

The Evolution of Medical *Cannabis*

Mark L. Rabe, MD

Saturday, February 27, 2016





Physicians Round Table & Discussion

The Endocannabinoid System: *Leveraging the Largest Receptor System in the Human Body*

"The Evolution of Medical *Cannabis*"

Mark L. Rabe, MD, ABIHM
Centric Wellness
Founder & Medical Director

"CBD – The Other Cannabinoid"

Stuart Tomc
VP of Human Nutrition
CannaVest Corporation

"Cannabinoids – Dosing & Treatment Options"

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Pres/Director Allegiance Wellness
Center & SD Pain Management

Saturday, February 27, 2016
Watergarden Business Park
5755 Oberlin Dr #301
San Diego, CA 92121



The Evolution of Medical *Cannabis*

Mark L. Rabe, MD

1. History of Medical *Cannabis*
2. The Endocannabinoid System
3. *Cannabis* as Medicine:
 - Relief of Pain
 - Antioxidation/Neuroprotection
 - Anti-Cancer
4. Cannabinoid Delivery Systems
5. The Future: Targeted Cannabinoid Chemotherapy
6. Integrating Medical *Cannabis* into Your Practice
7. Discussion



Disclosures

The presenter has a financial relationship with and/or receives or has received financial consideration from **Centric Wellness**, **Green Medical Solutions, LLC**, and **PharmaCyte Biotech, Inc.**

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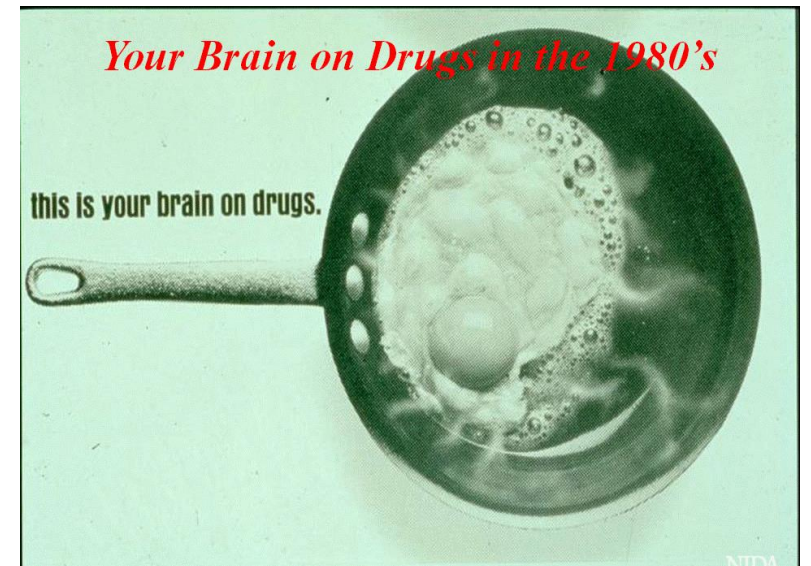
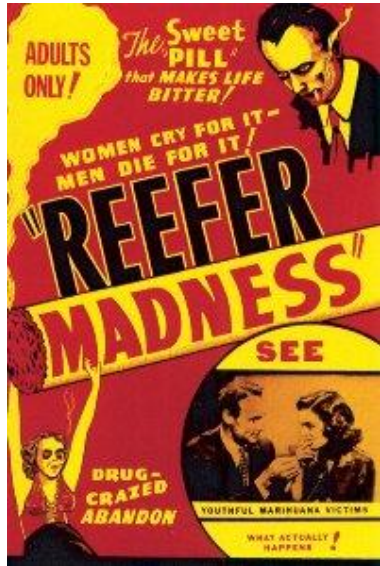
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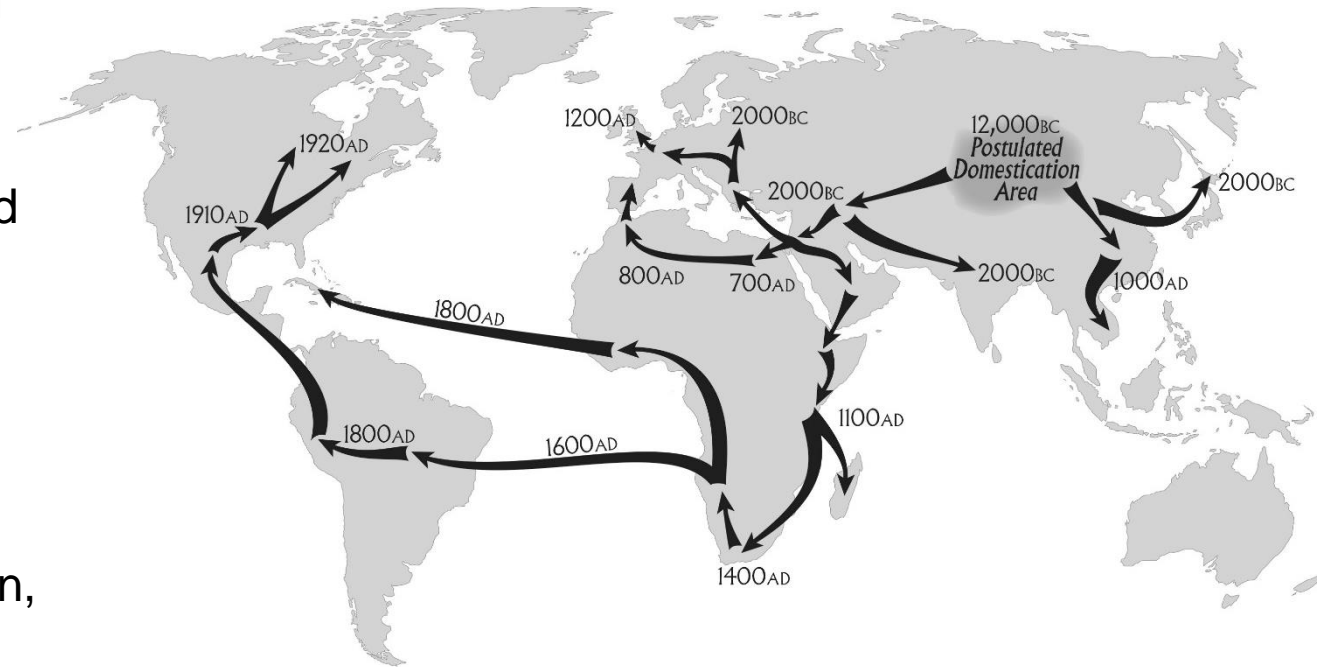
Marijuana "Education" Over the Past Century



The History of Medical *Cannabis*

The Migration of *Cannabis* Over Thousands of Years

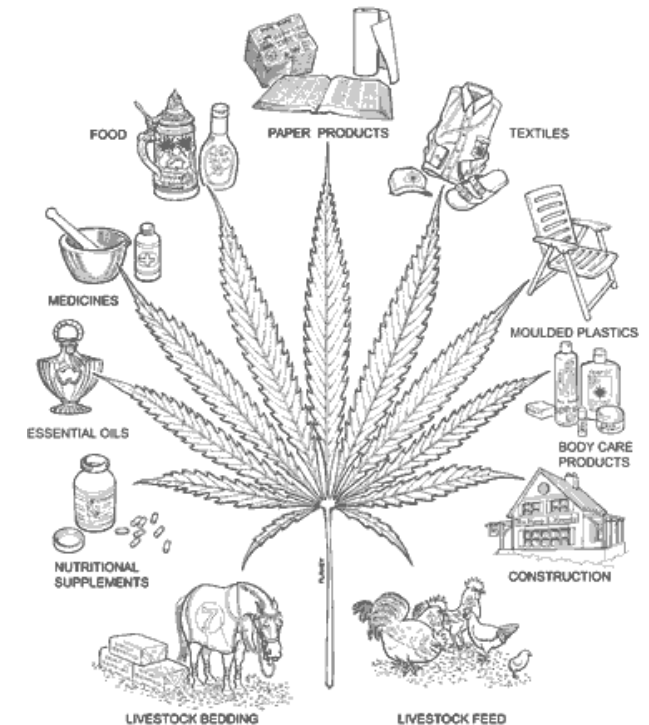
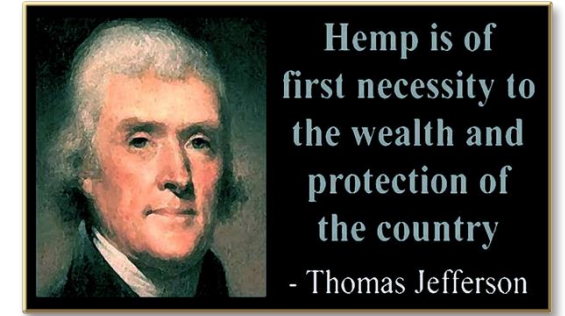
- Due to its psychoactive and medicinal properties, *Cannabis* has been a source of considerable spiritual, religious, and medicinal interest.
- From its earliest recorded use in China and India, the use of *Cannabis* as a medicine spread westward to Persia and Arabia.
- Many other ancient cultures such as the Greeks, Romans, and the Assyrians used *Cannabis* for many things – including the control of muscle spasms, reduction of pain, and for indigestion.



The History of Medical *Cannabis*

Hemp in the United States

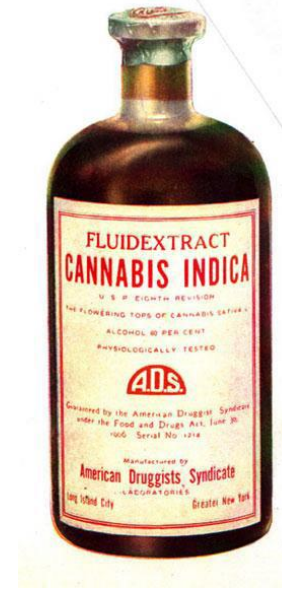
- In **1776**, the Declaration of Independence was drafted on hemp paper.
- Both President George Washington and President Thomas Jefferson were advocates of hemp as a valuable cash crop. Jefferson urged farmers to grow the crop in lieu of tobacco.
- By the **1850s**, hemp had become the third largest agricultural crop grown in North America. Hemp can be used as paper, fuel, fabric, and even food.



The History of Medical *Cannabis*

Cannabis – Recreational or Medicine?

- The question persisted: Is *Cannabis* a modern medicine or an intoxicant?
- In the years between the **1850's** and the **1930's** that *Cannabis* began to lose its image as a medicine as it was increasingly portrayed as an evil intoxicant.
- Nevertheless, in the **early 1900's**, at least **27** medicines containing *Cannabis* were available in the United States.

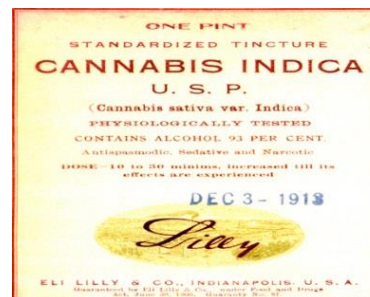


U.S. Pharma companies selling tinctures of *Cannabis* in the early 1900s, including Eli Lilly and Parke Davis.

A great clinical trial:



vs.




Results = ???



The History of Medical Cannabis

Marijuana Receives Bad Press...

- In 1936 the **International Narcotic Education Association** along with the **Federal Bureau of Narcotics** published statements in which “marihuana” was called a “*killer drug*” and a “*narcotic poison*.”
- **Reefer Madness** (aka “**Tell Your Children**”) is a 1936 film revolving around the tragic events that ensue when high school students are lured to try marijuana.
- **William Randolph Hearst**, who was strongly “anti-marijuana” and “anti-hemp,” joined the campaign by providing journalistic content and delivery.

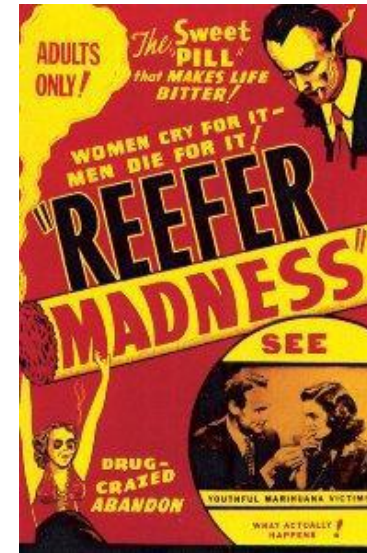
Beware! Young and Old—People in All Walks of Life!


This  may be handed you by the friendly stranger. It contains the Killer Drug “Marihuana”—a powerful narcotic in which lurks **Murder! Insanity! Death!**


WARNING! Dope peddlers are shrewd! They may put some of this drug in the  or in the  or in the tobacco cigarette.

WRITE FOR DETAILED INFORMATION, ENCLOSED 12 CENTS IN POSTAGE.—MAILING COST

Address: THE INTER-STATE NARCOTIC ASSOCIATION
(Incorporated not for profit)
53 W. Jackson Blvd. Chicago, Illinois, U. S. A.





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| New York Evening Journal | Chicago American | San Francisco Call-Bulletin |
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| Rochester Journal | Washington, D. C., Times | Los Angeles Examiner |
| Rochester Sunday American | Boston American | Los Angeles Herald |
| Syracuse Journal | Boston Sunday Advertiser | Wisconsin News |
| Syracuse Sunday American | Detroit Times | Seattle Post-Intelligencer |
| Atlanta Georgian | Baltimore News | San Antonio Light |
| Atlanta Sunday American | Baltimore Sunday American | Pittsburgh Sun-Telegraph |
| | Omaha Bee-News | |

The History of Medical *Cannabis*

Marijuana Use is Restricted

- Strong public reaction led to a federal anti-marijuana law in **1937** - the **Marijuana Tax Act** was signed by President Roosevelt. This act placed a tax of \$1 for medical use and \$100 for recreational use. This was a large factor why doctors stopped using *Cannabis* as a medicine.
- **After 1937** it became virtually impossible for physicians to obtain or prescribe *Cannabis* preparations for their patients.
- And the medical profession has been denied access to a versatile medicine with a history of therapeutic utility going back thousands of years.



MARIJUANA TAX STAMP of 1937 established governmental control over the transfer and sale of the plant. The stamp was never available for private use.

THE REAL REASON CANNABIS IS ILLEGAL: MEET HARRY ANSLINGER, HEAD OF THE DEA FROM 1930-1962

- Harry J. Anslinger, "Testimony to US Congress supporting Marihuana Tax Act, 1937"



Harry J. Anslinger
First commissioner of the
U.S. Treasury Department's
Federal Bureau of Narcotics
(now the DEA)

"There are 100,000 total marihuana smokers in the U.S. and most are Negroes, Hispanics, Filipinos, and entertainers. Their Satanic music, jazz, and swing, result from marihuana use. This marihuana causes white women to seek sexual relations with Negroes, entertainers, and any others."

"...the primary reason to outlaw marihuana is its effect on the degenerate races."

"Marihuana is an addictive drug which produces in its users insanity, criminality, and death."

"Reefer makes darkies think they're as good as white men."

"Marihuana leads to pacifism and communist brainwashing."

"You smoke a joint and you're likely to kill your brother."

"Marihuana is the most violence-causing drug in the history of mankind."

The History of Medical *Cannabis*

Marijuana Becomes a Schedule I Drug

- **Controlled Substances Act of 1970** – all drugs placed into “schedules.”
- Marijuana was provisionally placed into **Schedule I**, thereby defined as having high potential for abuse, no currently accepted medical use, and lack of accepted safety data.
- Other Schedule I controlled substances: heroin, LSD, MDMA (Ecstasy) and methaqualone (Quaaludes).
- Nixon shelved the “**Shafer Commission**” report of **March 22, 1972**, thereby keeping marijuana in Schedule I.
- The enforcement of **Schedule I** status acts as an **effective deterrent** to pharma companies, researchers, universities, healthcare systems, insurance providers, doctors, and patients.



