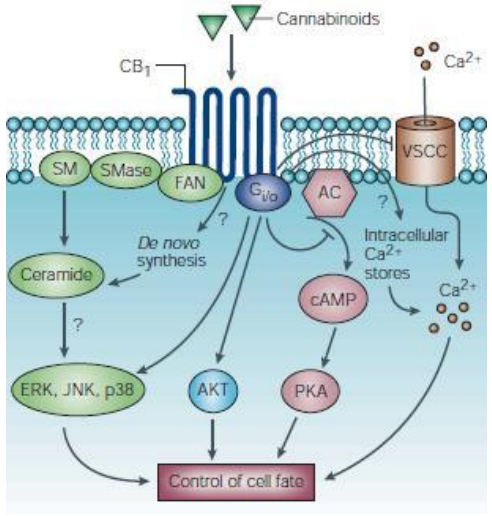

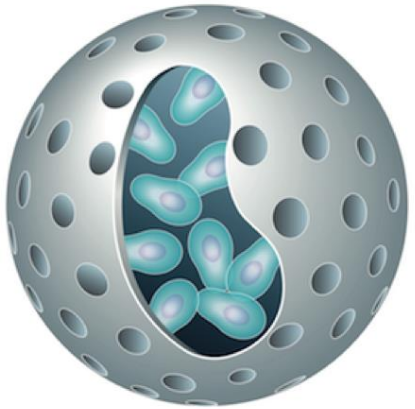

Medical *Cannabis* for Cancer

Mark L. Rabe, MD

Saturday, July 30, 2016

Cannabis for Cancer Forum

Hosted by the Association of Cannabis Professionals

Saturday, July 30, 2016

12:00 PM – 5:00 PM

Marina Village Conference Center
Anchor Room
1936 Quivira Way
San Diego, CA 92109

Medical *Cannabis* for Cancer

Mark L. Rabe, MD

1. Brief History
2. How Does *Cannabis* Work as Medicine?
3. Medical Effects of *Cannabis*
4. Research
5. Cannabinoid Delivery Systems
6. Practitioners: Integrating Medical *Cannabis*
7. Parting Thoughts…
8. Resources
9. References
10. Contact

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Brief History

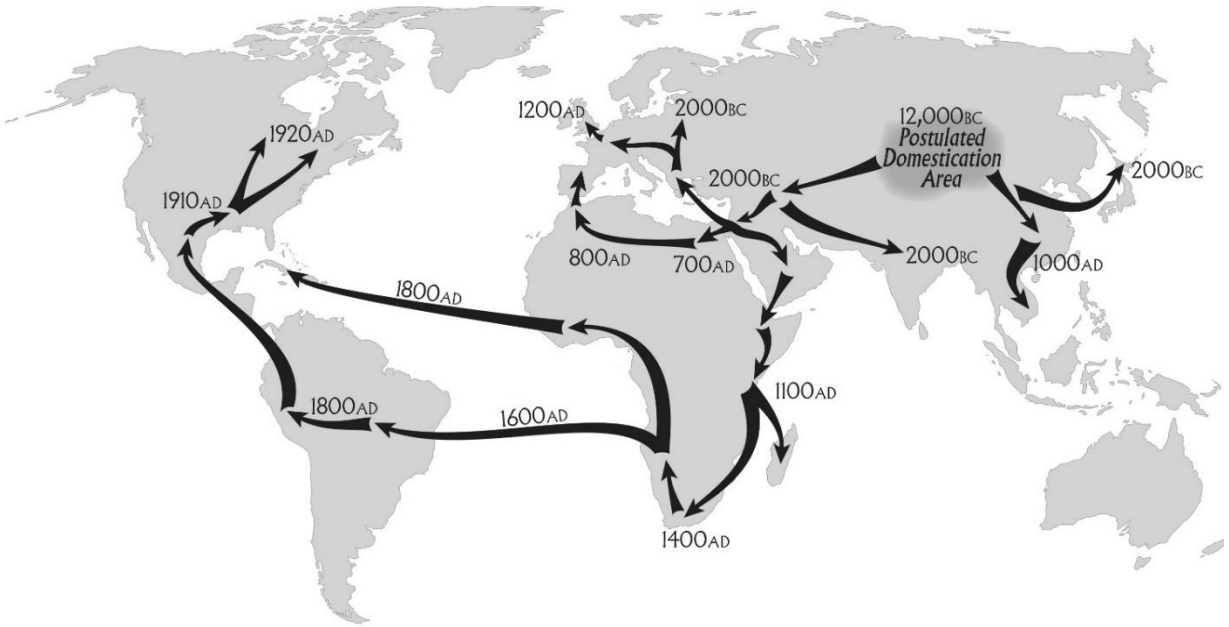
Cannabis: the “fragrant cane”…

The hemp plant has had a place in the history of many ancient cultures over thousands of years.

- **Kan** – ancient for cane, and hemp
- **Cana** – Sanskrit for hemp
- **Bis** – bosma (Aramaic for fragrant)
- **Cannabis** – kannabis (Greek for hemp)
- **Ma** – hemp in Chinese
- **Marijuana** – Portuguese word marigu-ano which means "intoxicant"
- **Marijuana** - derived from the Mexican words for "Mary Jane"

Brief History

The Migration of *Cannabis* Over Thousands of Years

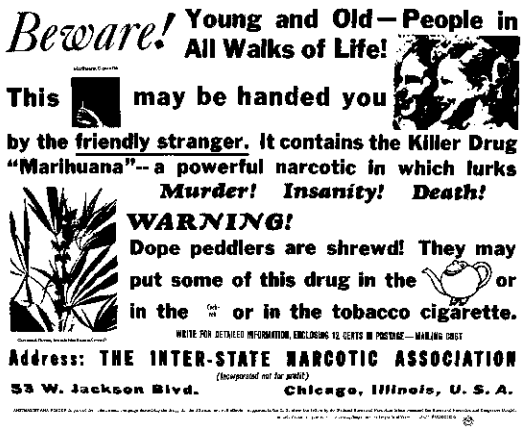


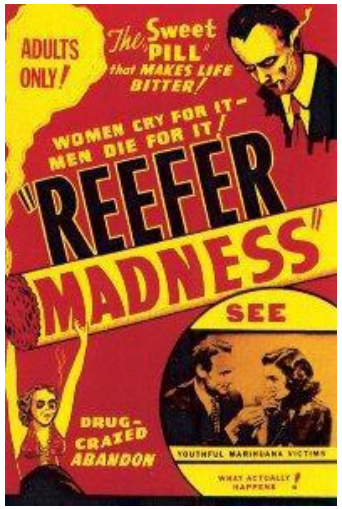
- **8000 BC**: the weaving of hemp fiber began as an industry in Asia and Persia
- **2700 BC**: according to the world's oldest pharmacopoeia, the ***pen-ts'ao ching*** ,the **Chinese Emperor Shen-Nung used "medical" *Cannabis* for the treatment of rheumatic pain, intestinal constipation, disorders of the female reproductive system, malaria, and other conditions**
- **2700 BC–1000 BC**: hemp was used in the Middle East and India for its many food, oil, fiber, and medicinal uses

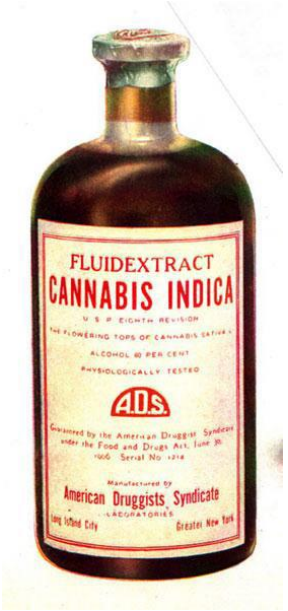
Brief History

Cannabis – Recreational or Medicine?

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





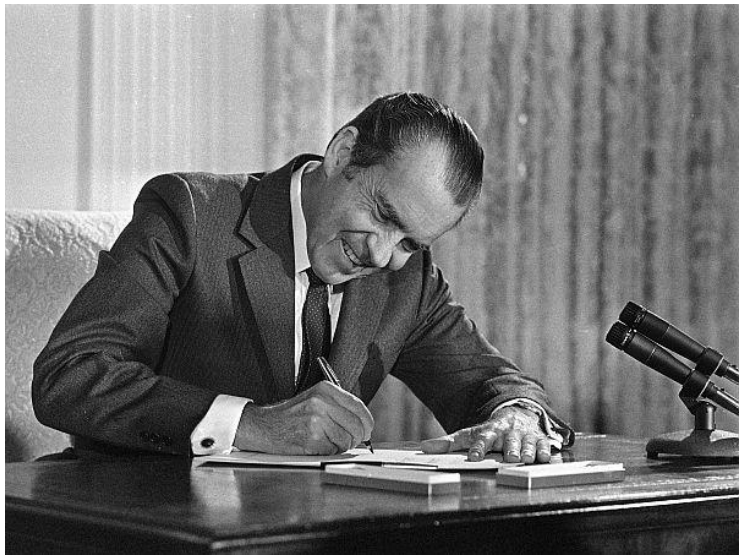


U.S. Pharma companies selling tinctures of *Cannabis* in the early 1900s, including Eli Lilly and Parke Davis.

