a Natural Herb to Heal Arthritis, Nausea, Pain, and Other Ailments
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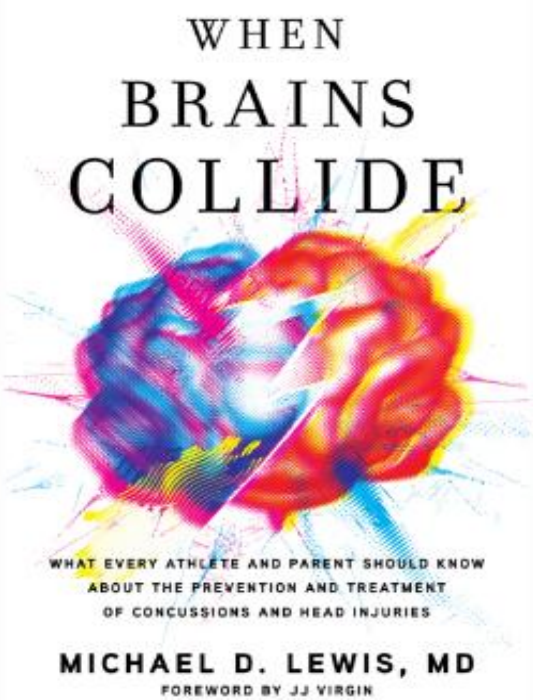



GOED Exchange 2014

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