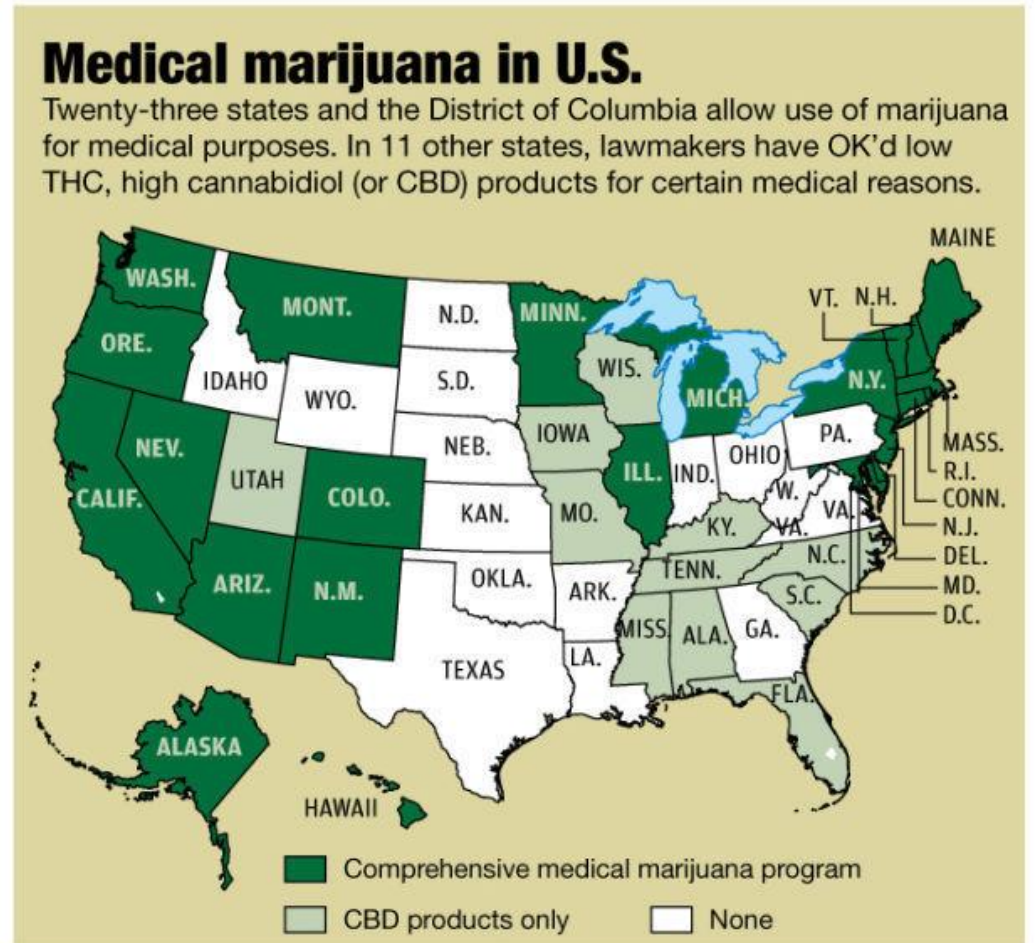
“ ... Therefore, the Commission recommends ... [that the] possession of marijuana for personal use no longer be an offense, [and that the] casual distribution of small amounts of marihuana for no remuneration, or insignificant remuneration, no longer be an offense.”
– Shafer Commission, 1972



The History of Medical *Cannabis*

“Medical Marijuana” in Present Times

- In **1996**, California became the first state to allow marijuana for medical use with passage of the **Compassionate Use Act of 1996 (Prop 215)**.
- **CA Prop 215** “...any serious condition for which marijuana provides relief.”
- By **2016**, **34 states** have enacted some form of medical marijuana-related legislation.
- **Four states (CO, OR, WA, AK)** have made marijuana legal for regulated adult use. More states (including CA Nov 2016) are considering similar legislation.



Source: National Conference of State Legislatures

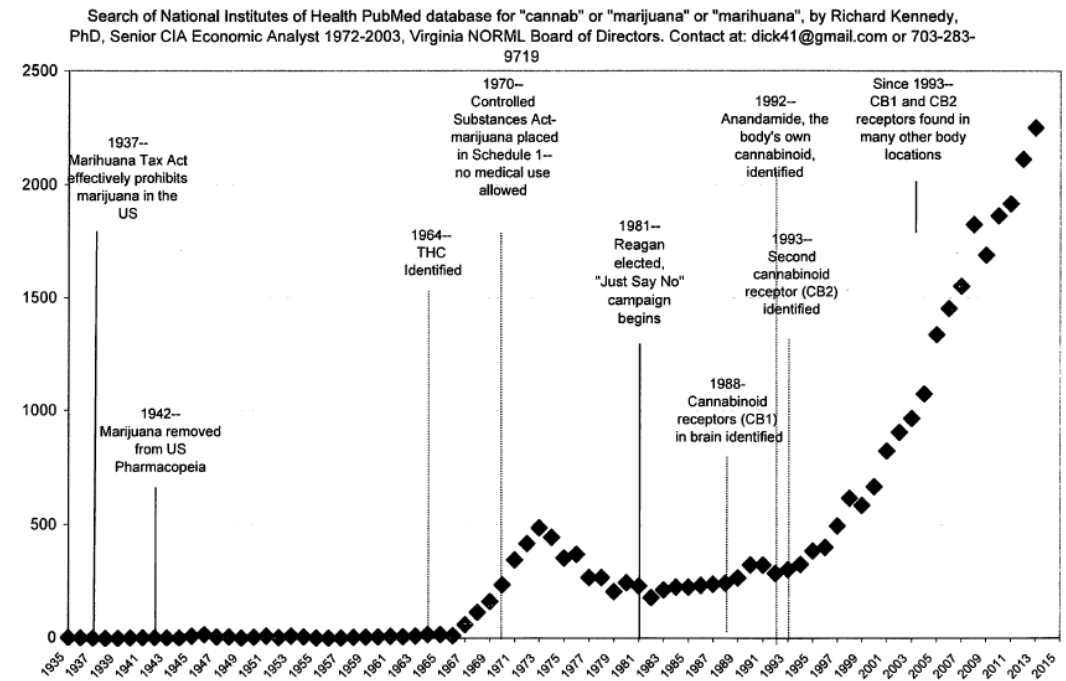
Sheila Story/Lee Enterprises

The History of Medical *Cannabis*

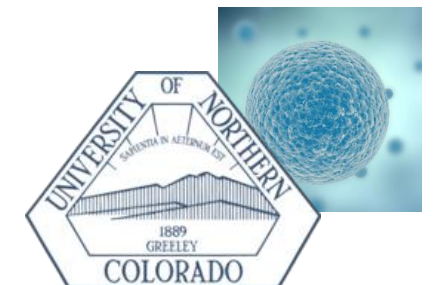
Cannabis/Cannabinoid Research Explodes

- **PubMed.gov: 37,000+** articles published in the medical literature; **7,000+** articles on endocannabinoids.
- **ClinicalTrials.gov: 241** trials underway.
- **DEA** has authorized **National Institute on Drug Abuse (NIDA)**, the sole federally legal source of research marijuana in the U.S., to significantly ramp up its marijuana production quota.

| Basic class—schedule I | Previously established 2014 quota (g) | Adjusted 2014 Quota (g) |
|------------------------|---------------------------------------|-------------------------|
| Marijuana | 21,000 | 650,000 |



cmcr.ucsd.edu



Cell-in-a-Box® + cannabinoids

The Endocannabinoid System

What are “Phytocannabinoids”?

- A group of molecular compounds unique to the *Cannabis* plant which exert a variety of medicinal actions in the human body.
- It is because of **phytocannabinoids** that the “**endocannabinoid system**” was discovered.



- 538 natural compounds identified in cannabis
- Of these, 108 are identified as “cannabinoids” (unique compounds with 21 carbon atoms)
 - 10 main types
 - 14 different subtypes

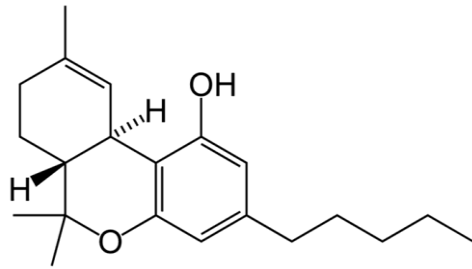
- **THC (delta-9-tetrahydrocannabinol)**
- **CBD (cannabidiol)**

Hanus LO. Pharmacological and Therapeutic Secrets of Plant and Brain (Endo)Cannabinoids. *Medicinal Research Reviews* 2009; 29(2)213-271. Hebrew University, Israel.



The Endocannabinoid System

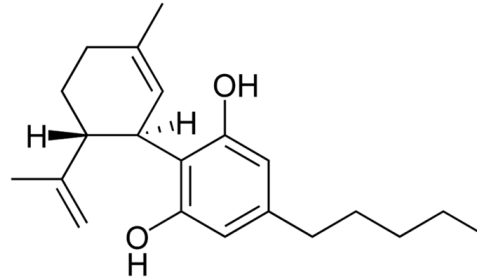
Phytocannabinoid Molecules Were Discovered in 1964



THC (delta-9-tetrahydrocannabinol)

Properties:

Pain relief, anti-inflammatory, antioxidant, anti-nausea, mood elevation, anti-cancer



CBD (cannabidiol)

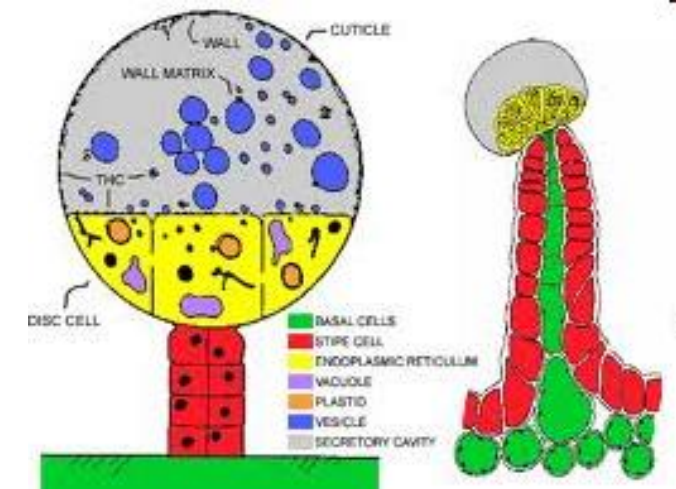
Properties:

Pain relief, anti-inflammatory, antioxidant, antispasmodic, anxiety relief, nerve protection, anti-cancer

Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc.* 1964; 86:1646–1647.



THC was discovered in Israel in 1964.



The Endocannabinoid System

Endocannabinoid Receptors Were Discovered in 1988

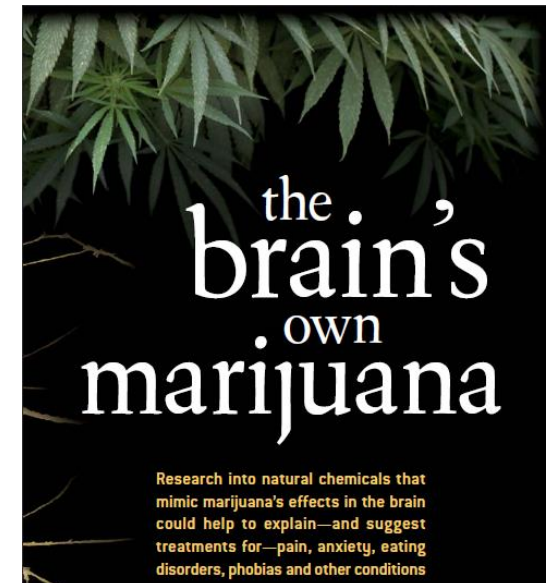
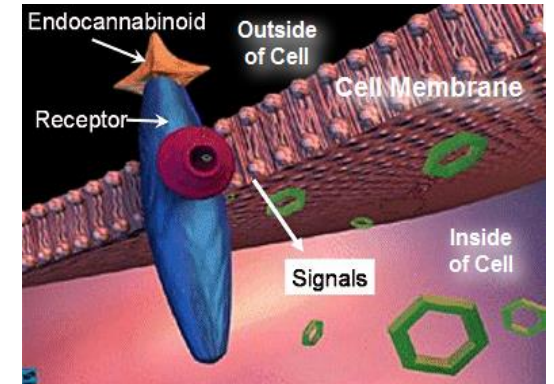
For over 20 years scientists wondered:

Q: “How does THC exert its actions in the human body?”

A: Endocannabinoid receptors.

- Three types of receptors have been described.
 - CB1** – distributed mainly in human **brain tissue**. Also found in **peripheral tissue** where important in maintaining cellular energy balance. On **enteric nerves** where mediates GI system. Mediates the vomiting reflex.
 - CB2** – found mainly in **immune tissues and cells**. Involved in antinociceptive and anti-inflammatory activity.
 - CB3** – theorized, but yet to be found in human brain.

Devane WA, et al. Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol*.1988;34:605–613.



Scientific American, 2004



The Endocannabinoid System

Endocannabinoid Receptors: Current Knowledge

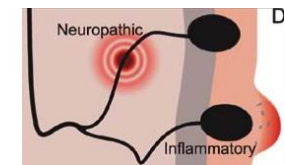
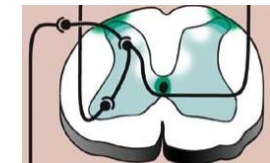
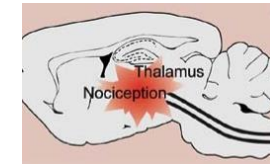
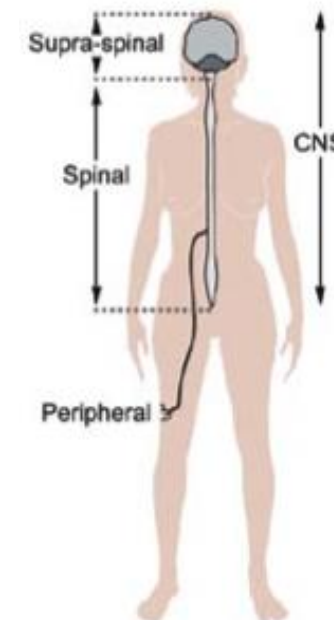
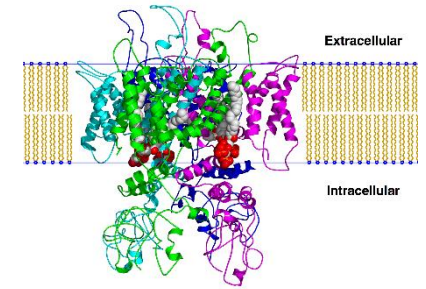
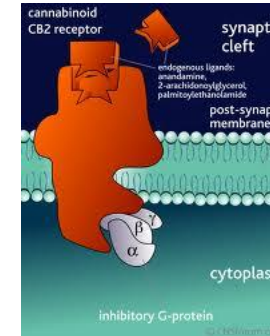
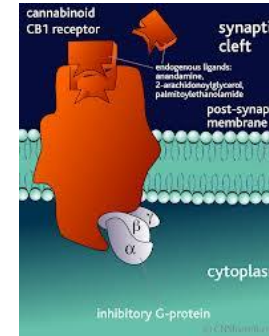
- Endocannabinoid receptors are G-protein coupled receptors located in cell membranes.
- Present throughout the pain pathway:

Central levels (CB1)

- Supraspinal (thalamus, amygdala, periaqueductal grey matter)
- Spinal (dorsolateral funiculus, surrounding the central canal, superficial dorsal horn)

Peripheral level

- Peripheral sensory nerve endings (**CB1**)
- Immune tissue and cells (**CB2**)



The Endocannabinoid System

Endocannabinoid Molecules Were Discovered in 1992

The presence of endocannabinoid receptors begged the question:

Q: “Is there an endogenous ligand(s)?”

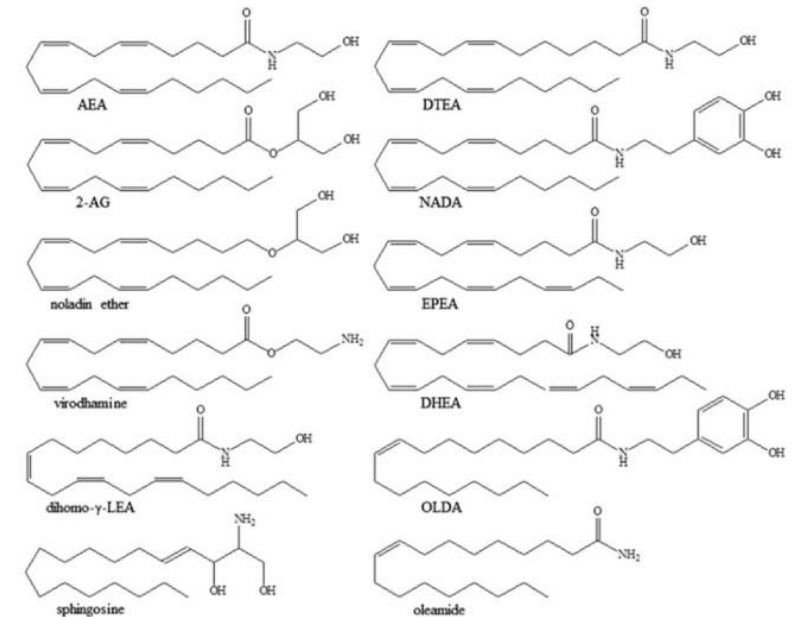
A: Yes.

- In 1992, the lipid arachidonoyl ethanolamide was isolated from porcine brain. It was named “**anandamide**,” Sanskrit for “bliss.”
- Anandamide bound to the cannabinoid receptor with reasonably high affinity and mimicked the behavioral actions of THC when injected into rodents.
- A second endocannabinoid, **2-arachidonoylglycerol (2-AG)**, was discovered in 1995.

Devane WA, et al. *Science (Wash DC)*. 1992; 258:1946–1949.

Mechoulam R, et al. *Biochem Pharmacol*. 1995; 50:83–90.

Sugiura T, et al. *Biochem Biophys Res Commun*. 1995; 215:89–97.



- To date, over a dozen compounds have been identified that can target cannabinoid receptors, either orthostatically or allosterically.