Brief History

Marijuana Becomes a Schedule I Drug

- **Controlled Substances Act of 1970** – all drugs placed into "schedules."
- Marijuana was originally placed into **Schedule I** provisionally, 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.

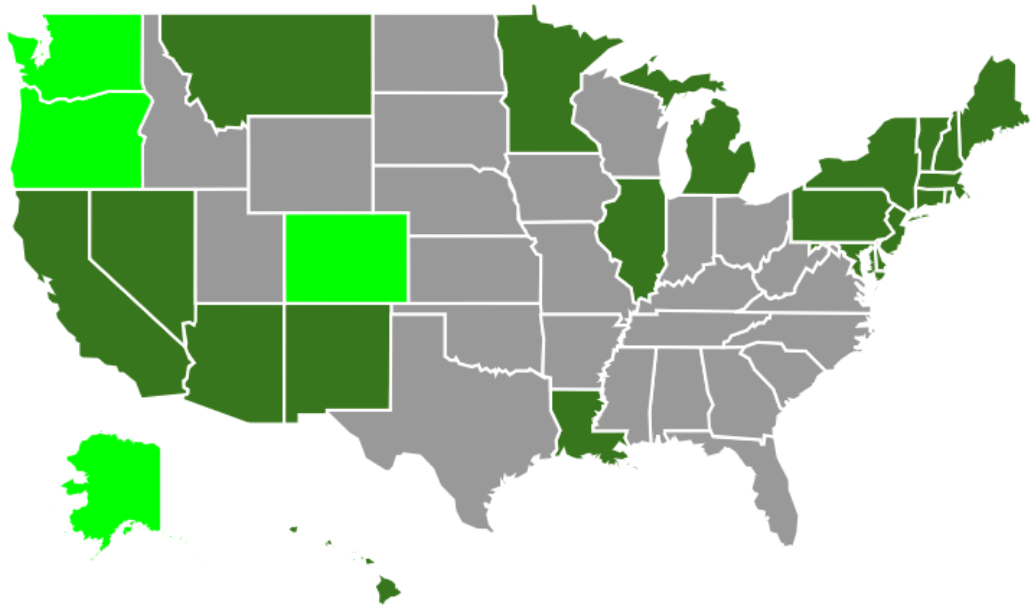


" … Therefore, the Commission recommends … [that the] possession of marijuana for personal use no longer be an offense, [and that the] casual distribution of small amounts of marihuana for no remuneration, or insignificant remuneration, no longer be an offense."
– Shafer Commission, 1972

Brief History

“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**, **25 states + DC** have enacted laws to legalize medical marijuana.
- **Four states (CO, OR, WA, AK)** have made marijuana legal for regulated adult use. More states (including CA Nov 2016) are considering similar legislation.



Marijuana Legalization Status: as of as of May 25, 2016

- Medical marijuana legalized
- Marijuana legalized for recreational use
- No laws legalizing marijuana

How Does *Cannabis* Work as Medicine?

Phytocannabinoids

- A group of molecular compounds unique to the *Cannabis* plant which exert a variety of medicinal actions in the human body.

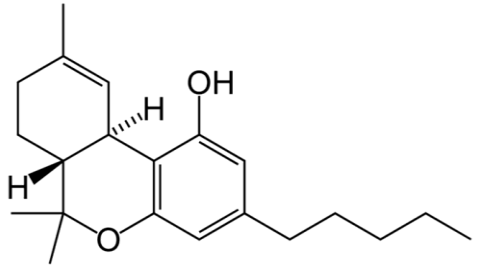
- 538 natural compounds identified in *Cannabis*
- Of these, 108 are identified as “cannabinoids” (unique compounds with 21 carbon atoms)
  - 10 main types
  - 14 different subtypes

- **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.

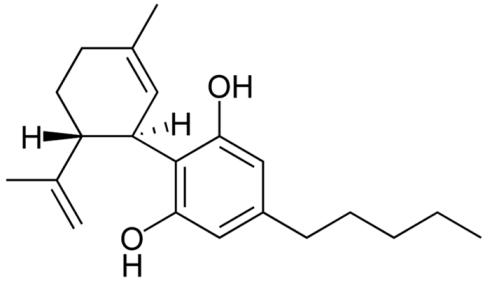
How Does *Cannabis* Work as Medicine?

Phytocannabinoids



THC (delta-9-tetrahydrocannabinol)

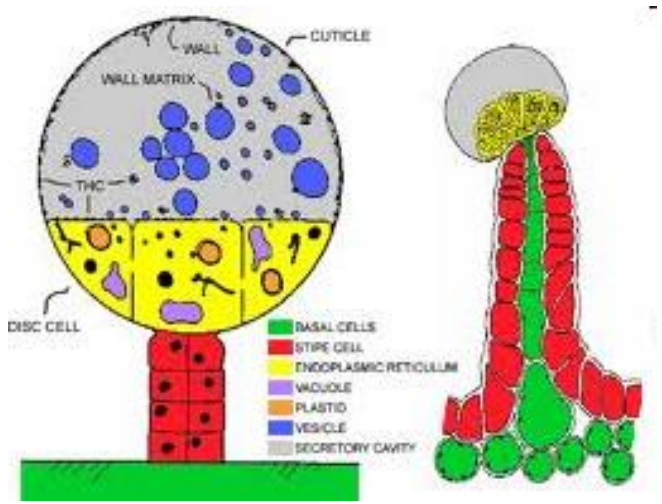
Properties:
Pain relief, anti-inflammatory, antioxidant, anti-nausea, mood elevation, anti-cancer



CBD (cannabidiol)

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

THC was discovered in Israel in 1964.



Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society.* 1964; 86:1646-7.

How Does *Cannabis* Work as Medicine?

The Endocannabinoid System

For over 20 years scientists wondered:

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

A: Endocannabinoid receptors were discovered in 1988.

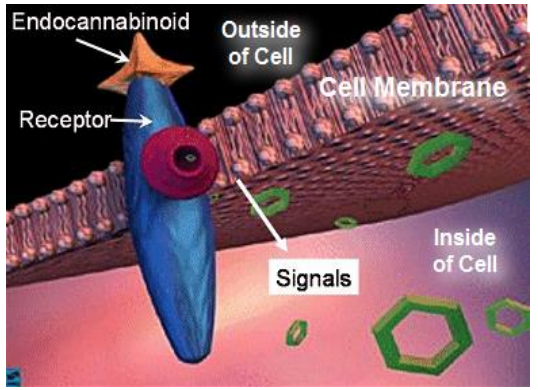
- Three types of receptors have been described.

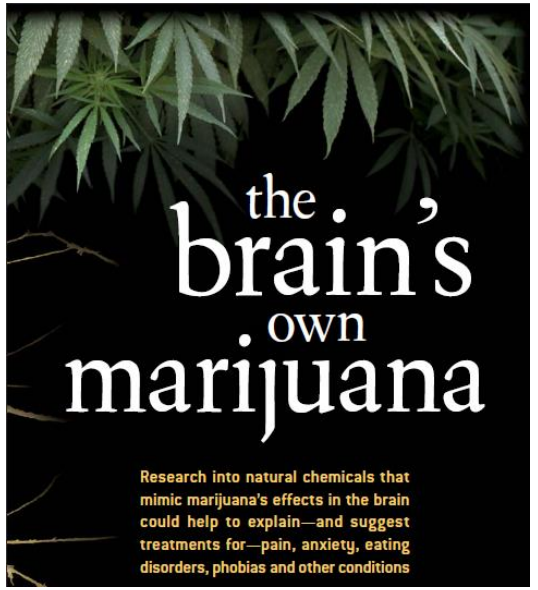
  CB1 – distributed mainly in human **brain tissue**. Also found in **peripheral tissue** where important in maintaining cellular energy balance. On **enteric nerves** where mediates GI system. Mediates the vomiting reflex.

  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. *Molecular Pharmacology*.1988;34:605-613.





***Scientific American*, 2004**

How Does *Cannabis* Work as Medicine?