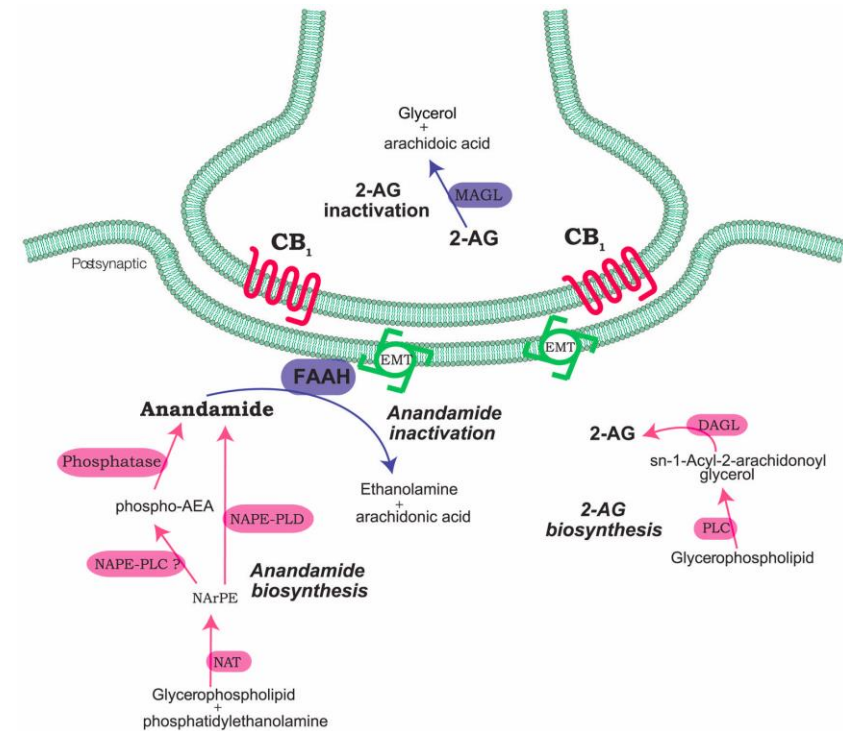
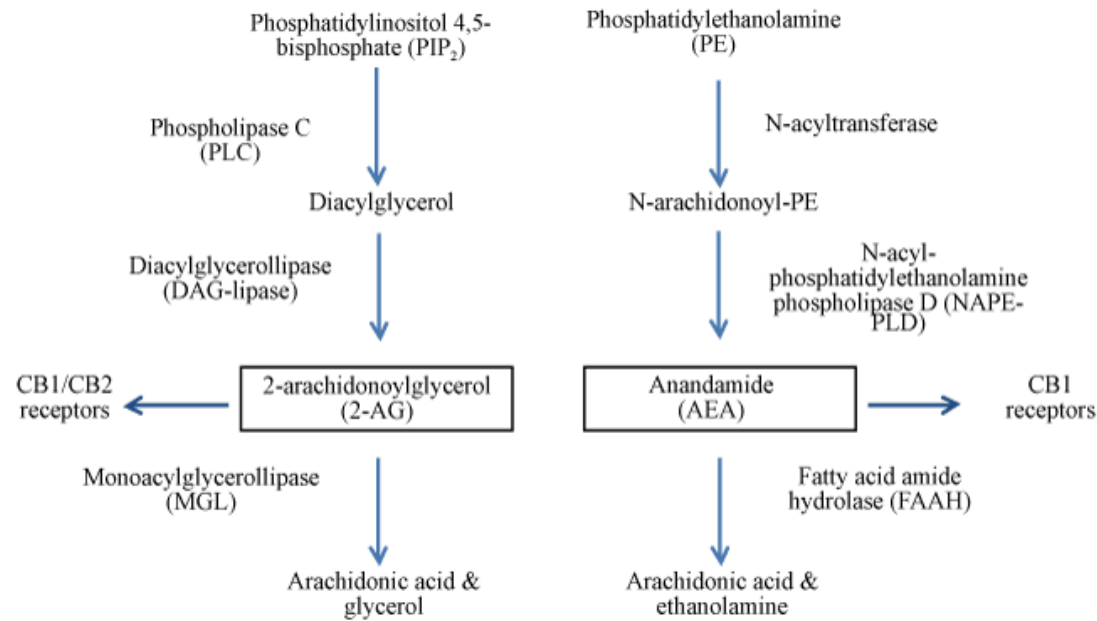
Pertwee, RW. *Endocannabinoids*. Handbook of Experimental Physiology. 2015. Springer International.



The Endocannabinoid System

Endocannabinoid Biosynthesis and Breakdown

- Endocannabinoids are produced on demand from the cell membrane.
- They act locally.
- And they are immediately metabolized after their action.



Endocannabinoid System in Pre- and Postsynaptic Neurons

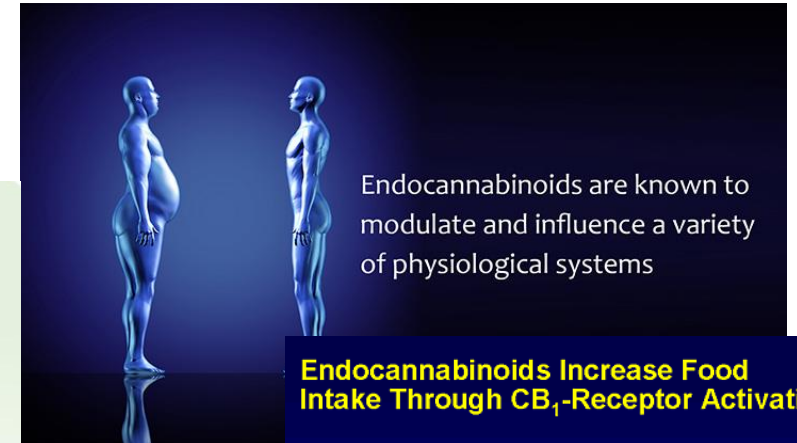
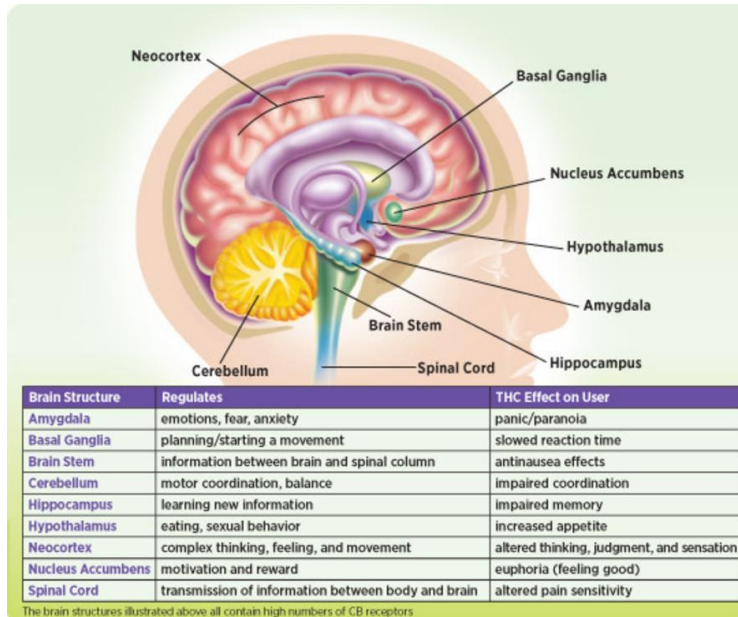


The Endocannabinoid System

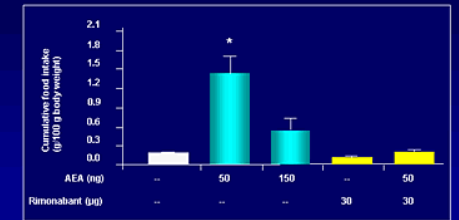
Role of the Endocannabinoid System

Maintain “**homeostasis**,” or the regulation of bodily systems.

- Pain perception
- Thought processing/higher cognitive function
- Stress reaction
- Regulation of muscles and movement
- Nausea/vomiting reflex
- Appetite
- Immune system and inflammatory response



Endocannabinoids Increase Food Intake Through CB₁-Receptor Activation



Anandamide administration into the ventromedial hypothalamus induces hyperphagia in presatiated rats

Jamshidi N, et al. Br J Pharmacol 2001;134:1151-1154.

The endocannabinoid system has been called the “**supercomputer**” that regulates the human body.

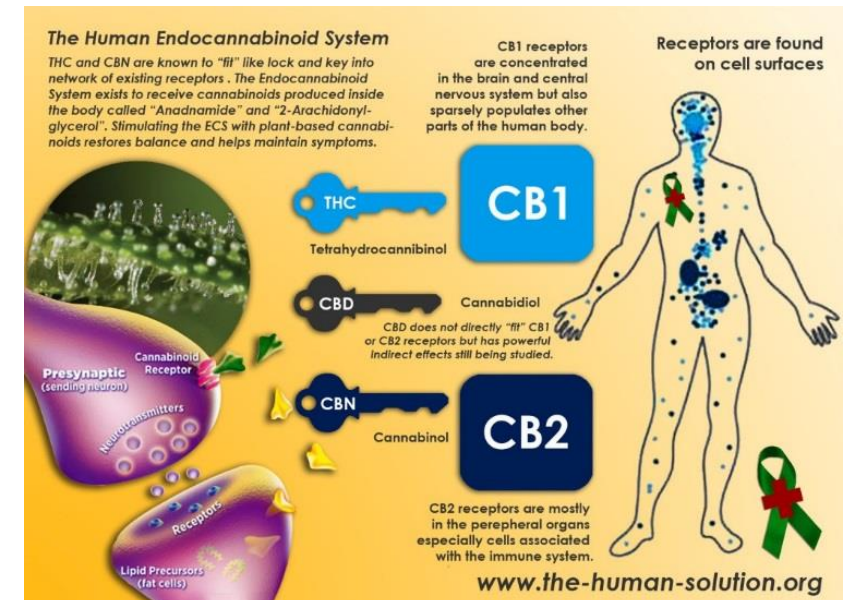
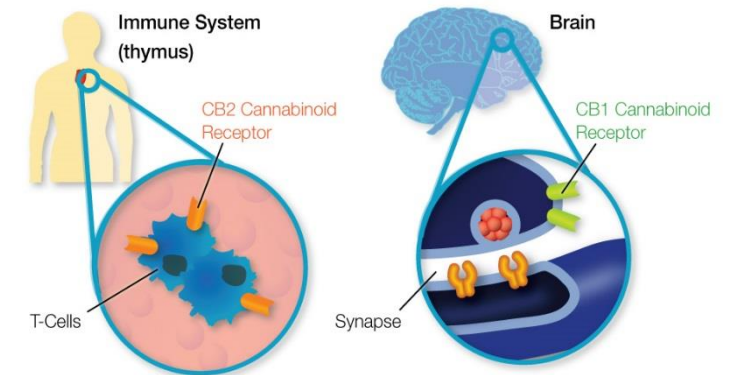
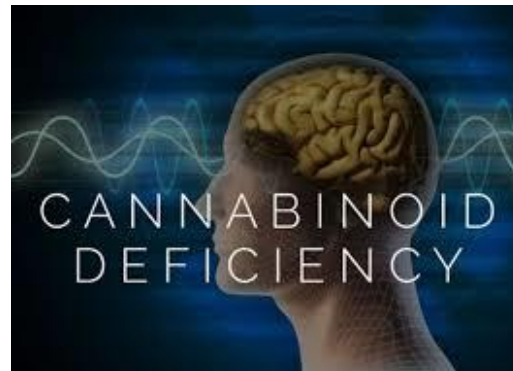
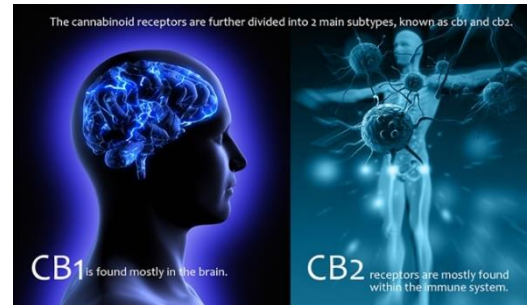


The Endocannabinoid System

ECS as a Target for Therapy

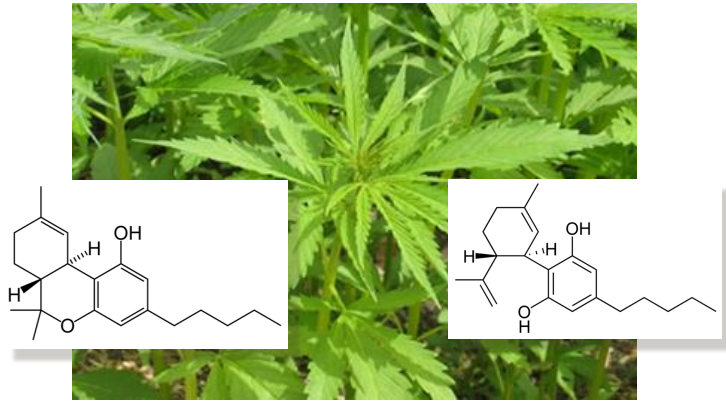
- The **Endocannabinoid System (ECS)** is an emerging target of pharmacotherapy.
- Because endocannabinoid receptors are found throughout the brain and in every major organ, the ***ECS is thought to be involved in most disease states.***
- It is theorized that some individuals may have an underlying “**Clinical Endocannabinoid Deficiency (CECD).**”

Russo EB. *Neuro Endocrinol Lett.* 2004; 25(1-2):31-9.



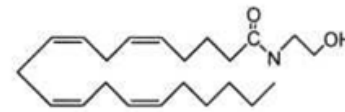
The Endocannabinoid System

ECS as a Target for Therapy

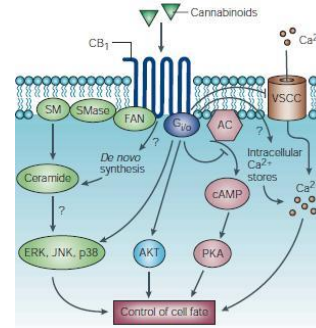


Possible approaches:

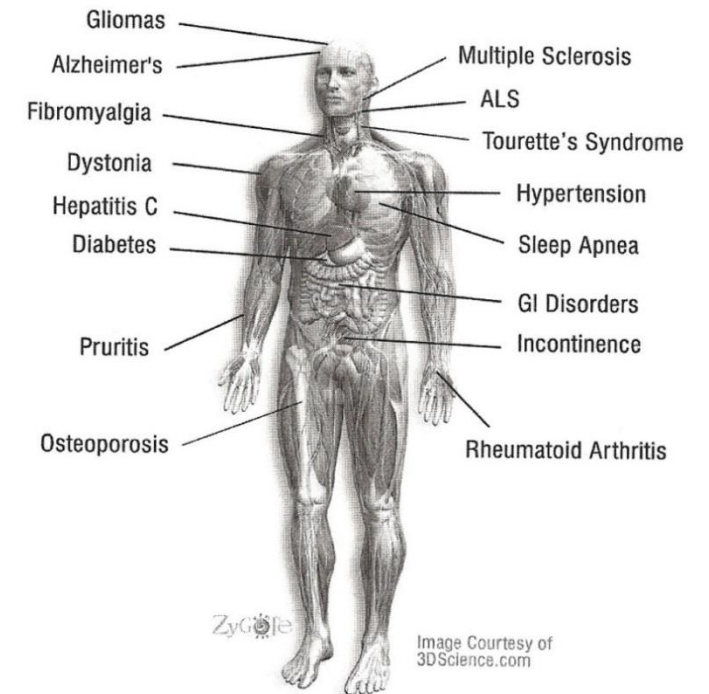
- Phytocannabinoid-based
- Endocannabinoid-based
- ECS optimization



Anandamide



Emerging Clinical Applications for Cannabis and Cannabinoids: A Review of the Recent Scientific Literature, 2000 – 2006



ZyGöfe

Image Courtesy of
3DScience.com

The Endocannabinoid System

ECS as a Target for Therapy

Potentially treatable conditions include:

- Pain and inflammation
- Disorders of appetite regulation
- Central nervous system disorders (eg, stroke, MS, spinal injuries, movement disorders, ALS, Alzheimer's Disease, epilepsy)
- Mental disorders
- Insomnia
- Nausea/vomiting
- Drug addiction/alcoholism
- Cardiovascular disorders
- Respiratory disorders
- Eye disorders (eg, retinopathy, glaucoma)
- Gastrointestinal
- Liver disorders
- Musculoskeletal disorders
- Reproductive disorders
- Cancer

Pacher P, Batkai S, Kunost G. The Endocannabinoid System as an Emerging Target of Pharmacotherapy. *Pharmacology Reviews*. 2006; 58(3): 389-462.



The Endocannabinoid System

ECS as a Target for Therapy: Metabolism

Current and past marijuana use both associated with lower prevalence of Metabolic Syndrome and most of its components.

Conclusions:

- Current and past “users” have lower odds of metabolic syndrome vs. “never users.”
- Individual metabolic syndrome component mean estimates were generally lower among “users” vs. “never users” (except BP).
- Prospective studies needed to examine the biological pathways of this association.



Metabolic Syndrome

Cluster of ≥ 3 risk factors:

- Waist circumference
- Systolic/diastolic BP
- HDL cholesterol
- Triglycerides
- Fasting glucose

X-Sectional Analysis:

- 20–59-year-olds
- N = 8478 (U.S.)
- 2005-2010 NHANES
- National Health and Nutrition Examination Survey
- A continuous survey by CDC's National Center for Health Statistics.

Among “emerging adults” (ages 20–30), current marijuana users were 54% less likely than “never users” to present with metabolic syndrome.

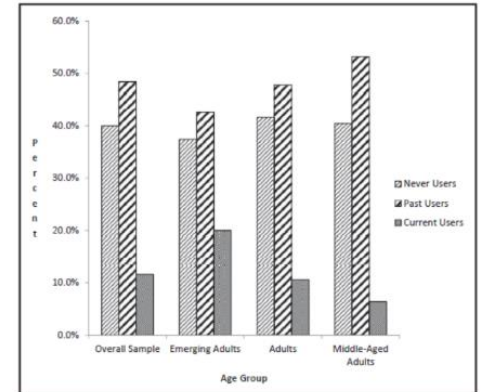


Figure 1 Prevalence of marijuana use by age group; National Health and Nutrition Examination Surveys, 2005-2010.

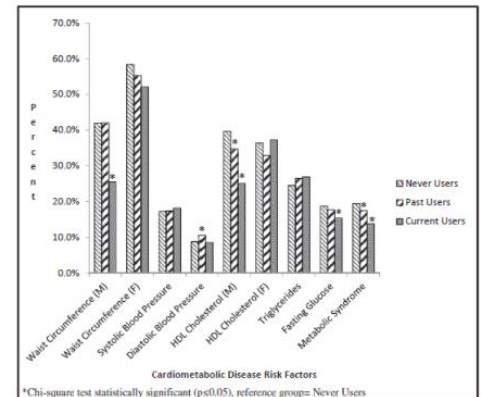


Figure 2 Prevalence of metabolic syndrome components by marijuana use categories among overall sample; National Health and Nutrition Examination Surveys, 2005-2010. *Chi-squared test statistically significant ($P \leq .05$), reference group = Never Users.

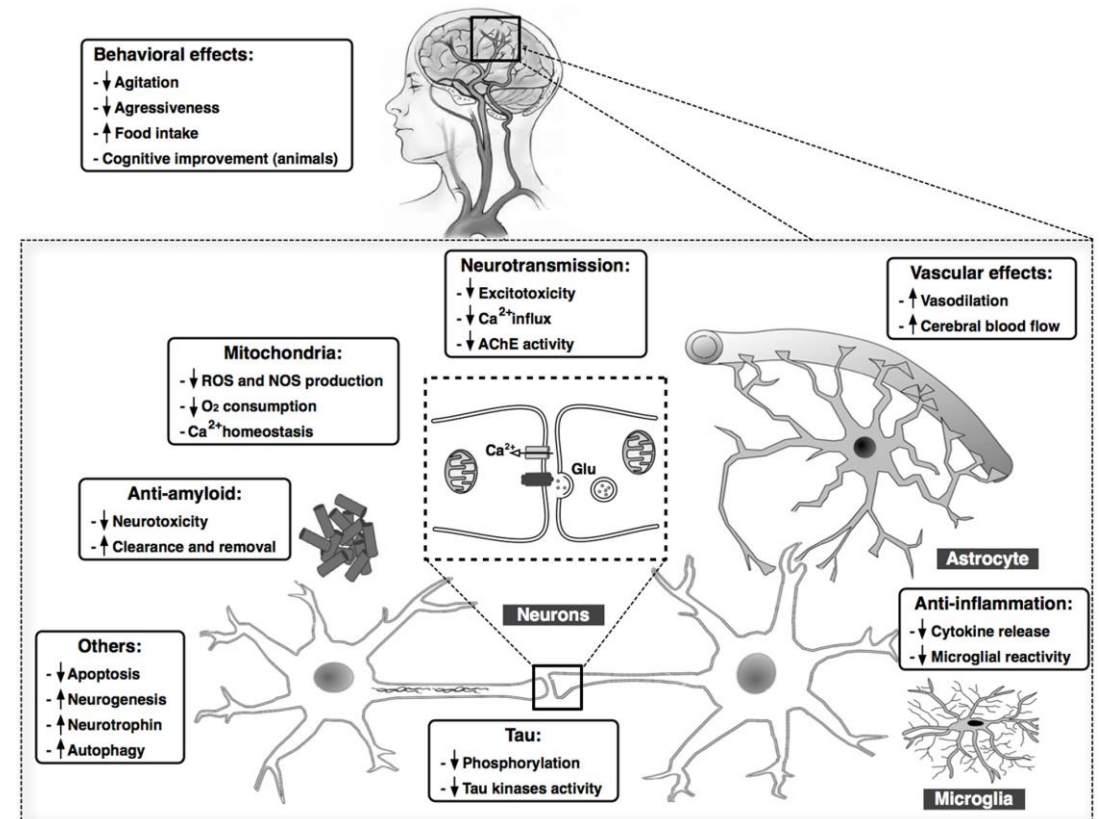
Vidot DC, et al. Metabolic Syndrome Among Marijuana Users in the United States: An Analysis of National Health and Nutrition Examination Survey Data. *The American Journal of Medicine*. 2016; 129(2):173-9.

The Endocannabinoid System

ECS as a Target for Therapy: Alzheimer's Disease (AD)

- Cannabinoids may target in parallel several processes that play key roles in AD, including:
 - $A\beta$ and tau aberrant processing
 - Chronic inflammatory responses
 - Excitotoxicity
 - Mitochondrial dysfunction
 - Oxidative stress
 - Among others
- Improvement in behavior is also noted in patients with AD after treatment with cannabinoids.

Aso E and Ferrer I. Cannabinoids for Treatment of Alzheimer's Disease: Moving Toward the Clinic. *Frontiers in Pharmacology*. 2014; 5(37):1-11.



Summary of beneficial effects of cannabinoids in AD models.

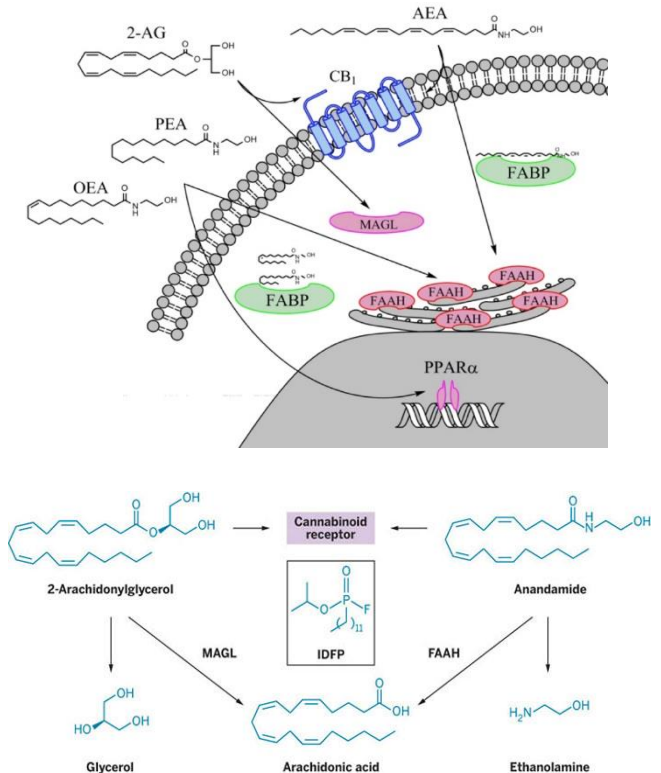


The Endocannabinoid System

ECS as a Target for Therapy: Fatty Acid Amide Hydrolase (FAAH)

FAAH:

- Integral membrane hydrolase, single N-terminal transmembrane domain.
- Esterase and amidase activity *in vitro*.
- *In vivo*, **FAAH** is the **principal catabolic enzyme** for a class of bioactive lipids called the **fatty acid amides (FAAs)**, including:
 - Anandamide
 - Other non-endocannabinoid N-acyl ethanolamines (eg, N-oleoylethanolamine, N-palmitoylethanolamine)
 - The sleep-inducing lipid oleamide
 - N-acyltaurines, which are agonists of the transient receptor potential (TRP) family of calcium channels
- Due to the ability of **FAAH** to regulate nociception, FAAH is currently viewed as a particularly **attractive drug target** for the **treatment of pain**.



Pacher P, et al. The Endocannabinoid System as an Emerging Target of Pharmacotherapy. *Pharmacology Reviews*. 2006; 58(3): 389-462.



The Endocannabinoid System

ECS as a Target for Therapy: Studying FAAH

- FAAH knockout (KO) mice display highly elevated (>15-fold) levels of N-acylethanolamines and N-acyltaurines in various tissues. Due to high anandamide levels, the mice showed **reduced pain sensation** in the hot plate test, the formalin test, and the tail flick test.
- Because of their impaired ability to degrade anandamide, FAAH KOs also display **supersensitivity to exogenous anandamide**, a cannabinoid receptor (CB) agonist.
- Other conditions in which FAAH levels likely play a role:
 - A mutation in the FAAH gene has been linked to **drug abuse and dependence**.
 - Individuals with the mutation have higher levels of anandamide because of lower levels of FAAH, which may reduce **anxiety** and **post-traumatic stress disorder**.

Cravatt BF, et al.. The endogenous cannabinoid system and its role in nociceptive behavior. *Journal of Neurobiology*. 2004; 61(1):149-60.

Patricelli MP, et al. Fatty acid amide hydrolase competitively degrades bioactive amides and esters through a nonconventional catalytic mechanism. *Biochemistry*. 1999; 38(43):14125-30.

Sipe JC, et al. A missense mutation in human fatty acid amide hydrolase associated with problem drug use. *Proceedings of the National Academy of Sciences of the United States of America*. 2002; 99(12):8394-9.

"The Feel-Good Gene". *New York Times*. 6 March 2015.



The Endocannabinoid System

Targeting the Endocannabinoid System Can Be Dangerous

Pot Painkiller Trial Leaves Man in Coma



© Charles Platiau / Reuters

JANUARY 15, 2016 | NEWS



News Release

As part of a clinical trial that was being held in a Phase 1 clinical trial unit in France, since June 2015, with an experimental molecule of BIAL, we were informed that five participants showed severe symptoms. Following the best international medical practices, they were immediately transferred by the company responsible for conducting the clinical trial to observation at the University Hospital of Rennes, being currently under permanent medical supervision.

Phase 1 Clinical Trial: FAAH Enzyme Inhibitor

- 1 patient dies
- 5 hospitalized, showing signs of improvement



Cannabis as Medicine: Relief of Pain

Pain is a Critical National Health Problem/Crisis

Congress declared 2001 to 2010 the “Decade of Pain Control and Research” (Title VI, Sec. 1603, of H.R. 3244).

- Pain is the most common reason for medical appointments in the U.S.
- Pain costs the U.S. over \$600 billion each year in health care and lost productivity.
- Chronic pain affects more than 100 million Americans and over 1.5 billion people worldwide.

Committee on Advancing Pain Research, Care, and Education, Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. 2011. Washington, DC: National Academies Press.

American Academy of Pain Medicine Facts and Figures on Pain
http://www.painmed.org/patientcenter/facts_on_pain.aspx (2/2/16)

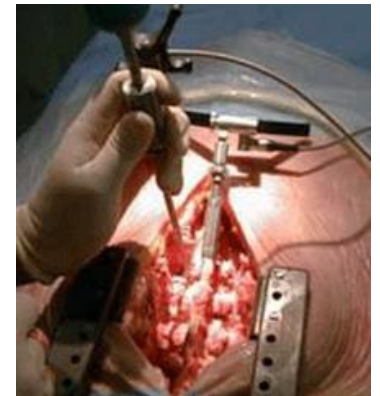
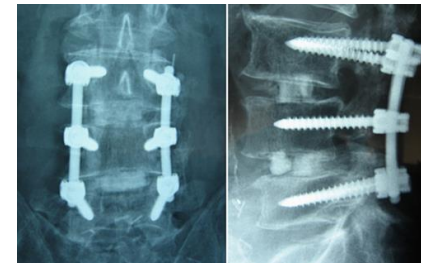
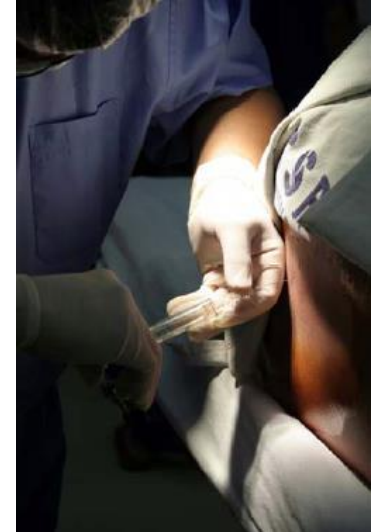


Cannabis as Medicine: Relief of Pain

Common Conventional Therapies

- Anti-inflammatories
- Opioid pain meds
- Muscle relaxants
- Nerve pain meds
- Sleeping pills
- Anxiolytics
- Antidepressants
- Surgery

Side effects, however, are a limiting, even deadly, problem.



Cannabis as Medicine: Relief of Pain

Concerns About Prescription Drug Safety: Especially the Use of Opioids for Chronic Pain

EDITORIAL

Editorials represent the opinions of the authors and JAMA and not those of the American Medical Association.

Weighing In on Opioids for Chronic Pain The Barriers to Change

Daniel P. Alford, MD, MPH

JAMA
The Journal of the American Medical Association

It is estimated that approximately 100 million US residents have chronic pain, costing more than \$600 billion per year in direct medical treatment and lost productivity costs.¹ In the 1980s, several reports began to support use of opioid therapy for chronic noncancer pain.² Over the ensuing decades, a 4-fold increase in opioid prescribing has occurred, but has been associated with a 4-fold increase in unintentional opioid overdose deaths and a 6-fold increase in substance abuse treatment admissions for prescription opioid addiction.³ With such severe risks associated with opioid use, decreasing the need

Because opioids are customarily the treatment of last resort, have federal and state laws and regulations limiting how they can be prescribed (eg, few or no refills), are becoming more difficult to obtain in certain settings (eg, emergency departments), and are now commonly prescribed with strict monitoring procedures (eg, treatment agreements, informed consents, urine drug testing, pill counts), it is not surprising that these medications are perceived by patients and society as the most powerful and desirable painkillers for chronic pain. Why would any patients want to risk losing access to this now-

Alford DP. Weighing In on Opioids for Chronic Pain – The Barriers to Change. *JAMA*. 2013; 310(13):1351-2.



In the 1980s, the medical establishment began to support the use of opioids.

Over the ensuing decades:

- 4-fold increase in opioid prescribing
- 4-fold increase in unintentional opioid overdose deaths
- 6-fold increase in substance treatment admissions for rx opioid addiction

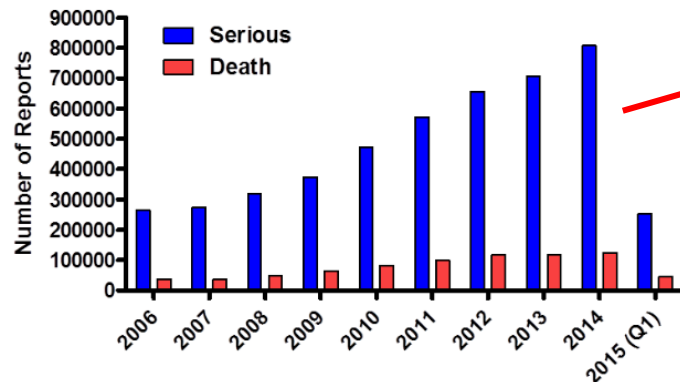
“...with such severe risks associated with opioid use, decreasing the need for chronic opioid therapy is a worthy clinical goal.”



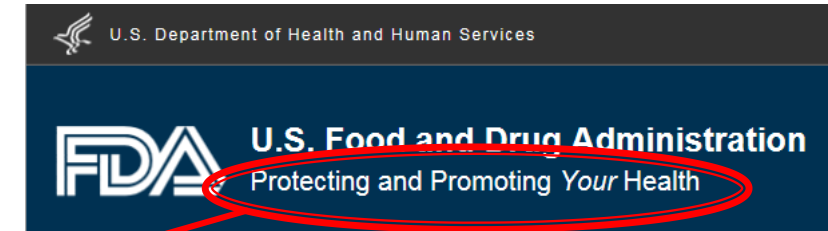
Cannabis as Medicine: Relief of Pain

U.S. Drug Safety Statistics

- FDA-approved drugs **killed 123,927** people in **2014**.
- **1,000,000+** “**serious**” outcomes expected in **2015**.



Really?