Endocannabinoid Receptors

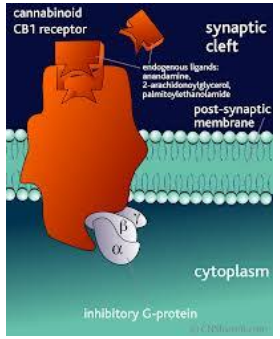
- Endocannabinoid receptors are G-protein coupled receptors located in cell membranes.
- Present throughout the pain pathway:

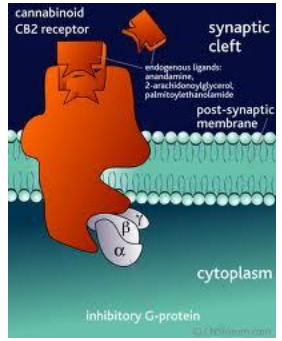
Central levels (CB1)

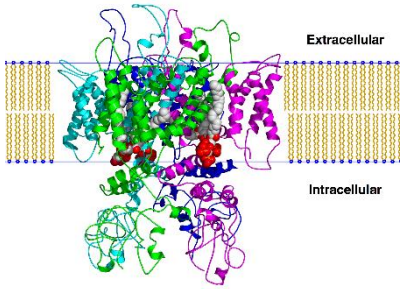
- Supraspinal (thalamus, amygdala, periaqueductal grey matter)
- Spinal (dorsolateral funiculus, surrounding the central canal, superficial dorsal horn)

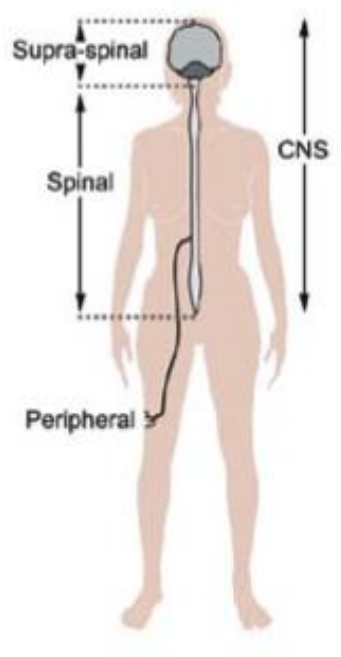
Peripheral level

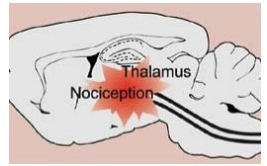
- Peripheral sensory nerve endings **(CB1)**
- Immune tissue and cells **(CB2)**

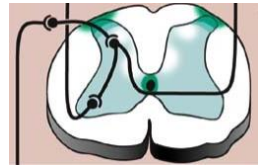


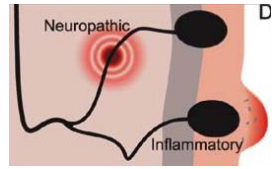












How Does *Cannabis* Work as Medicine?

Endocannabinoid Molecules

The presence of endocannabinoid receptors begged the question:

Q: "Is there an endogenous ligand(s)?"

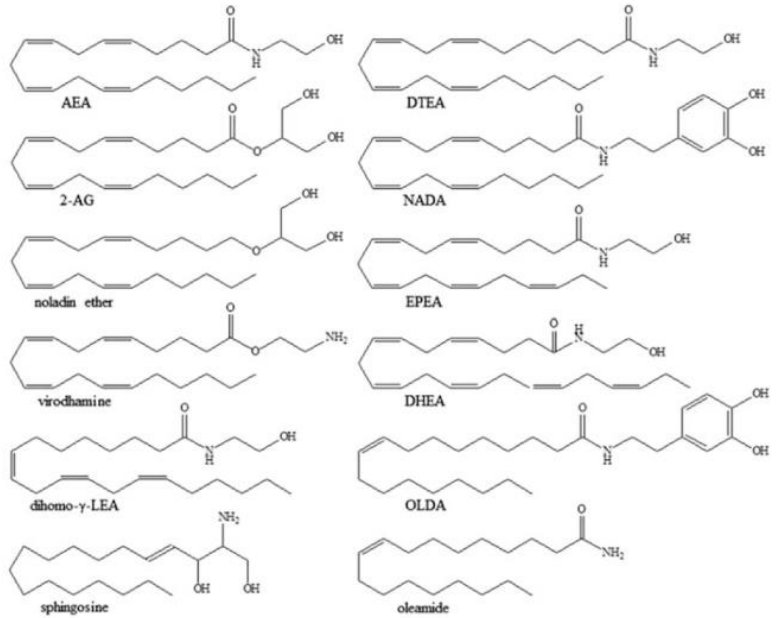
A: Yes.

- 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.* 1992; 258:1946-1949.

Mechoulam R, et al. *Biochemical Pharmacology.* 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.

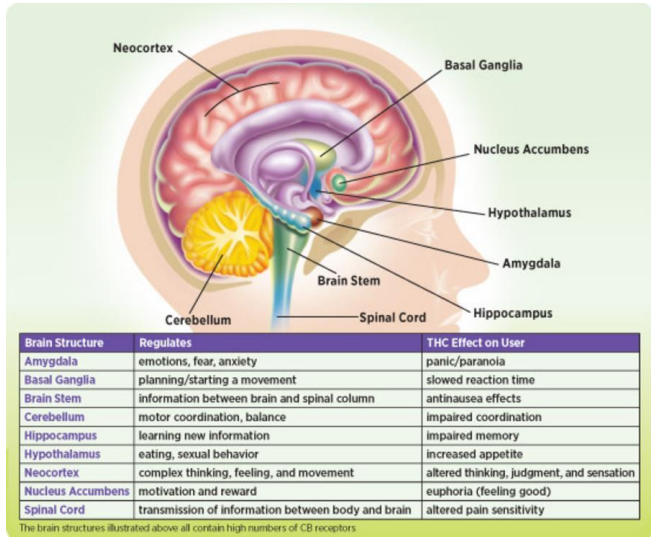
Pertwee, RW. *Endocannabinoids.* Handbook of Experimental Physiology. 2015. Springer International.

How Does *Cannabis* Work as Medicine?

Role of the Endocannabinoid System

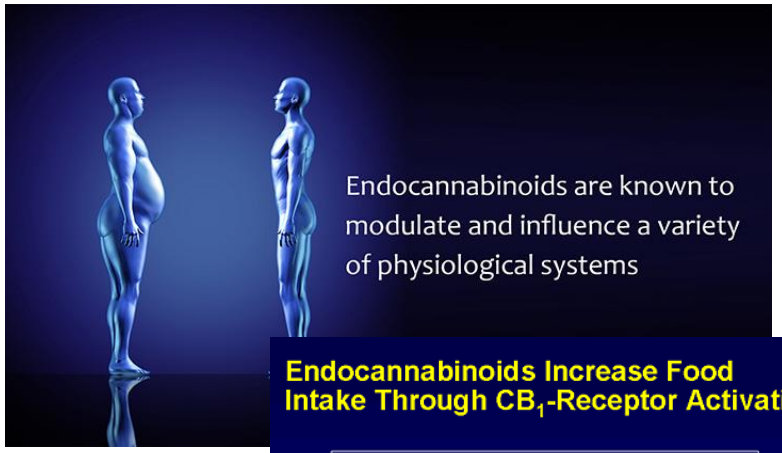
Maintain **"homeostasis,"** or the regulation of bodily systems.

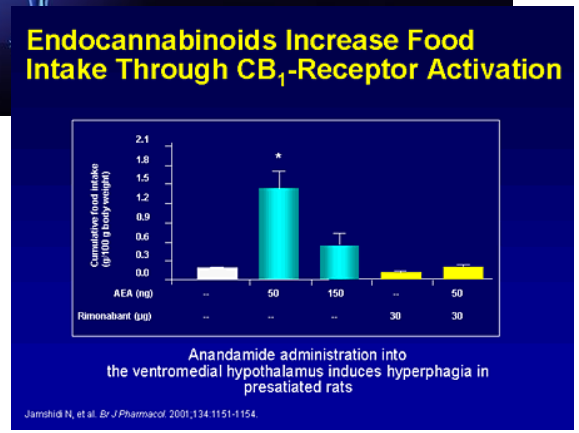
- Pain perception
- Thought processing/higher cognitive function
- Stress reaction
- Regulate muscles & movement
- Nausea/vomiting reflex
- Appetite
- Immune system and inflammatory response
- **Cellular reproduction**



Brain Structure	Regulates	THC Effect on User
Amygdala	emotions, fear, anxiety	panic/paranoia
Basal Ganglia	planning/starting a movement	slowed reaction time
Brain Stem	information between brain and spinal column	antinausea effects
Cerebellum	motor coordination, balance	impaired coordination
Hippocampus	learning new information	impaired memory
Hypothalamus	eating, sexual behavior	increased appetite
Neocortex	complex thinking, feeling, and movement	altered thinking, judgment, and sensation
Nucleus Accumbens	motivation and reward	euphoria (feeling good)
Spinal Cord	transmission of information between body and brain	altered pain sensitivity