FAERS Reporting by Patient Outcomes by Year

| Year | Deaths | Serious |
|----------|---------|---------|
| 2006 | 37,309 | 264,227 |
| 2007 | 36,689 | 272,324 |
| 2008 | 49,699 | 318,536 |
| 2009 | 63,830 | 373,471 |
| 2010 | 82,704 | 471,243 |
| 2011 | 98,469 | 572,992 |
| 2012 | 117,202 | 656,613 |
| 2013 | 116,388 | 707,593 |
| 2014 | 123,927 | 807,270 |
| 2015(Q1) | 44,693 | 253,017 |

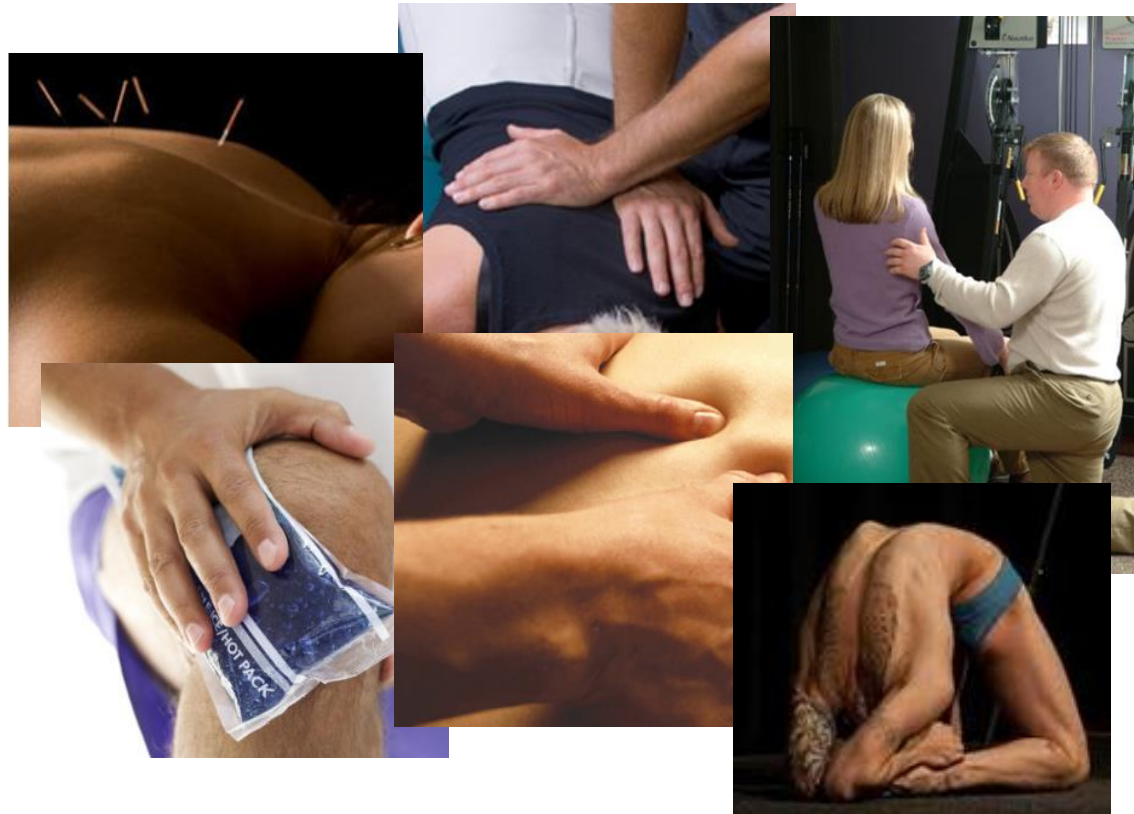
Patient outcomes from the Federal Adverse Event Reporting System (FAERS)

***Serious outcomes** include death, hospitalization, life-threatening, disability, congenital anomaly and/or other serious outcome.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070461.htm>

Cannabis as Medicine: Relief of Pain

Patients are Increasingly Seeking Alternative Therapies – Especially Medical *Cannabis*



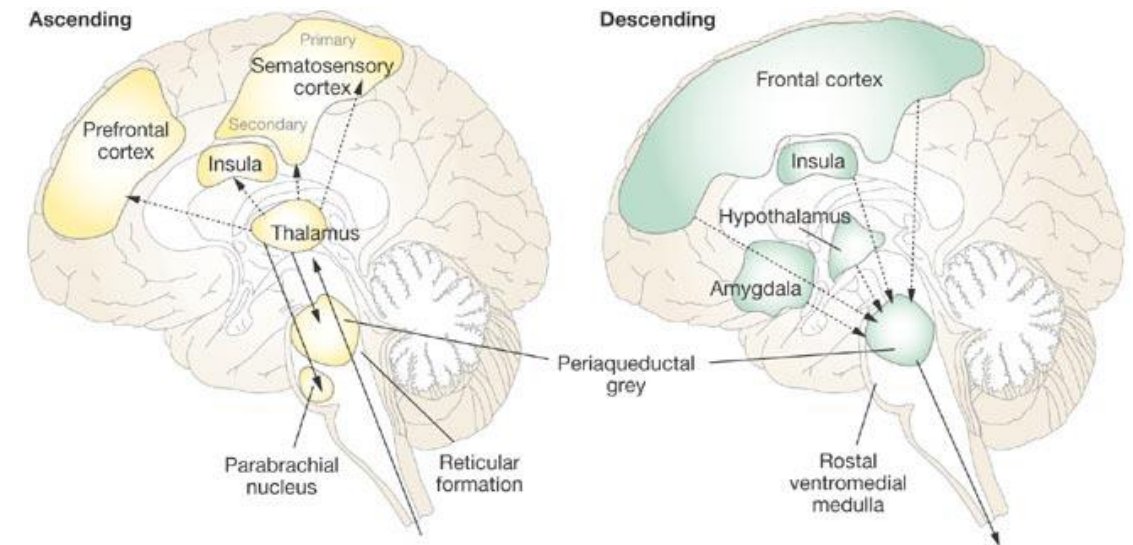
Medical Cannabis



Cannabis as Medicine: Relief of Pain

Cannabinoid Anti-Pain Mechanism #1: Pain Perception

- Increased levels of the CB1 receptor are found in regions of the brain that regulate nociceptive processing (similar to opioid receptors).
- The effects of cannabinoids on nociceptive neurotransmission are receptor-mediated, reversible, and selective for painful as opposed to non-painful somatic stimuli.
- The endogenous cannabinoid anandamide plays an important role in a cannabinergic pain-suppression system existing within the dorsal and lateral PAG.



Walker JM, et al. The neurobiology of cannabinoid analgesia. *Life Sci* 1999; 65(6-7):665-73.

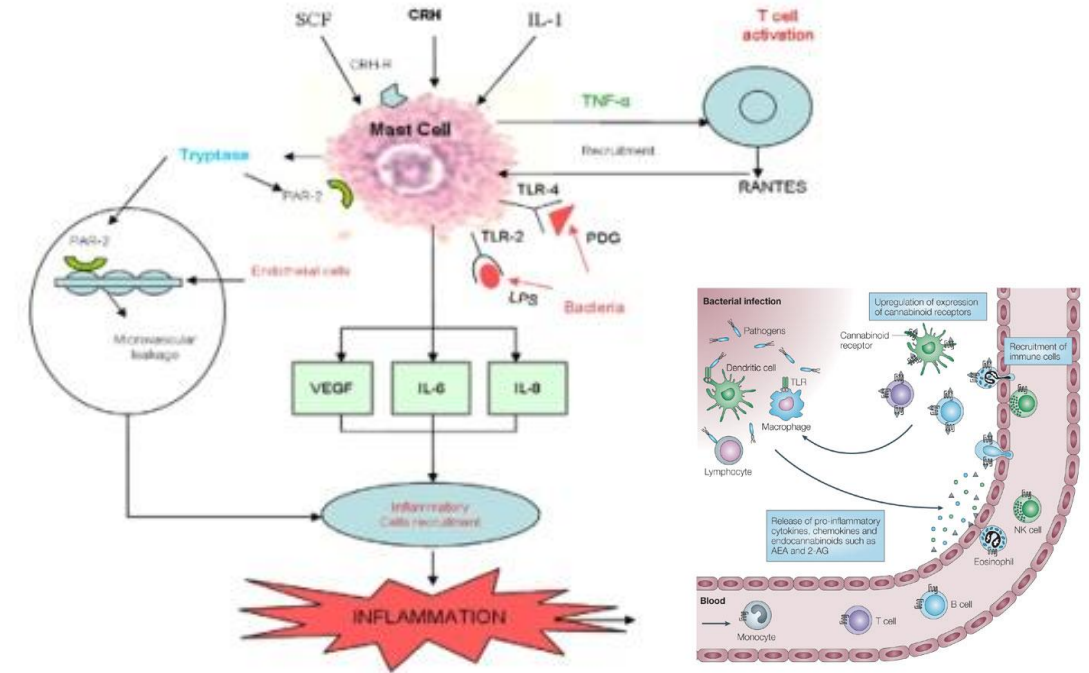
Walker JM, et al. Pain modulation by release of the endogenous cannabinoid anandamide. *Proc Natl Acad Sci USA*. 1999; 96 (21):12198-203.



Cannabis as Medicine: Relief of Pain

Cannabinoid Anti-Pain Mechanism #2: Anti-Inflammation

- Cannabinoids may also contribute to pain modulation through an anti-inflammatory mechanism.
- Both CB1 and CB2 receptors have been detected in non-neuronal cells participating in immune and inflammatory processes near primary afferent nerve terminals.
- A CB2 effect has been described...with cannabinoids acting on mast cell receptors to attenuate the release of inflammatory agents (eg, histamine and serotonin).



Facci L, et al. *Proc Natl Acad Sci USA*. 1995; 92(8):3376-80.

Ibrahim MM, et al. *Proc Natl Acad Sci USA*. 2005; 102(8):3093-8.

Richardson JD, et al. *Pain*. 1998; 75(1):111-9.

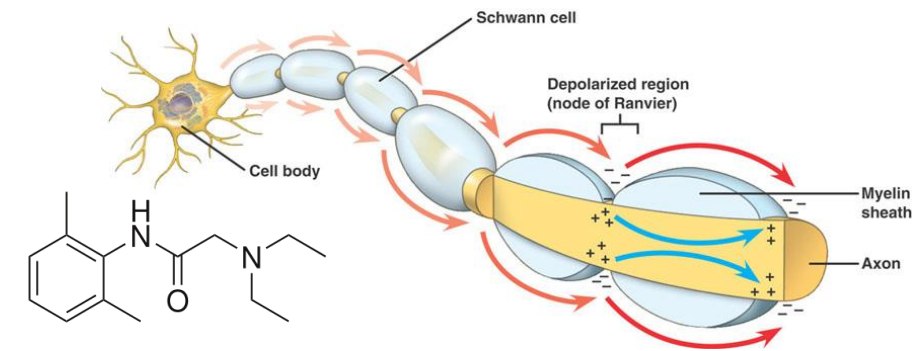
Klein TW. *Nature Reviews Immun*. 2005; 5:400-11.



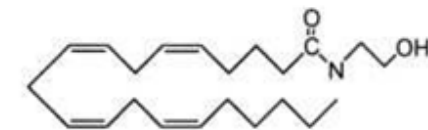
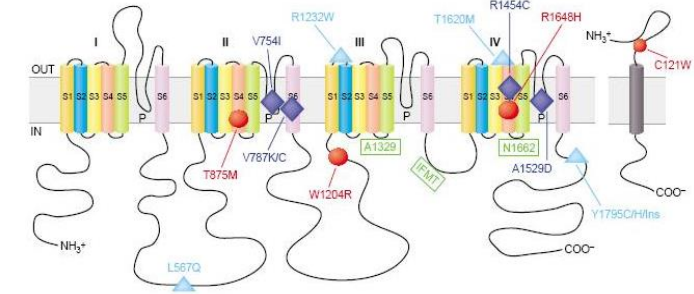
Cannabis as Medicine: Relief of Pain

Cannabinoid Anti-Pain Mechanism #3: Inhibition of Pain Transmission

- Voltage-gated sodium channels provide the inward current that generates the upswing of an action potential in response to supra-threshold depolarizations of the membrane potential.
- At present, α - (Nav1.1 to Nav1.9) and β -subunits have been characterized.
- Local anesthetics (eg, lidocaine) bind to and block sodium channels.
- Sodium channels may play a role in various chronic pain situations.
- Anandamide was shown to inhibit the function of α subunits in neuronal sodium channels Nav1.2, Nav1.6, Nav1.7, and Nav1.8.



Lidocaine



Anandamide

Okura DI, et al. The endocannabinoid anandamide inhibits voltage-gated sodium channels Nav1.2, Nav1.6, Nav1.7, and Nav1.8 in *Xenopus oocytes*. *Anesth Analg*. 2014; 118(3):554-62.



Cannabis as Medicine: Relief of Pain

Research: Cannabinoid Receptor Agonists Show Efficacy Comparable to Morphine

- Murine model of tumor pain – synthetic CB1 and CB2 receptor agonists were studied for potency and efficacy.
- CB1 receptor agonist: reduced pain by activation of peripheral CB1 but not CB2 receptors.
- CB2 receptor agonist: reduced pain by activation of peripheral CB2 but not CB1 receptors.
- Both agonists had an efficacy comparable with that of morphine, with analgesic effects independent of opioid receptors.
- CB1 and CB2 receptor agonists interacted synergistically to reduce pain.
- **Conclusion: peripheral cannabinoid receptors are a promising target for the management of cancer pain and mixed cannabinoid receptor agonists may have a therapeutic advantage over selective agonists.**

Khasabova IA, et al. CB1 and CB2 receptor agonists promote analgesia through synergy in a murine model of tumor pain. *Behavioral Pharmacology*. 2011; 22(5-6):607-16.



Cannabis as Medicine: Relief of Pain

Research: Cannabinoids Decrease Patients' Need for Opioids

- 21 individuals with chronic pain on a regimen of twice-daily doses of sustained-release morphine or oxycodone were admitted for a 5-day inpatient stay.
- Participants were asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2-4, and in the morning of day 5.
- Blood sampling was performed at regular intervals, and the extent of chronic pain was assessed daily.
- Pain was decreased by 27% (95% confidence interval) after the addition of vaporized cannabis.
- **Conclusion: Vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.**

Abrams DI, et al. Cannabinoid-opioid interaction in chronic pain.
Clin Pharmacol Ther. 2011; 90(6):844-51.
San Francisco General Hospital, UCSF



Cannabis as Medicine: Antioxidation/Neuroprotection



US006630507B1

(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**

Related U.S. Application Data

(60) Provisional application No. 60/082,589, filed on Apr. 21, 1998, and provisional application No. 60/095,993, filed on Aug. 10, 1998.

OTHER PUBLICATIONS

Windholz et al., The Merck Index, Tenth Edition (1983) p. 241, abstract No. 1723.*

Mechoulam et al., "A Total Synthesis of d1- Δ^1 -Tetrahydrocannabinol, the Active Constituent of Hashish¹," *Journal of the American Chemical Society*, 87:14:3273-3275 (1965).

Mechoulam et al., "Chemical Basis of Hashish Activity," *Science*, 18:611-612 (1970).

Ottersen et al., "The Crystal and Molecular Structure of Cannabidiol," *Acta Chem. Scand. B* 31, 9:807-812 (1977).

Cunha et al., "Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients¹," *Pharmacology*, 21:175-185 (1980).

Consroe et al., "Acute and Chronic Antiepileptic Drug Effects in Audiogenic Seizure-Susceptible Rats," *Experimental Neurology*, Academic Press Inc., 70:626-637 (1980).

Turkanis et al., "Electrophysiologic Properties of the Cannabinoids," *J. Clin. Pharmacol.*, 21:449S-463S (1981).

Carlini et al., "Hypnotic and Antiepileptic Effects of Cannabidiol," *J. Clin. Pharmacol.*, 21:417S-427S (1981).

Karler et al., "The Cannabinoids as Potential Antiepileptics," *J. Clin. Pharmacol.*, 21:437S-448S (1981).

Consroe et al., "Antiepileptic Potential of Cannabidiol Analogs," *J. Clin. Pharmacol.*, 21:428S-436S (1981).

(List continued on next page.)

Primary Examiner—Kevin E. Weddington

(74) Attorney, Agent, or Firm—Klarquist Sparkman, LLP

(57) **ABSTRACT**

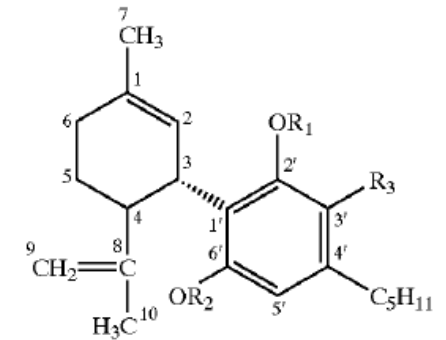
Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This

Cannabis as Medicine: Antioxidation/Neuroprotection

U.S. Patent 6,630,507

Abstract excerpts...

- Cannabinoids have been found to have antioxidant properties...this “new found property” makes cannabinoids useful in the **treatment and prophylaxis** of a wide variety of “**oxidation associated diseases**” such as ischemic, age-related, inflammatory, and autoimmune diseases.
- Cannabinoids...have particular application as **neuroprotectants**...for example, in limiting neurologic damage following ischemic insults...such as stroke/trauma, or in the treatment of neurodegenerative conditions (eg, Alzheimer’s Disease, Parkinson’s disease, and HIV dementia).
- Nonpsychoactive cannabinoids such as cannabidiol... are particularly advantageous...because they avoid toxicity...at high doses...useful in the method of the present “**invention.**”



26 Claims, 7 Drawing Sheets

Cannabidiol (CBD)

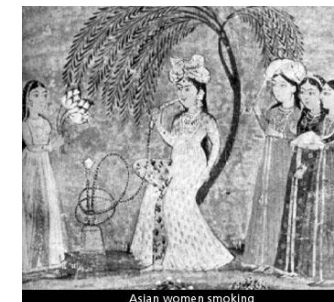
-R groups = H

Cannabidiolic Acid (CBDA)

-R3 group = COCH3



Interesting...a novel
discovery by HHS?



Asian women smoking



Cannabis as Medicine: Antioxidation/Neuroprotection

U.S. Patent 6,630,507

“Oxidation associated diseases” include, without limitation, *free radical associated diseases* such as:

- Autoimmune diseases (e.g. rheumatoid arthritis or diabetes)
- Cataract formation
- Cerebrovascular accidents (eg, hemorrhagic or thromboembolic or stroke) that can lead to ischemia or brain infarct
- Crohn’s disease
- Down’s syndrome
- Emphysema
- Gastric ulcers
- Ischemia, ischemic reperfusion injury
- Inflammatory diseases
- Lupus erythematosus
- Myocardial ischemia or infarction
- Neoplasia
- Operative ischemia
- Oxygen toxicity
- Radiation sickness
- Spinal cord trauma
- Traumatic hemorrhage (eg, hypovolemic stroke) that can lead to CNS hypoxia or anoxia
- Uveitis
- Undesired cellular apoptosis
- and others.



Cannabis as Medicine: Antioxidation/Neuroprotection

Q: How many U.S. citizens could potentially benefit from cannabinoids?

| Condition | Affects | Citation | Source |
|---------------|--------------|---|--|
| Arthritis | 52.5 million | An est.52.5 million adults in the United States reported being told by a doctor that they have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia | MMWR 2013; 62 (44) 869– 873. [Data 2010– 2012 NHIS] |
| Heart Disease | 26.6 million | Number of non-institutionalized adults with diagnosed heart disease = 26.6 million | Summary Health Stat for US Adults: Nat'l Health Interview Survey, 2012 |
| Diabetes | 25.8 million | Diabetes affects 25.8 million people, or 8.3 % of the U.S. population | 2011 National Diabetes Fact Sheet |
| Cancer | 13.0 million | Estimated cancer prevalence in the United States as of January 1, 2010, All invasive cancer sites: 13,028,000 | National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program |

A: **ALL 320 MILLION.** Based on U.S. Patent 6,630,507 claims, ~118 million Americans (1 in 3) could benefit from the antioxidative and neuroprotective effects of cannabinoids to ***treat*** their common diseases. The other 2 in 3 could benefit from cannabinoids to ***prevent*** these same diseases.



Cannabis as Medicine: Antioxidation/Neuroprotection

Study: Decreased Prevalence of Diabetes in Marijuana Users.

Data Source: A cross-sectional study involving 10,896 NHANES III participants aged 20-59 years.

Rajavashisth TB, Shaheen M, et al.
Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III.
BMJ Open. 2012; 2(1): e000494, 1-9.

JANUARY 2011 • FAMILY PRACTICE NEWS

Marijuana Smoking Appears Protective Against Diabetes

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE
AMERICAN PUBLIC HEALTH ASSOCIATION

DENVER – Marijuana use may be associated with a markedly decreased risk of diabetes.

A provocative new analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) indicates marijuana users had 66% lower odds of having diabetes after adjustment for numerous potential confounding factors, Dr. Magda Shaheen reported at the meeting.

Marijuana use may be associated with a markedly decreased risk of diabetes.

...marijuana users had a 66% lower odds of having diabetes...

Prospective studies need to be performed...to determine a causal relationship between cannabinoid receptor activation and diabetes.



Cannabis as Medicine: Antioxidation/Neuroprotection

Case Study:

UT
San Diego

Pot med is life changer for tiny Sadie

By J. Harry Jones April 28, 2015



“Doctors at the Mayo Clinic identified her disorder as Schinzel-Giedion and gave her less than a year to live, her parents said.”

At age 9 months, when Sadie began cannabinoid-based therapy, she was experiencing >100 seizures/day, on six different meds that were doing nothing other than causing serious side effects.

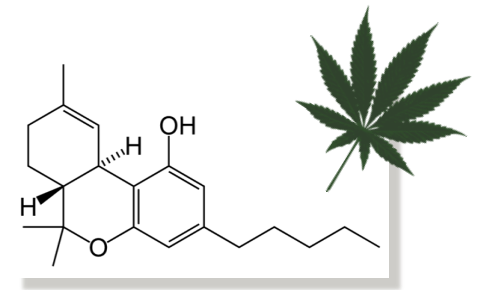
Current Status: Sadie is now almost 3 years old, outliving the Mayo Clinic doctors’ predictions. She is **SEIZURE-FREE OFF ALL MEDS**. Her **TUMORS HAVE REGRESSED**. She is interacting with her family and is trying to speak. She will begin attending a special-needs pre-school Spring 2016.



Cannabis as Medicine: Anti-Cancer

U.S. Govt. Funded Research: *Cannabis* has Anti-Tumor Effects

- Medical *Cannabis* and cannabinoids have long been accepted in the **palliative** treatment of cancer and the side-effects of cancer therapies:
 - Pain, nausea, vomiting, weight loss, and lack of appetite.
- The first documented U.S. study on the **anti-tumor effects** of *Cannabis* was funded by the U.S. government in **1974** at the Medical College of Virginia.
- Instead *JAMA* or *NEJM*, results were quietly reported in the ***Washington Post*** newspaper under the headline “**Cancer Cure is Studied**”:
 - “THC slowed the growth of lung cancers, breast cancers and a virus-induced leukemia in laboratory mice, and prolonged their lives by as much as 36 percent.”



The Washington Post

August 18, 1974



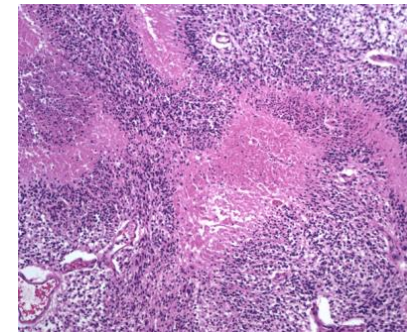
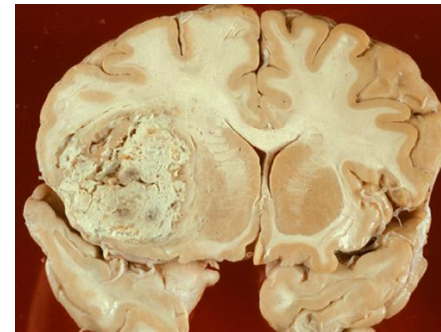
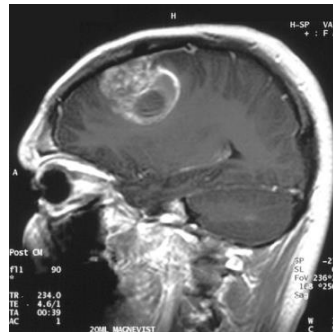
Cannabis as Medicine: Anti-Cancer

U.S. Govt. Reconfirms Anti-Cancer Effects...and Research Slowly Broadens

- In **1997**, a \$2 million study conducted by the U.S. National Toxicology Program concluded:
 - Rats and mice treated with THC over long periods of time had greater protection against malignant tumors than those left untreated.
- In **2006**, a small pilot study *with human subjects* conducted by a research team in Spain showed:
 - Possible anti-tumor activity of THC administered directly into aggressive glioblastoma multiforme brain tumors.

Toxicology and Carcinogenesis Studies of THC (TR-446). *Federal Register*. Sept 4 1997; 62(171):46751.

Guzman M, et al. A pilot clinical study of D9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *British Journal of Cancer*. 2006;95:197-203.

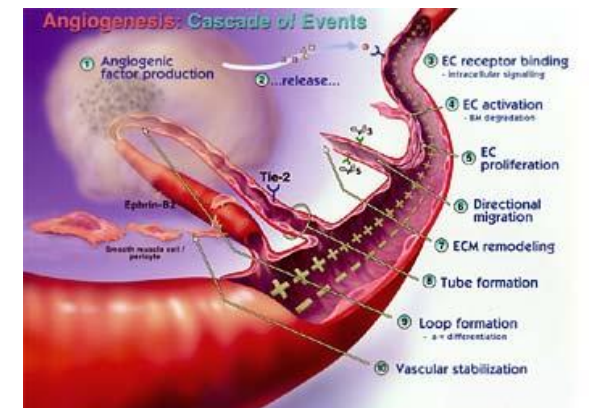
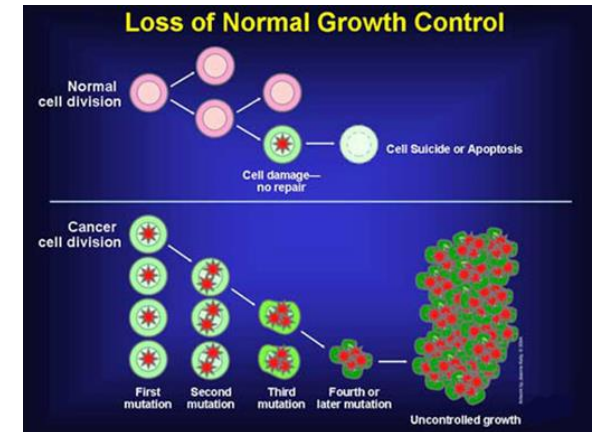
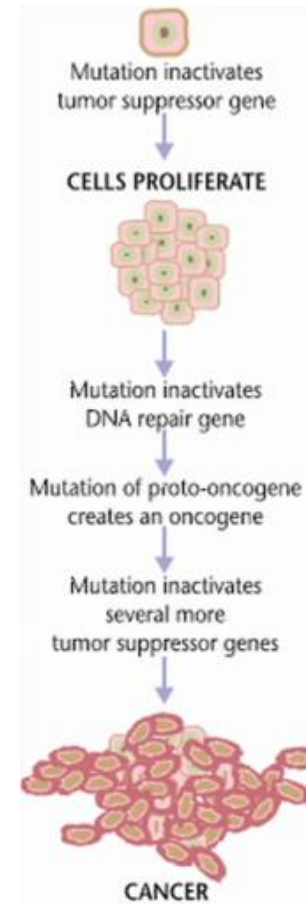


Cannabis as Medicine: Anti-Cancer

Numerous Studies Now Demonstrate the Anti-Cancer Effects of Cannabinoids

- Properties of cannabinoids (eg, THC and CBD):
 - anti-proliferative
 - anti-metastatic
 - anti-angiogenic
 - pro-apoptotic
- *In vitro* and *in vivo* models.
- The anti-cancer effects of cannabinoids are broad:
 - lung, brain, thyroid, lymphoma, liver, skin, pancreas, uterus, breast, prostate...

Alexander, et al. Mini-Review: Cannabinoids in the treatment of cancer. *Cancer Letters*. 2009; 285(1):6-12.



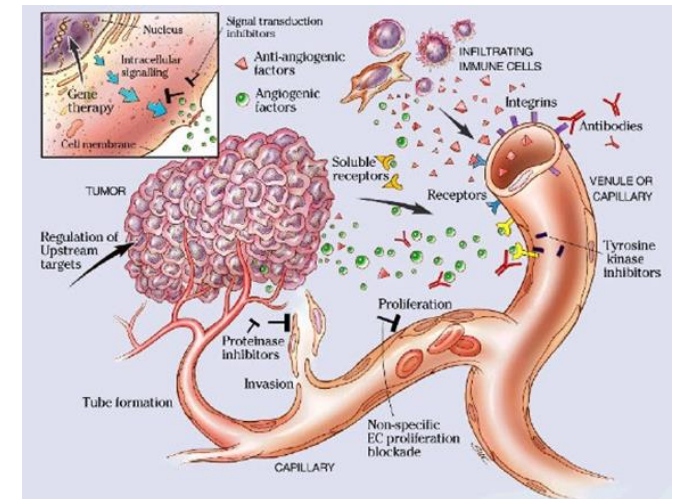
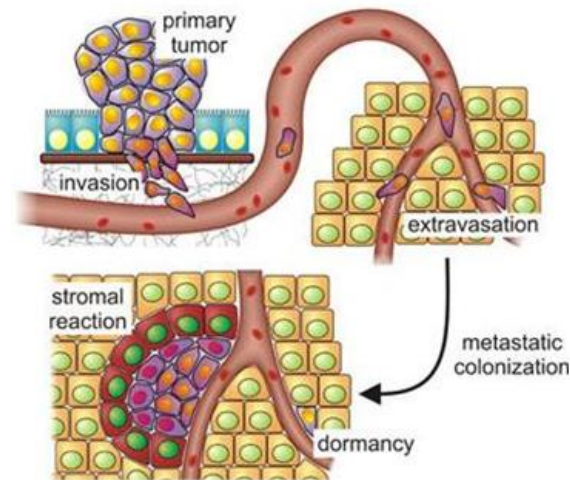
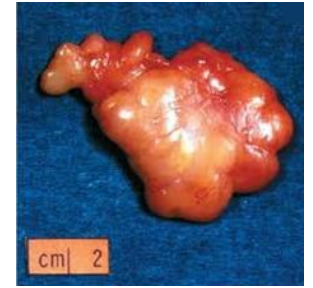
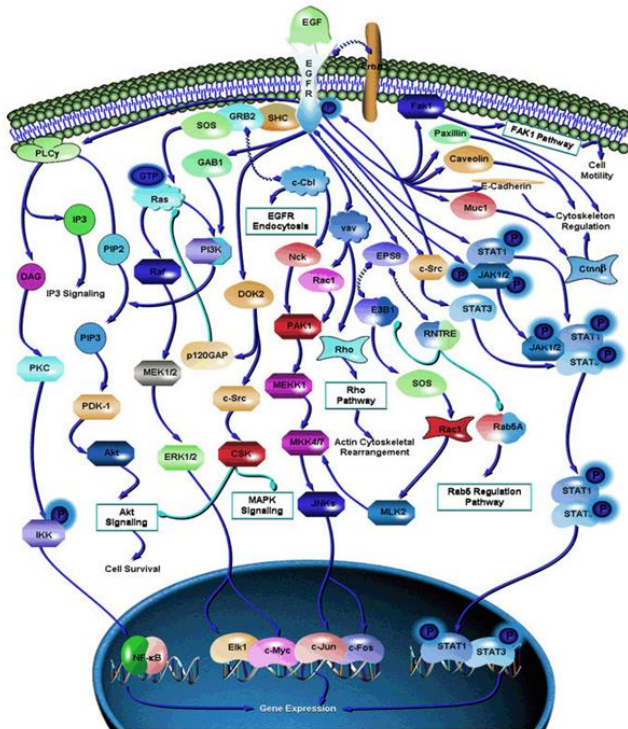
Cannabis as Medicine: Anti-Cancer

Review Article: Cannabinoids in the Treatment of Cancer

Alexander, et al. *Cancer Letters*. 2009.

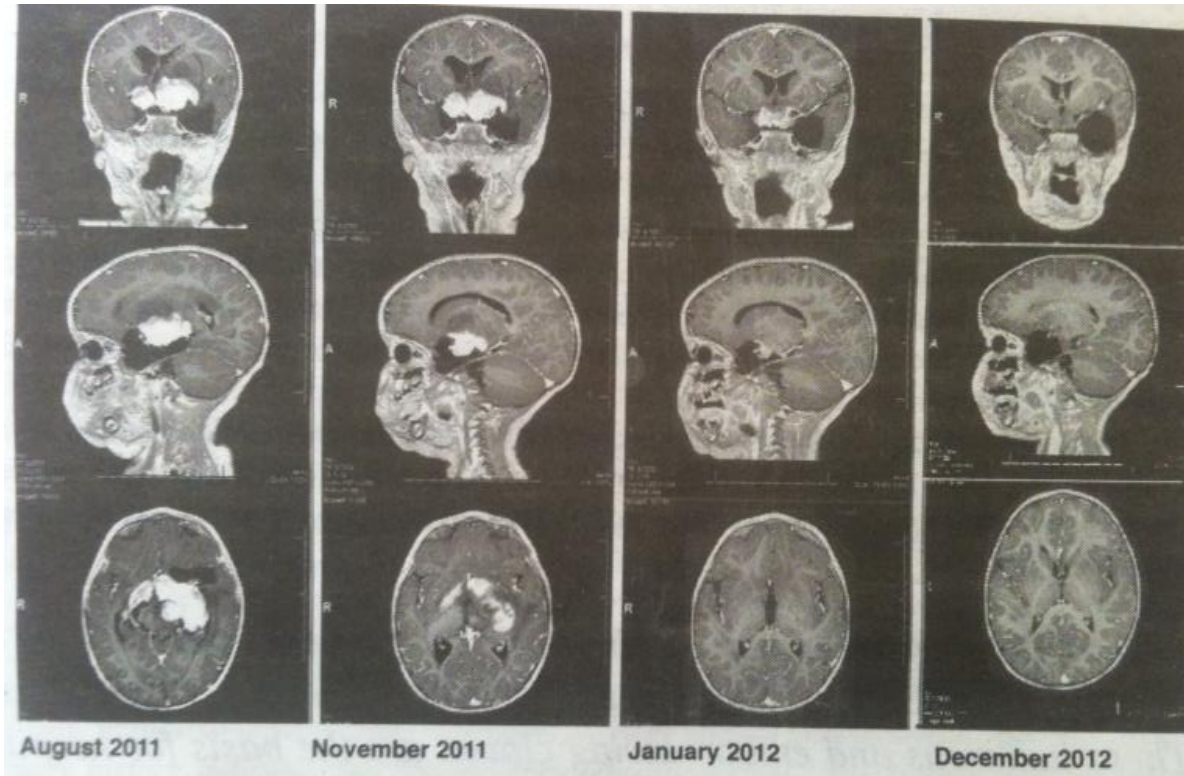
Review of 51 studies:

“...cannabinoids could be useful in the treatment of cancer due to their ability to regulate cellular signaling pathways critical for cell growth and survival.”