The brain structures illustrated above all contain high numbers of CB receptors

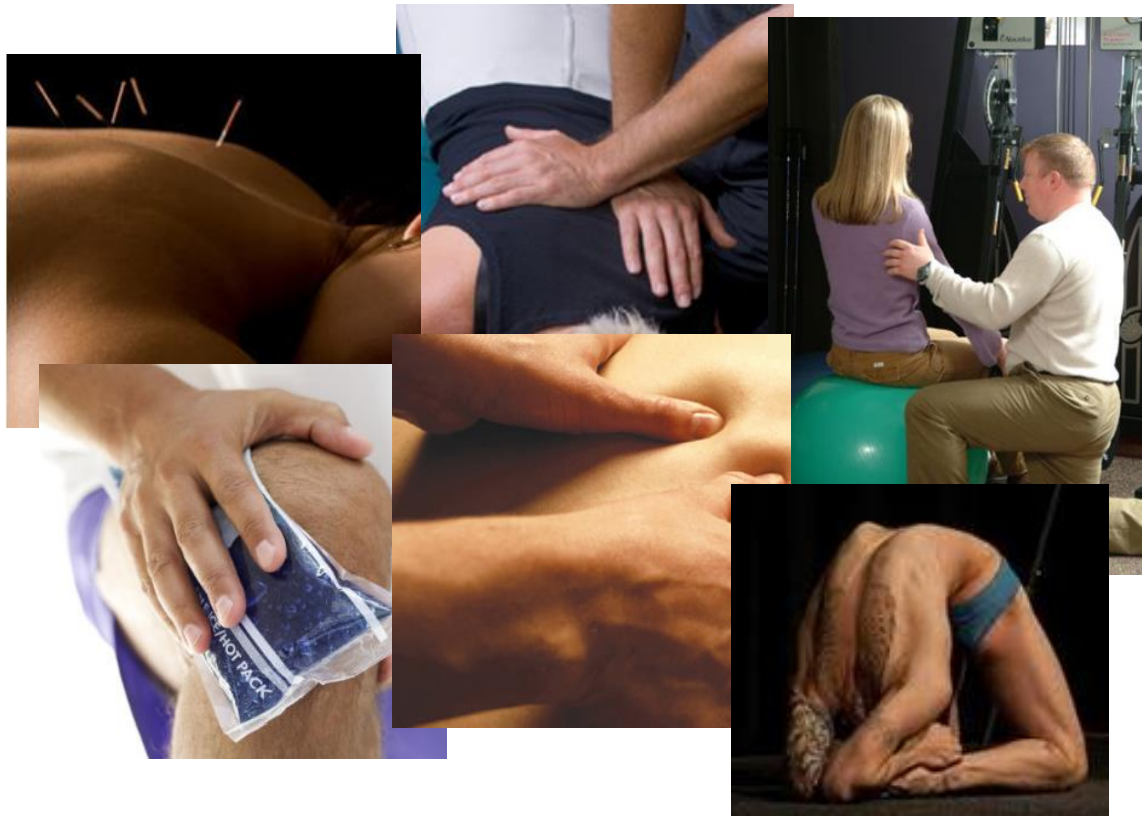




The endocannabinoid system has been called the **"supercomputer"** that regulates the human body.

Medical Effects of *Cannabis*

Patients are Increasingly Seeking Alternative Therapies…

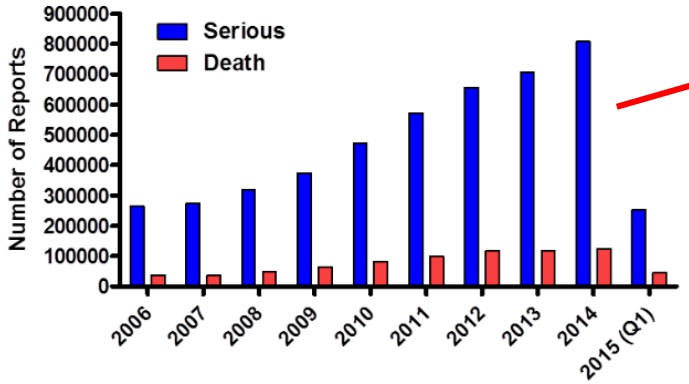


Medical *Cannabis*

Medical Effects of *Cannabis*

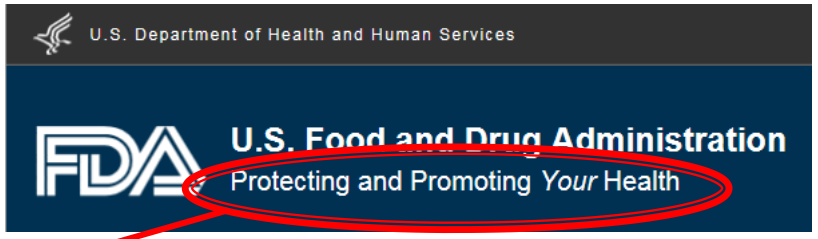
…Fueled by U.S. Drug Safety Statistics

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



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.



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

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

Medical Effects of *Cannabis*

What's it good for?

Indications: "any serious condition for which marijuana provides relief."

AN ANALYSIS OF APPLICANTS PRESENTING TO A MEDICAL MARIJUANA SPECIALTY PRACTICE IN CALIFORNIA

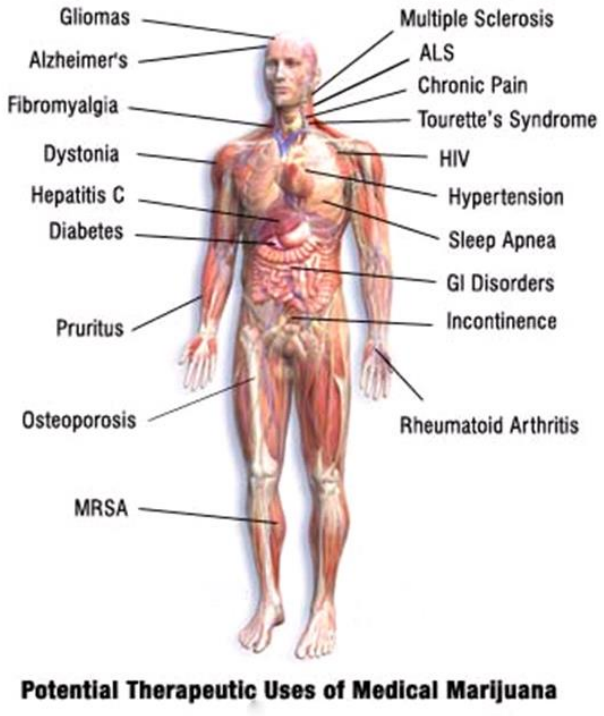
Helen Nunberg, MD, MPH
Beau Kilmer, PhD
Rosalie Liccardo Pacula, PhD
James Burgdorf

ABSTRACT

For more than a decade, medical marijuana has been at the forefront of the marijuana policy debate in the United States. Fourteen states allow physicians to recommend marijuana or provide a legal defense for patients and physicians if prosecuted in state courts; however, relatively little is known about those individuals using marijuana for medicinal purposes and the symptoms for which they use it. This study provides descriptive information from 1,655 patients seeking a physician's recommendation for medical marijuana, the conditions for which they sought treatment, and the diagnoses made by the physicians. It presents a systematic analysis of physician records and patient questionnaires obtained from consecutive patients seen during a three month period at a medical marijuana specialty practice operating throughout the state of California. The analysis yields a number of insights that may be useful for future research on medical marijuana and marijuana policy, including: 1) The most common diagnoses reported were for chronic pain, mental health conditions (primarily anxiety and depression), and sleep disorders; and 2) 50% of the applicants reported using marijuana as a substitute for prescription drugs.

1. INTRODUCTION

Medicinal marijuana has been at the forefront of the marijuana policy debate in the United States for almost 15 years. As of July 2010, fourteen states allow doctors to recommend marijuana or provide medical marijuana users with a medical necessity defense if they are prosecuted in state courts (NORML, 2010). There is a small literature about whether these laws influence the overall demand for marijuana (Gorman & Charles, 2007; Pacula et al., 2010) and a tremendous amount of public discussion about how medicinal marijuana is distributed. This is especially true in California where the City of Los Angeles is in the process of shutting down over 400 dispensaries (Hoeffel, 2010a) and the City of Oakland recently approved licensing four industrial-scale growing facilities for medicinal marijuana (Hoeffel, 2010b).