Cannabis as Medicine: Anti-Cancer

Case Report: *Glioblastoma multiforme* Brain Tumor in an 8 Month-Old Boy



Oct. 24, 2012: University of California San Francisco
CME Course MMJ13001A:
One speaker, Jeffrey Hergenrather, MD, described a particularly dramatic case seen by a San Diego colleague: a 90% reduction in the size of an infant's brain tumor achieved over the course of a year by parents applying hemp oil to the baby's pacifier before naptime and bedtime.

Source: *O'Shaughnessy's* and course attendance.



Cannabinoid Delivery Systems

Smoking

- Joints, pipes, and water pipes (bongs).
- Rapid onset and easy titration to desired effect.
- No first-pass through the liver.
- Pyrolysis; combustion byproducts result.
- **Harm reduction / risk mitigation strategy** = use fewer puffs of more potent strains.
- Vaporizing is better.

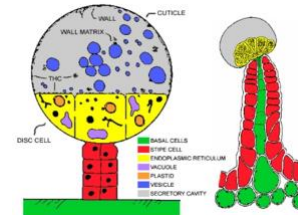


Cannabinoid Delivery Systems

Vaporization

- When cannabinoids are heated to the correct temperature, they boil and vaporize, like water turning into steam.
- The smoke-free vapor is then inhaled.
- Vaporization avoids the smoke and ash that are produced by burning, and allows more of the active ingredients to remain intact.

THC vaporization temp = 315°F
CBD vaporization temp = 356°F
Combustion > 400°F



Cannabinoid Delivery Systems

Edible Products

- *Cannabis* may be incorporated into a variety of edible products (cookies, brownies, candy, etc).
- Dosing is a concern, so it is important not to accidentally eat too much.
- Duration of action 6-8+ hours.

Issues:

1. Estimating dose (watch out!)
2. Delayed onset of action
3. Junk food and sugar



PHOTOS: ROBYN TWOMEY



PHOTOS: MARIJUANA TIMES



Cannabinoid Delivery Systems

Tinctures

A tincture is a medicinal extract of cannabis that is consumed.

- Oil, alcohol, or vegetable glycerin-based.
- Excellent delivery method:
 - Safe
 - Simple
 - Accurate dosing
 - Rapid onset
 - Sustained effect
- Standardized strain-specific, whole-plant tinctures with lab-tested and reported components are most desirable.



Cannabinoid Delivery Systems

“Rick Simpson Oil”

- Rick Simpson maintains that he used an alcohol (ethanol) extract of cannabinoids to cure his prostate cancer.
- The end-product of using the century’s-old technique of **herbal alcohol extraction** has become known as “Rick Simpson Oil.”
- Such concentrates contain **75-80%+ cannabinoids**.
- “Rick Simpson Oil” can be made using any variety of *Cannabis* (eg, high THC, high CBD, 50/50 THC:CBD, etc).



Cannabis Oil - Miracle Natural Medicine with NO SIDE EFFECTS



Cannabinoid Delivery Systems

Topical Applications

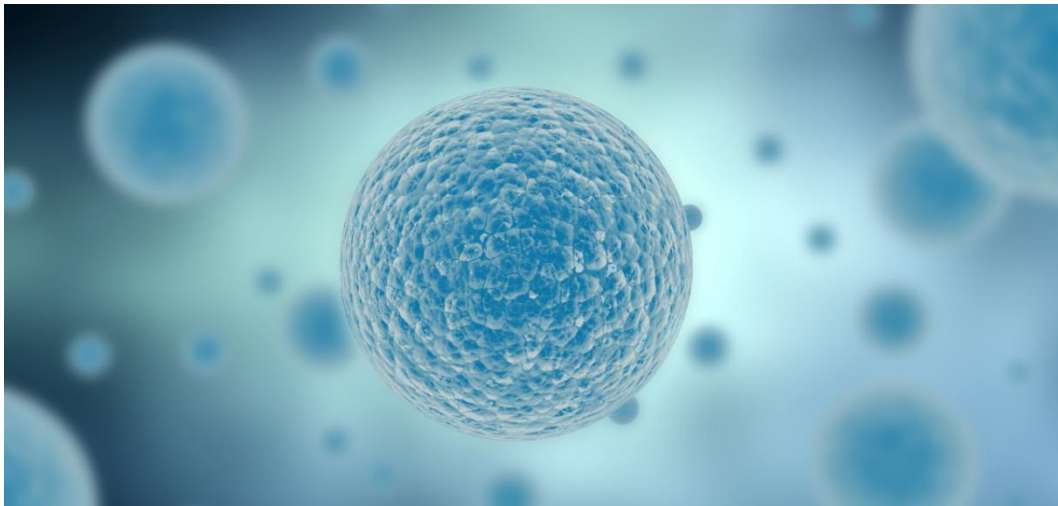
- Topical preparations of cannabis may be applied as an ointment, cream, or salve.
- Effective for local pain relief.
- Effective for the treatment of dermatologic conditions such as dermatitis, eczema, and psoriasis.
- Potential treatment for skin cancer.



Cannabinoid Delivery Systems

Cell-in-a-Box™

PHARMACYTE
B I O T E C H



PharmaCyteBiotech.com
OTCQB: PMCB

PharmaCyte Biotech is a clinical stage biotech company developing targeted treatments for Cancer and Diabetes.

Viridis Biotech, Inc. is a wholly-owned subsidiary of PharmaCyte Biotech, Inc.

Through Viridis Biotech, it is the mission of **PMCB** to develop treatments for serious diseases utilizing the constituents of *Cannabis*.

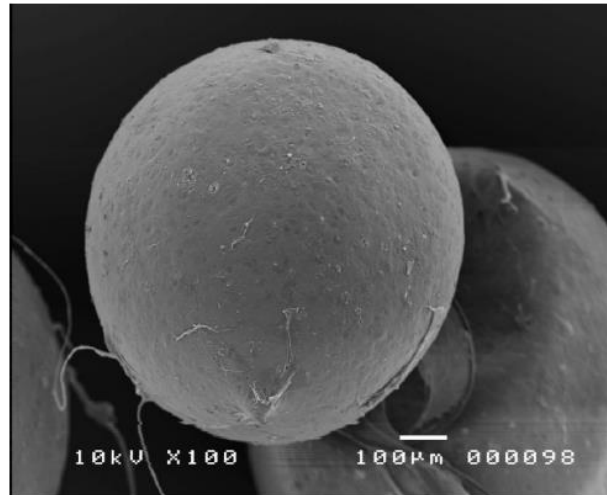
Cell-in-a-Box™ live-cell encapsulation technology serves as the platform for the development of such treatments.



The Future: Targeted Cannabinoid Chemotherapy

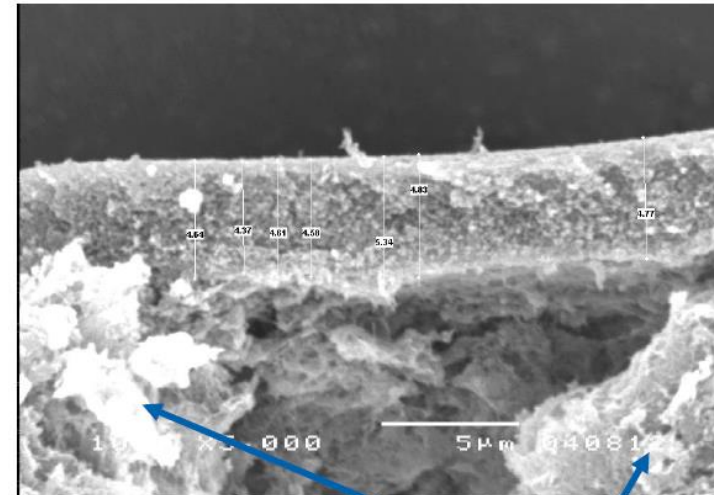
Cell-in-a-Box[®] Capsules: Microscopy

PHARMACYTE
BIOTECH



0.7 mm

View of a Single Capsule



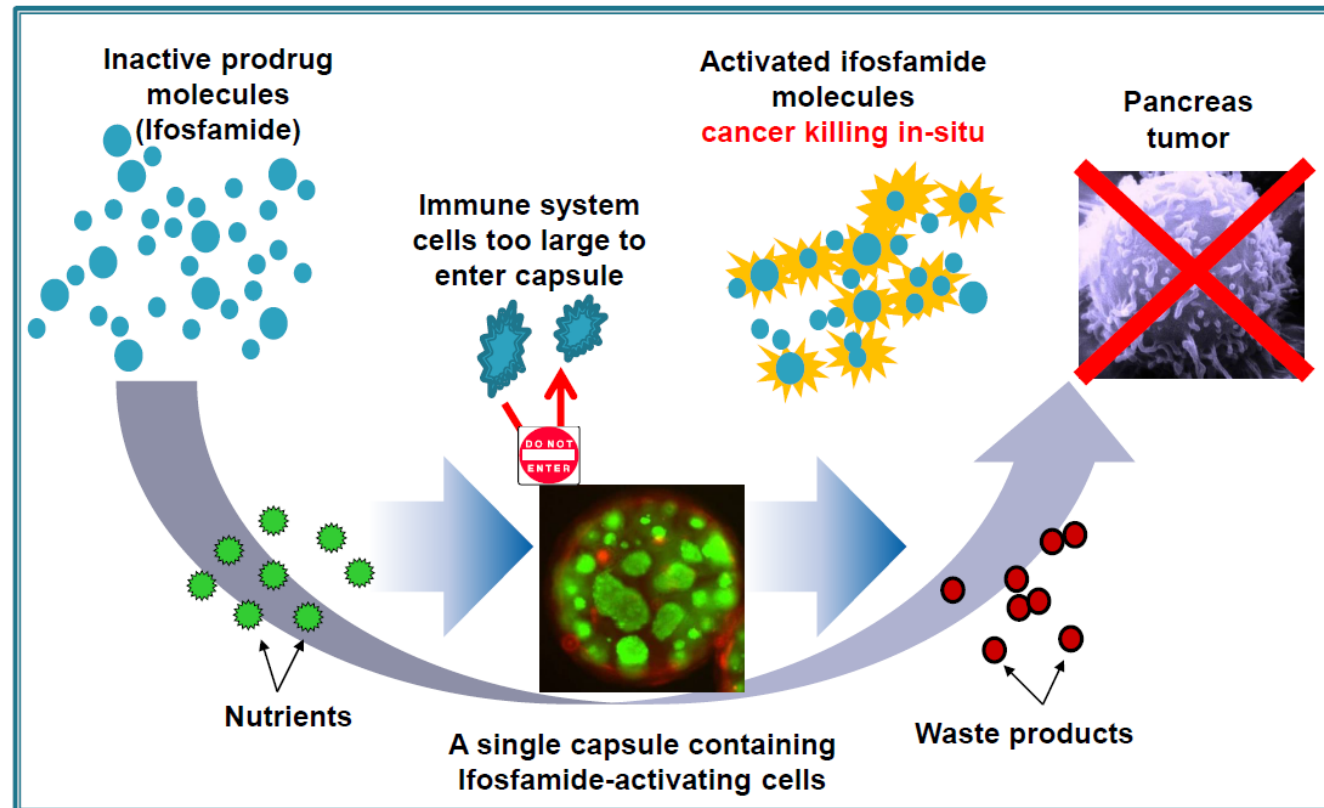
Capsule Cross Section Showing
Cancer Prodrug-activating Cells



The Future: Targeted Cannabinoid Chemotherapy

PHARMACYTE
BIOTECH

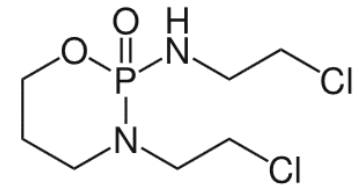
Cell-in-a-Box® Capsules– How They Work for Pancreatic Cancer Treatment



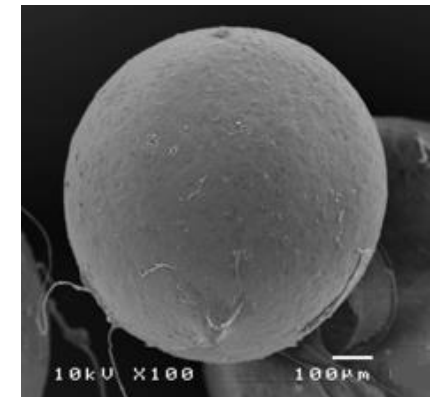
The Future: Targeted Cannabinoid Chemotherapy

Phase 1/2 Pancreatic Cancer Trial

- Fourteen evaluable patients with advanced, inoperable pancreatic cancer were treated.
- Compared to historical data for Gemzar®:
 - **Median survival time was increased from 23 to 44 weeks.**
 - **1-year survival rate was increased from 18% to 36%.**
- **No treatment-related serious adverse events were seen** – probably because only 1/3 of the “usual” dose of ifosphamide was used.
- **No “inflammation”** of the tissues near the capsules was apparent.
- Some **metastatic tumors in the liver were reduced in size.**
- **Encapsulated cells remained alive and functioning for >2 years** after implantation.



Ifosphamide



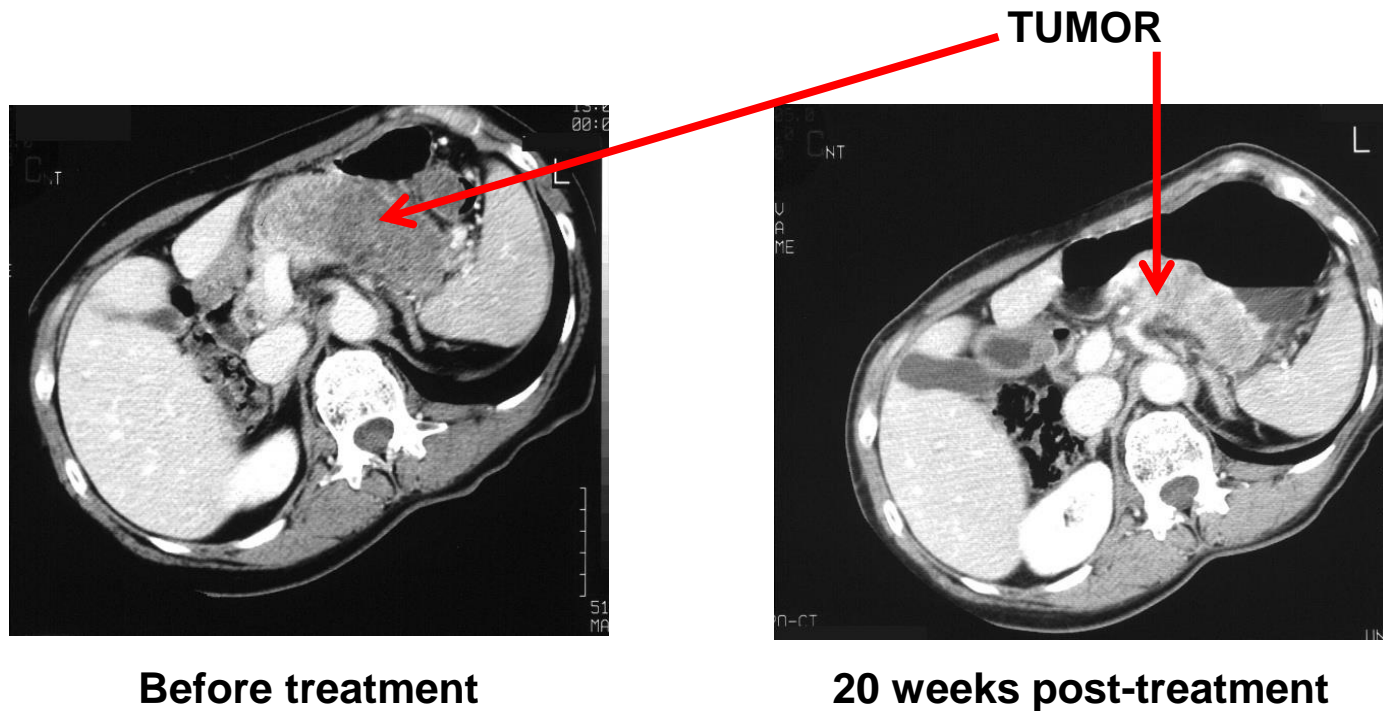
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The Future: Targeted Cannabinoid Chemotherapy

Phase 1/2 Pancreatic Cancer Trial

CT Scans of Pancreatic Cancer



Microencapsulated cell-mediated treatment of inoperable pancreatic carcinoma. Löhr M, et al. *Lancet*. 2001; (357):1591.

Safety, feasibility and clinical benefit of localized chemotherapy using microencapsulated cells for inoperable pancreatic cancer in a phase I/II trial. Löhr M, et al. *Cancer Therapy*. 2003; (1):121.



The Future: Targeted Cannabinoid Chemotherapy

Pipeline

PHARMACYTE
BIOTECH

Pancreatic Cancer:

Encapsulated live cells converting
Ifosfamide – antitumor effectiveness
and pain control



Ascites Fluid Accumulation:

Encapsulated live cells converting
Ifosfamide – delaying accumulation
of malignant ascites fluid



Diabetes:

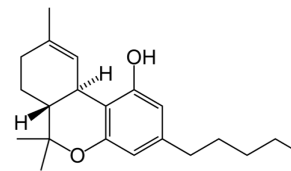
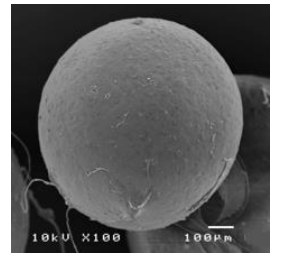
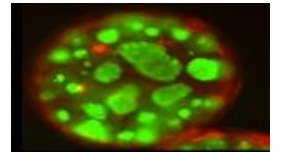
Encapsulated live cells produce,
store and secrete insulin on
demand



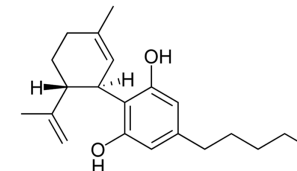
The Future: Targeted Cannabinoid Chemotherapy

Objective: Safe and Effective Cannabinoid-Based Treatments

- Cell-in-a-Box™ capsules are implanted using simple radiographic techniques .
- Capsules are bio-inert and encapsulated cells can remain alive and functioning for long periods of time in the body (2+ years).
- Cannabinoids are plant-based, sustainable, and have broad anti-cancerous and other medicinal properties, as well as an excellent safety profile.
- The raw materials brought to the “factory” are safe and biosustainable.
- The “factory” itself is safe, bioinert, and biosustainable.
- Pre-clinical investigations are underway at the **University of Northern Colorado** under a **Schedule I license** granted by the **DEA**.



THC

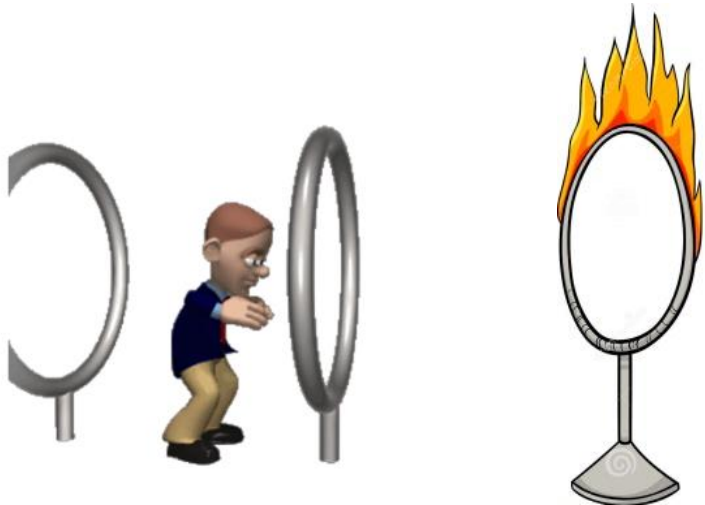
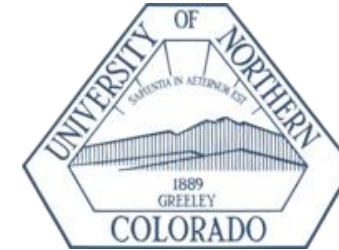


CBD



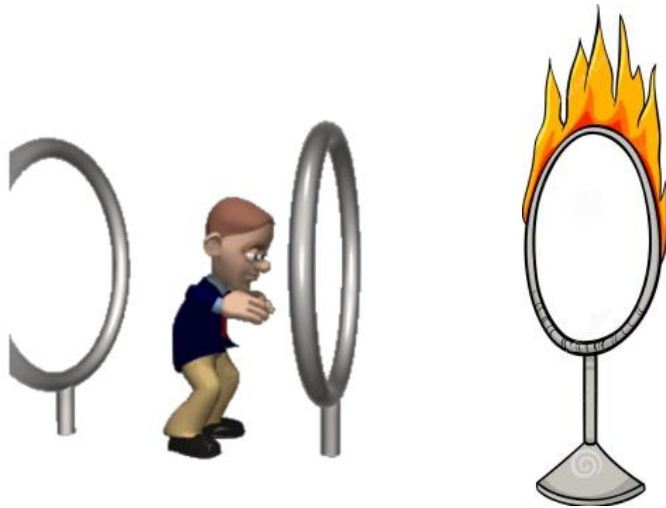
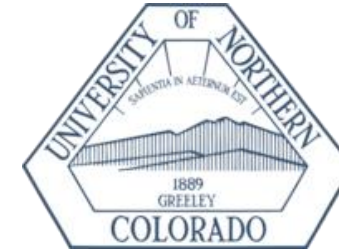
The Future: Targeted Cannabinoid Chemotherapy

Schedule I License Application Process



The Future: Targeted Cannabinoid Chemotherapy

Then, You Must Obtain Research *Cannabis*



The Future: Targeted Cannabinoid Chemotherapy

Early training to get a Schedule I license...

CONTROLLED SUBSTANCE REGISTRATION CERTIFICATE
UNITED STATES DEPARTMENT OF JUSTICE
DRUG ENFORCEMENT ADMINISTRATION
WASHINGTON D.C. 20537

| DEA REGISTRATION NUMBER | THIS REGISTRATION EXPIRES | FEE PAID |
|-------------------------|---------------------------|------------|
| RU0475029 | 05-31-2015 | FEE EXEMPT |

| SCHEDULES | BUSINESS ACTIVITY | ISSUE DATE |
|-----------|-------------------|------------|
| 1, | RESEARCHER (I) | 01-30-2015 |

Form DEA-223 (4/07)

UNIVERSITY OF NORTHERN COLORADO, ,
ROSS HALL
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GREELEY, CO 80639-0000

Restricted to Government personnel for official duties only.

Sections 304 and 1008 (21 USC 824 and 958) of the Controlled Substances Act of 1970, as amended, provide that the Attorney General may revoke or suspend a registration to manufacture, distribute, dispense, import or export a controlled substance.

THIS CERTIFICATE IS NOT TRANSFERABLE ON CHANGE OF OWNERSHIP, CONTROL, LOCATION, OR BUSINESS ACTIVITY, AND IT IS NOT VALID AFTER THE EXPIRATION DATE.



Source: *Crystal Lake Tribune*, 1977.
Crystal Lake, Illinois



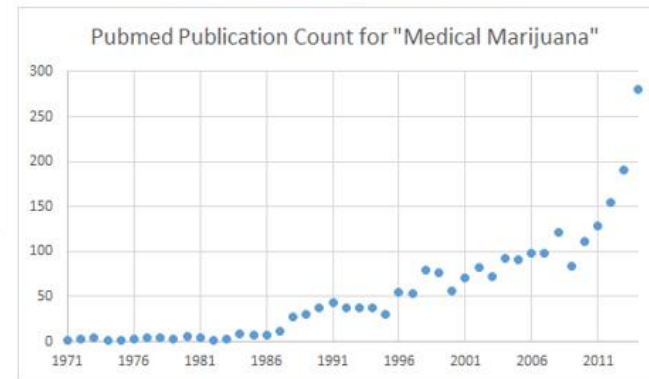
Integrating Medical *Cannabis* into Your Practice

Medical Marijuana in the Spotlight

- Increased media presence
- Increased clinical research interest
- Increased patient interest



"Here's my list of meds...
Is cannabis right for me?"



JAMA Internal Medicine

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Original Investigation | October 2014

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD^{1,2,3}, Brendan Saloner, PhD^{1,4}, Chinazo O. Cunningham, MD, MS⁵, Colleen L. Barry, PhD, MPP^{1,5}

[+]- Author Affiliations

JAMA Intern Med. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005.



Integrating Medical *Cannabis* into Your Practice

Legality in California

- Compassionate Use Act (1996)
- Senate Bill 420 (2003)
- People v. Kelly (2008/2010)
- Medical Marijuana Regulation Safety Act (2015)

AB 266

AB 243

AB 643

“...no physician in this state shall be punished or denied any right or privilege, for having recommended marijuana to a patient for medical purposes”

MBOC



Marijuana for Medical Purposes

This statement was adopted by the full Medical Board on May 7, 2004 and amended in October 2014.

On November 5, 1996, the people of California passed Proposition 215. Through this Initiative Measure, Section 11362.5 was added to the Health and Safety Code, and is also known as the Compassionate Use Act of 1996. The purposes of the Act include, in part:

“(A) To ensure that seriously ill Californians have the right to obtain and use marijuana for medical purposes where the medical use is deemed appropriate and has been recommended by a physician who has determined that the person's health would benefit from the use of marijuana in the treatment of cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, or any other illness for which marijuana provides relief; and

(B) To ensure that patients and their primary caregivers who obtain and use marijuana for medical purposes upon the recommendation of a physician are not subject to criminal prosecution or sanction.”

Furthermore, Health and Safety Code section 11362.5(c) provides strong protection for physicians who choose to participate in the implementation of the Act. “Notwithstanding any other provision of law, no physician in this state shall be punished, or denied any right or privilege, for having recommended marijuana to a patient for medical purposes.”

The Medical Board of California developed this statement since marijuana is an emerging treatment modality. The Medical Board wants to assure physicians who choose to recommend marijuana for medical purposes to their patients, as part of their regular practice of medicine, that they WILL NOT be subject to investigation or disciplinary action by the Medical Board if they arrive at the decision to make this recommendation in accordance with accepted standards of medical responsibility. The mere receipt of a complaint that the physician is recommending marijuana for medical purposes will not generate an investigation absent additional information indicating that the physician is not adhering to accepted medical standards.

These accepted standards are the same as any reasonable and prudent physician would follow when recommending or approving any other medication, and include the following:

1. History and an appropriate prior examination of the patient.
2. Development of a treatment plan with objectives.
3. Provision of appropriate consent including discussion of side effects.
4. Periodic review of the treatment's efficacy.



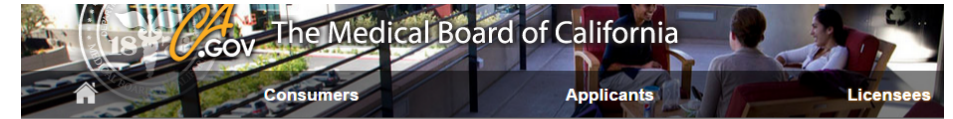
Integrating Medical *Cannabis* into Your Practice

Legality in California

- History and good faith exam
- Development of treatment plan with objectives
- Discussion of side effects
- Periodic review of efficacy
- Consultation as necessary
- Proper record keeping

“...in other words, if physicians use the same care in recommending marijuana to patients as they would recommending or approving medications, they have nothing to fear from the Medical Board.”

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1. History and an appropriate prior examination of the patient.
2. Development of a treatment plan with objectives.
3. Provision of appropriate consent including discussion of side effects.
4. Periodic review of the treatment's efficacy.
5. Consultation, as necessary.
6. Proper record keeping and maintenance thereof that supports the decision to recommend the use of marijuana for medical purposes.

In other words, if physicians use the same care in recommending marijuana to patients as they would recommending or approving medications, they have nothing to fear from the Medical Board.



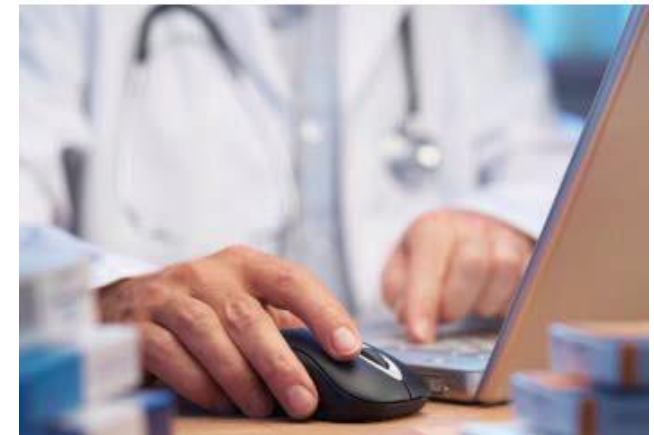
Integrating Medical *Cannabis* into Your Practice

Doctors' Dilemmas

- **Recommendations**
 - Dispensaries required standardized 8.5"x11.0" embossed documents for access.
- **Online Patient Verification**
 - Dispensaries only recognize online verification systems in order to identify patients.
- **Record Storage & Retrieval**
 - HIPAA considerations, easy access and use, save a tree.
- **Compliance**
 - State law, Federal law (DEA), MBOC "Standard of Care," HIPAA.
- **Supporting Forms**
 - Informed Consent, Patient Agreement, Authorization to Verify.
- **Education**
 - Practitioner, patient.



Integrating Medical *Cannabis* into Your Practice



Integrating Medical *Cannabis* into Your Practice

Benefits of Integrating Medical *Cannabis* into Your Practice

Improved patient care by...

- Maintaining existing doctor-patient relationships.
- Promoting open discussion of available, safe treatment options.
- Allowing doctors to tailor their practices through empiric experiences with their own patients.
- Creating opportunities for further clinical research.
- **BETTER CLINICAL RESULTS, FEWER SIDE EFFECTS**



Integrating Medical *Cannabis* into Your Practice

Customized Solutions to Meet Your Needs

- Easy-to-use electronic medical record platform.
- Reduce paperwork and increase efficiency.
- Create digitally-signed medical record documents.
- Generate patient recommendations and receipts.
- 24/7/365 Verification.
- Convenient online patient intake form.
- Consulting services to build your practice.
- Physician and patient education.



- **Software**
- **Education**
- **Consulting**

Why Us?

- Convenient patient-focused system
- Doctor designed & tested
- Cost-effective plans to fit every budget
- Turnkey & customizable solutions
- Microsoft®-certified support team
- Unparalleled industry experience

Security & Compliance

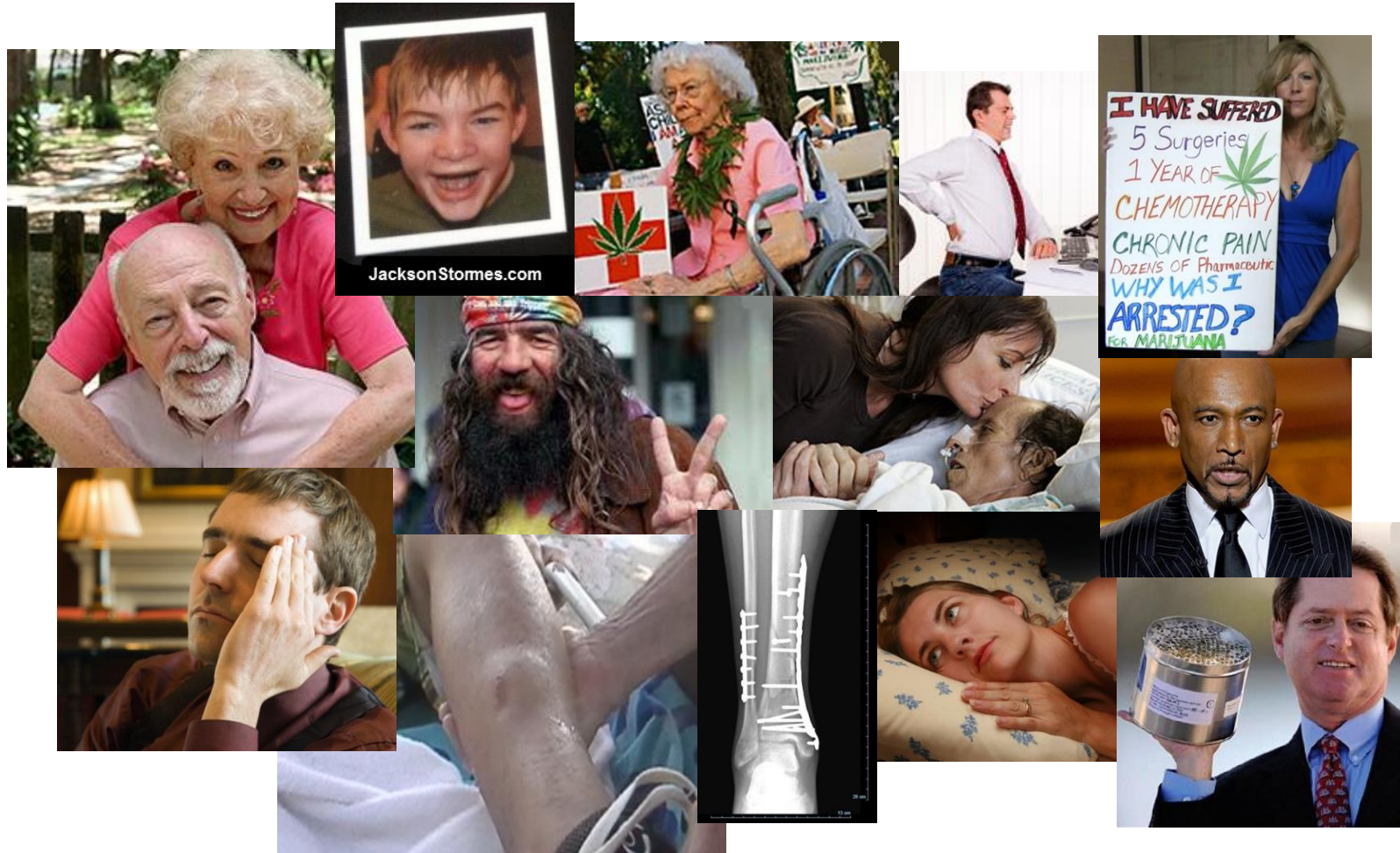
- Secure remote server-based technology (in the “cloud”)
- SSL technology
- 256-bit encryption
- HIPAA-compliant platform
- Create defensible medical records

Expertise & Extras

- Personalized strategies & assistance
- Online data and record storage
- Create accounting reports
- Generate patient recall lists
- Manage multiple providers & practices
- e-Learning courses



Parting Thoughts...



Marijuana should be regulated, not scheduled.

Medical marijuana should not be taxed.



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