Potential Therapeutic Uses of Medical Marijuana

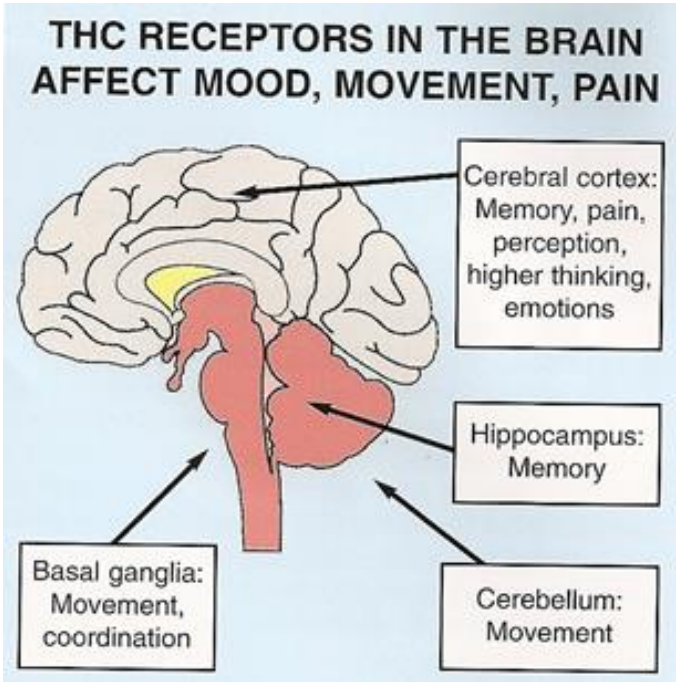
An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California

Nausea & Appetite Loss	113	4.60%		
Spasms, Convulsions	228	9.20%		
Analgesia / [3]Immunomodulatory /	1133	45.70%		
(A) Migraine and Neuralgias			179	7.20%
(B) Arthritis			433	17.50%
(C) Spinal & Skeletal Disorders:			366	14.80%
(D) Injury, trauma			57	2.30%
(E) Gastrointestinal:			68	2.70%
(F) Other Inflammatory			30	1.20%
Mood Disorders	660	26.60%		
Insomnia	71	2.90%		
Harm Reduction / Substitution	136	5.50%		
Glaucoma & eye diseases	24	1.00%		
Asthma:	53	2.10%		
Miscellaneous:	62	2.50%		

Nunberg, et al. *Journal of Drug Policy Analysis.* 2011; 4(1):1-14.

Medical Effects of *Cannabis*

Brain

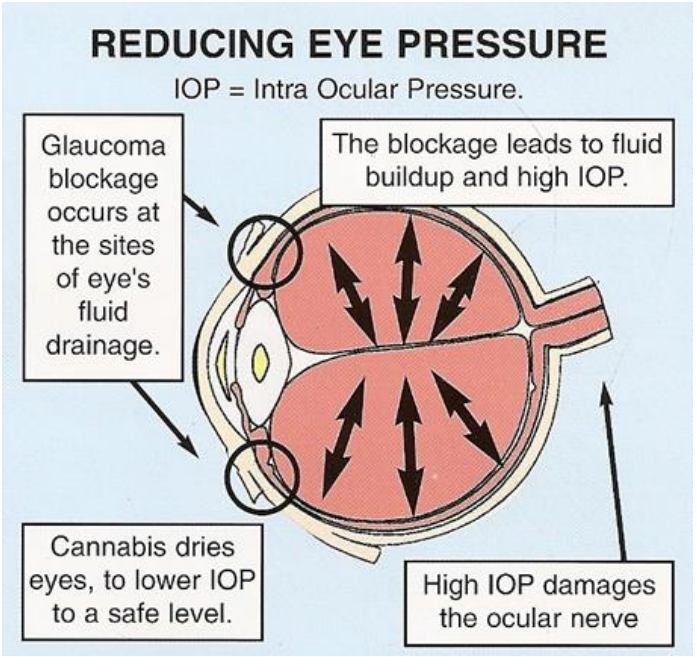


- Stimulates special receptor sites in the brain that affect multiple body systems
- Initial stimulant effect, followed by relaxation and overall reduction in stress
- Analgesic effect
- Blocks migraine and seizures
- Control symptoms of MS, spinal injury, epilepsy
- Enhances sense of humor, well-being
- Has synergistic effects with opiates/other drugs
- May cause drowsiness, distraction, paranoia, anxiety

* Not all cannabis has the same potency/effects.

Medical Effects of *Cannabis*

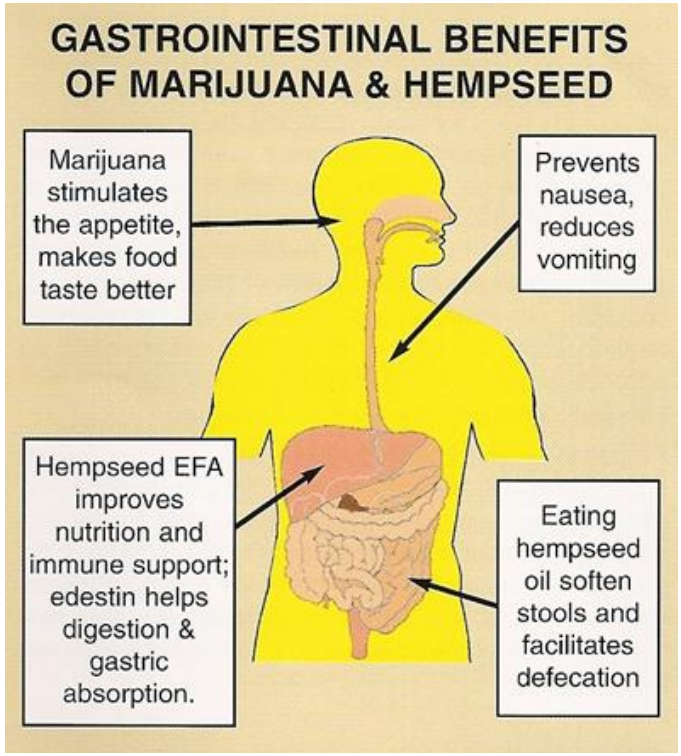
Eyes



- Dehydrates the eyes, lowering intra-ocular pressure (IOP).
- Duration has been measured at 3-4 hours.
- Side effects may include dry eye, and redness.
- Neuroprotective against retinal degeneration.

Medical Effects of *Cannabis*

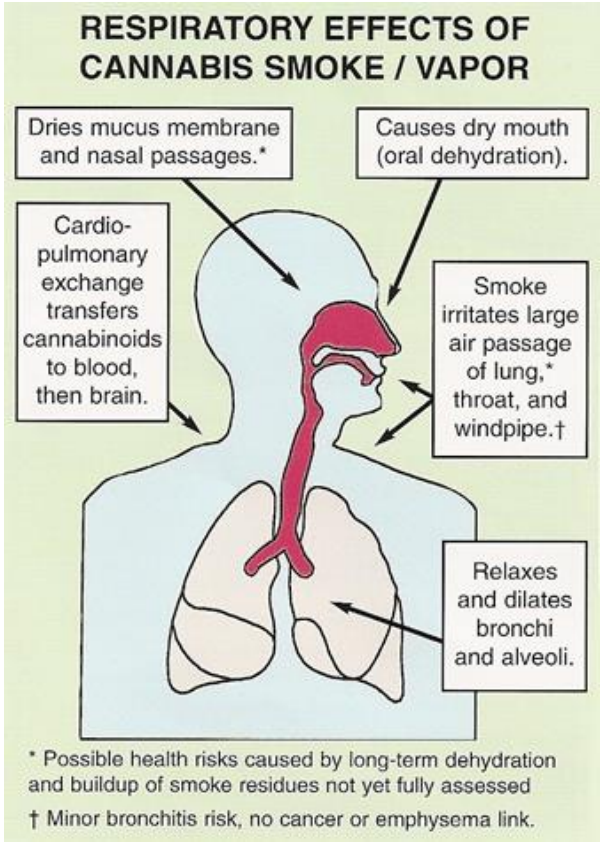
GI System



- Dehydrates the mouth
- Stimulates appetite, enhances flavors and taste
- Slows gastric emptying time (calms stomach)
- Reduces nausea and vomiting (antiemetic)
- Decreases muscle spasm of the GI tract
- Anti-inflammatory for treatment of colitis
- Soothes motion sickness and various side effects of radiation and chemotherapy

Medical Effects of *Cannabis*

Lungs



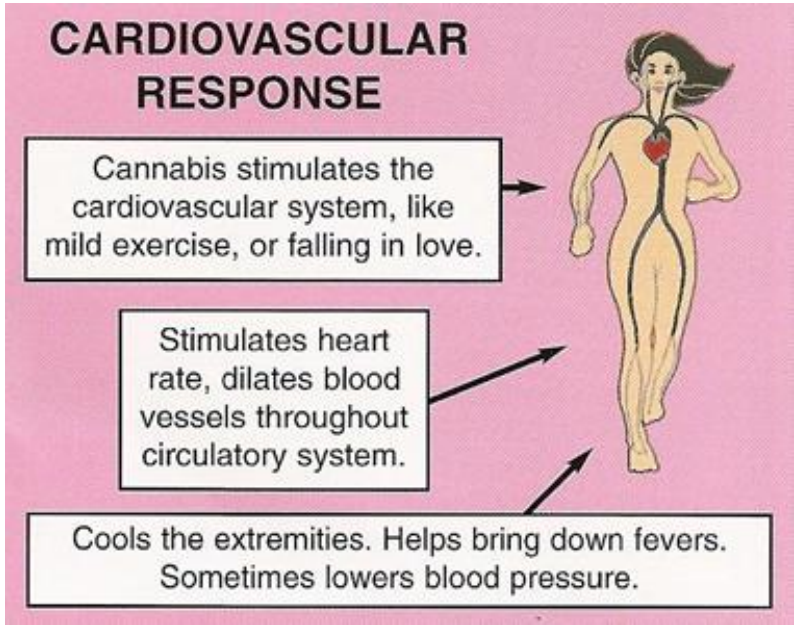
- Bronchodilator effect improves oxygen intake for the relief of asthma
- Anti-phlegmatic and expectorant effects help to clear the lungs

Quick Delivery System: When cannabinoids are inhaled into the lungs, the the bloodstream then carries them directly to the brain – providing an extremely fast and effective delivery system.

Method: Smoking releases tars, carbon monoxide, acids, combustion byproducts, and particulate irritants – irritating the mouth, throat and respiratory system. Vaporization, oral ingestion can mitigate these effects.

Medical Effects of *Cannabis*

Heart and Cardiovascular System



Acute effects:

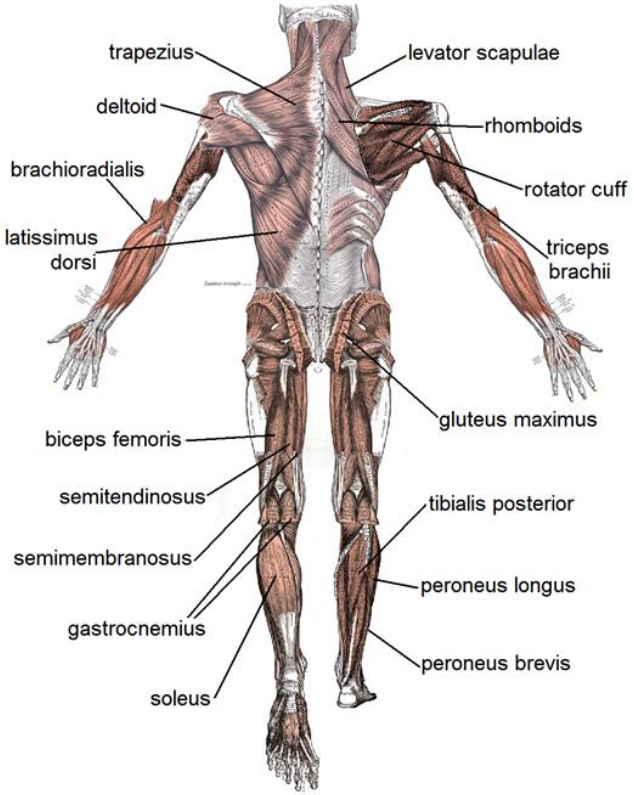
- Produces tachycardia with a decrease in orthostatic blood pressure. This is a risk for users with angina or CHF.

Chronic effects:

- Vasodilatory
- Long term use may result in a lowering of blood pressure.
- Cardioprotective – may reduce infarct size.

Medical Effects of *Cannabis*

Musculoskeletal System



Soothes joints…

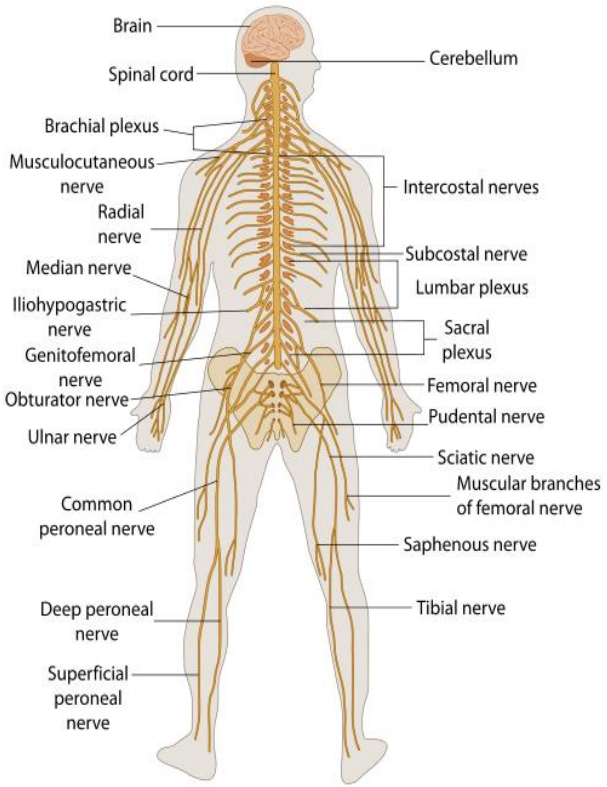
- Analgesic effect reduces pain
- Anti-inflammatory effect helps arthritis (orally or topically)

Relaxes muscles…

- Reduces muscle cramps
- Relieves spasticity
- Reduces tremor
- Anti-ataxic (decreases the gross lack of coordinated muscle movements seen in some neurodegenerative disorders)

Medical Effects of *Cannabis*

Nervous System



- Increased regional cerebral blood flow
- EEG changes – increase in alpha wave activity consistent with relaxation and drowsiness
- Reduction in REM sleep
- More total sleep time
- Sensory alterations
- Psychomotor slowing/decreased coordination
- Impairment of recent memory
- Neuroprotective (eg, after head trauma, in MS)
- Anti-convulsant effects

Medical Effects of *Cannabis*

Mental Health

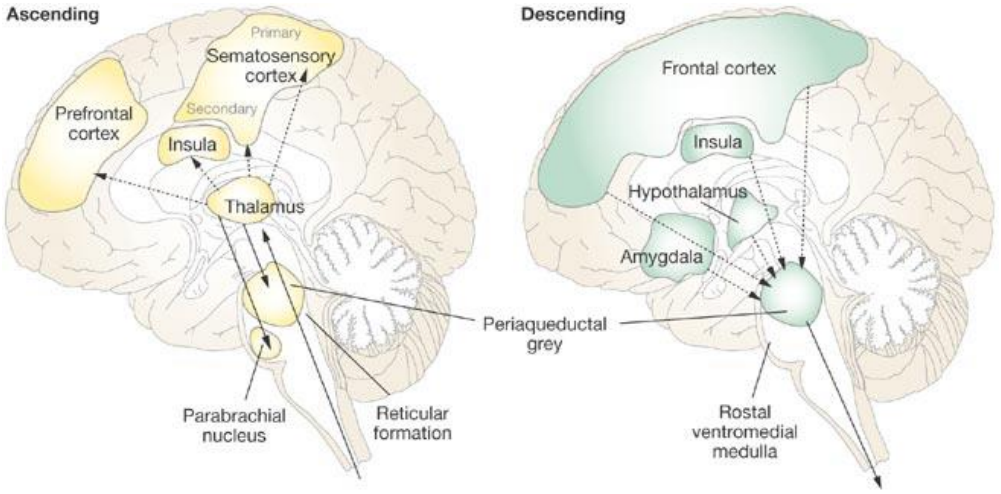
Mental Health Diagnoses: out of 39,305 total patients

MediCann Mental Health Diagnoses (2009) N = 39,305					
Insomnia	16,449	Anger Reaction	674	Tourette's Disorder	17
Anxiety	9,118	Anorexia Nervosa	198	Stuttering	6
Anxiety/ Depression	4,631	OCD	182	**Harm Reduction**	
Depression	2,392	Schizophrenia	132	Alcohol Dependence	258
PTSD	1,316	Nightmares	105	Opioid Dependence	62
ADD/ADHD	1,312	Agoraphobia	75	Cannabis Dependence	31
Bipolar Disorder	1,200	**Other**		Cocaine Dependence	1
Panic Disorder	1,092	Bruxism	54		

Medical Effects of *Cannabis*

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.



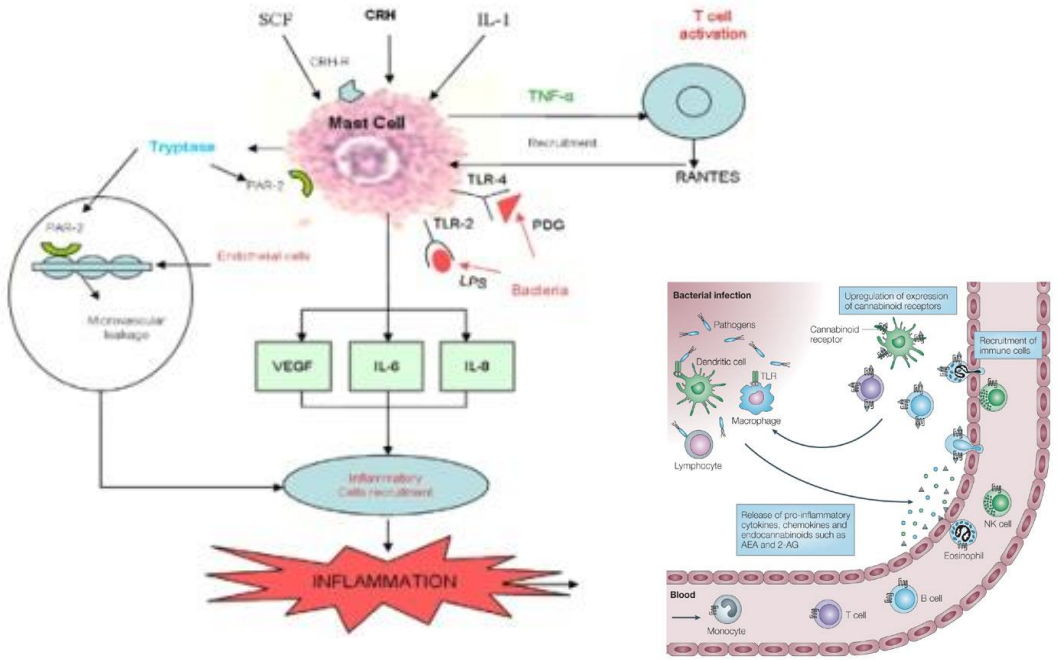
Walker JM, et al. The neurobiology of cannabinoid analgesia. *Life Sciences* 1999; 65(6-7):665-73.

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

Medical Effects of *Cannabis*

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.

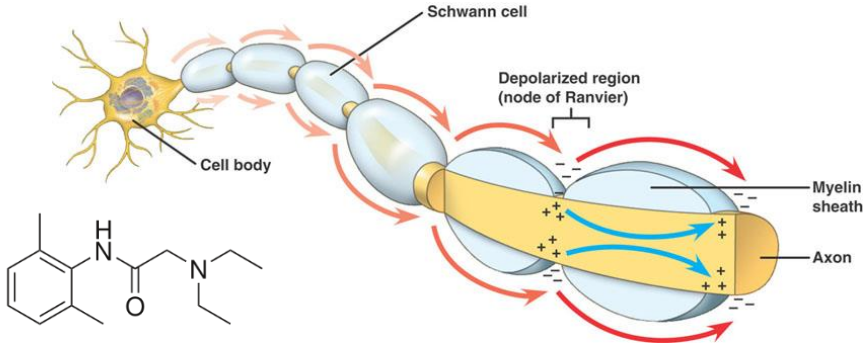
Richardson JD, et al. *Pain*. 1998; 75(1):111-9.

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

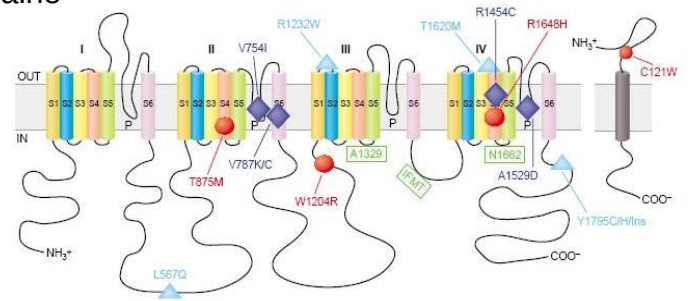
Medical Effects of *Cannabis*

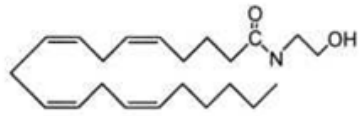
Anti-Pain Mechanism #3: Inhibition of Pain Transmission

- 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
- 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 states
- Anandamide was shown to inhibit the function of α subunits in neuronal sodium channels Nav1.2,1.6, 1.7, and 1.8



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. *Anesthesia and Analgesia..* 2014; 118(3):554-62.

Medical Effects of *Cannabis*

Research: Cannabinoids Decrease Cancer Patients' Need for Opioids

- Subjects: 21 individuals with chronic pain on twice-daily doses of sustained-release morphine or oxycodone.
- Participants used vaporized cannabis.
- The extent of chronic pain was assessed daily.
- Pain was decreased by 27% (95% confidence interval).
- **<u>Conclusion</u>: Vaporized cannabis augments analgesic effects of opioids without altering plasma opioid levels.**
- **<u>Conclusion</u>: The combination may allow for opioid treatment at lower doses with fewer side effects.**

San Francisco General Hospital, UCSF
Abrams DI, et al. Cannabinoid-opioid interaction in chronic pain. *Clinical Pharmacology and Therapeutics*. 2011; 90(6):844-51.

Opioid-Induced Side Effects

- Common side effects
  - Constipation
  - Nausea
  - Sedation
  - Confusion
  - Hallucination
  - Sweats
  - Dry mouth
- Uncommon side effects
  - Urinary retention
  - Pruritis
  - Delirium
  - Myoclonus
  - Hyperalgesia
  - Seizures
  - Respiratory depression

Medical Effects of *Cannabis*

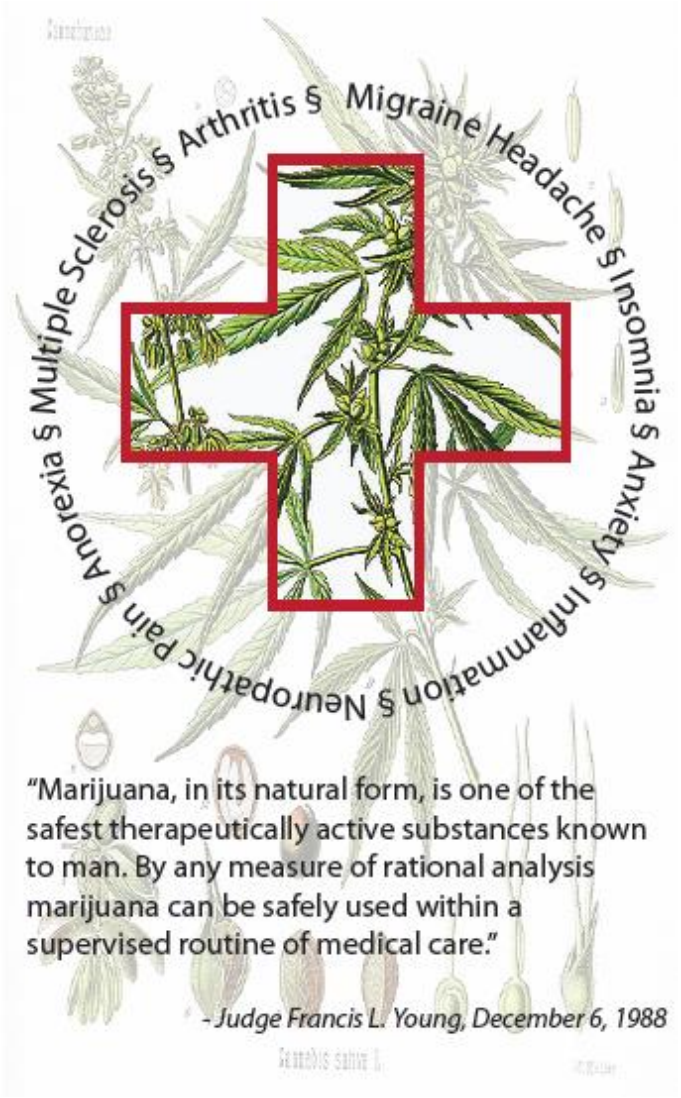
Safety

Most Commonly Reported Side Effects of Medical *Cannabis*

- Dry mouth
- Red eyes
- Increased appetite
- Sedation
- Psychoactivity

OPINION AND RECOMMENDED RULING, FINDINGS OF FACT, CONCLUSIONS OF LAW AND DECISION OF USA DRUG ENFORCEMENT ADMINISTRATION (DEA) LAW JUDGE, DATED: SEPT. 6 1988.

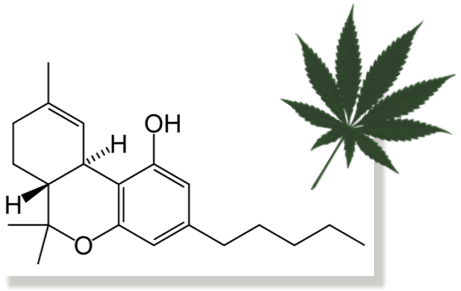
"… By contrast, marijuana's therapeutic ratio, like its LD-50, is impossible to quantify because it is so high. In strict medical terms marijuana is far safer than many foods we commonly consume. For example, eating ten raw potatoes can result in a toxic response. By comparison, it is physically impossible to eat enough marijuana to induce death."



Medical Effects of *Cannabis*

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 <u>funded by the U.S. government</u> 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

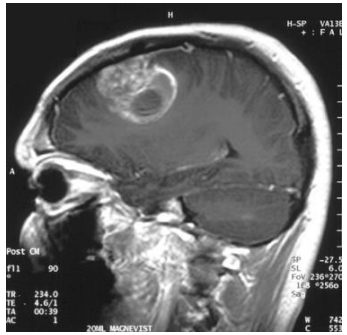
Medical Effects of *Cannabis*

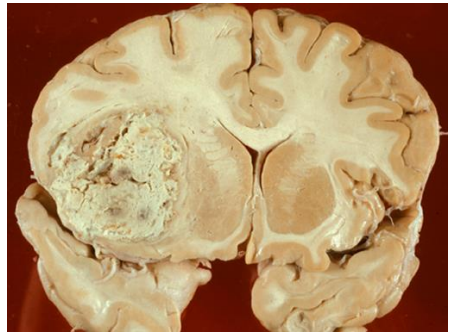
U.S. Govt. Reconfirms Anti-Cancer Effects…and Research Slowly Broadens

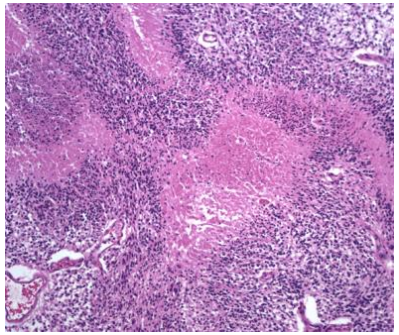
- In **1997**, a $2 million study conducted by the U.S. National Toxicology Program concluded:
  - **Rats and mice treated with THC over long periods of time had greater protection against malignant tumors than those left untreated.**
- In **2006**, a small pilot study *with human subjects* conducted 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.





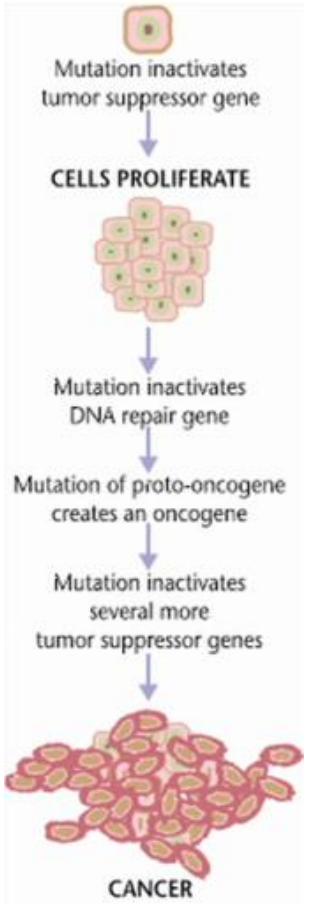


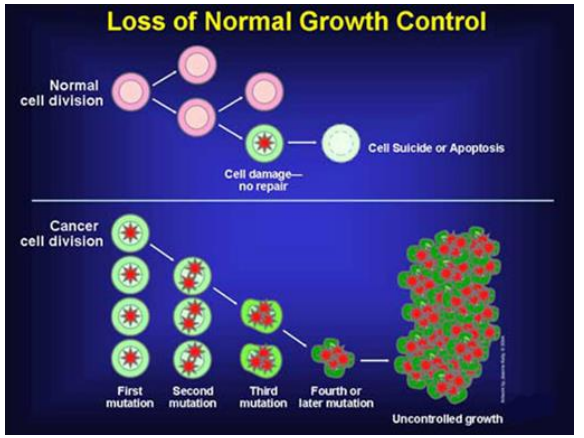
Medical Effects of *Cannabis*

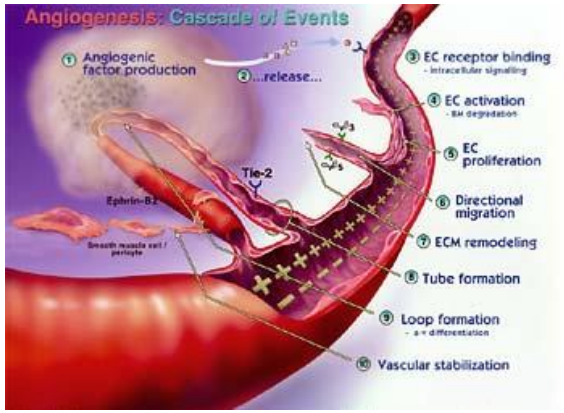
Numerous Studies Now Demonstrate the Anti-Cancer Effects of Cannabinoids

- 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.

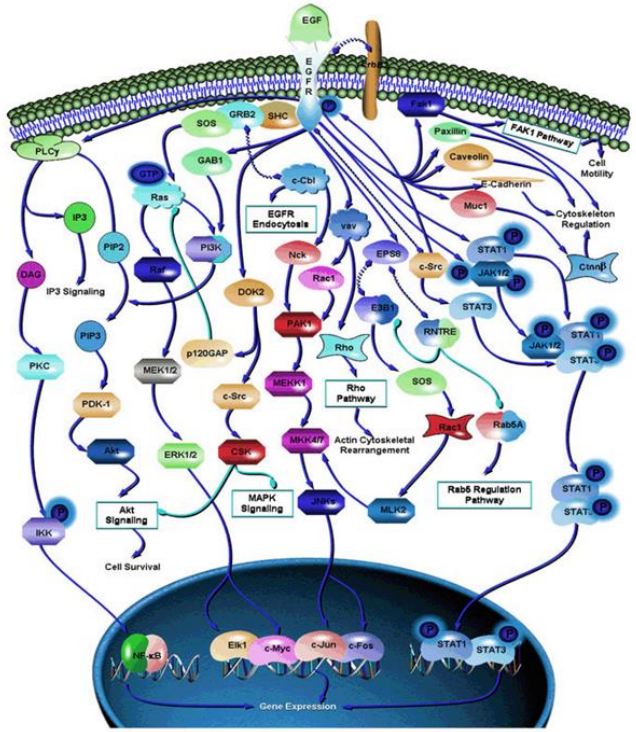






Medical Effects of *Cannabis*

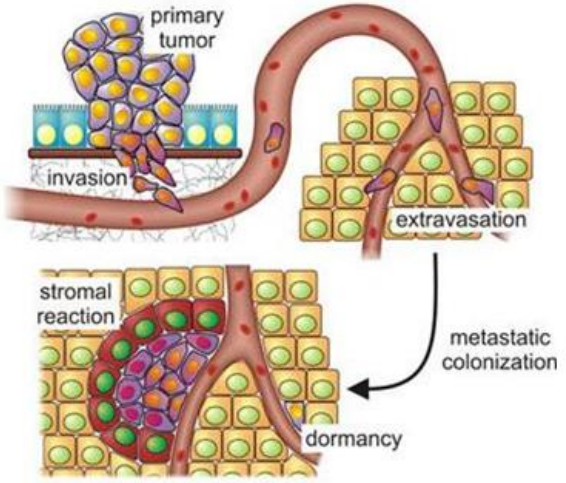
Review Article: Cannabinoids in the Treatment of Cancer

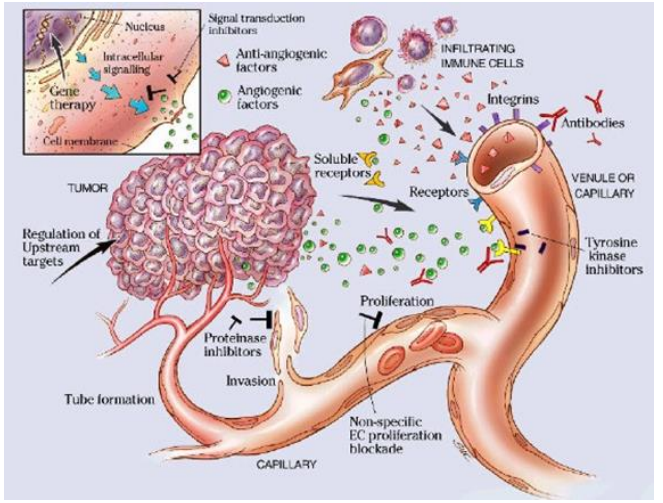


Alexander, et al. *Cancer Letters*. 2009.

Review of 51 studies:

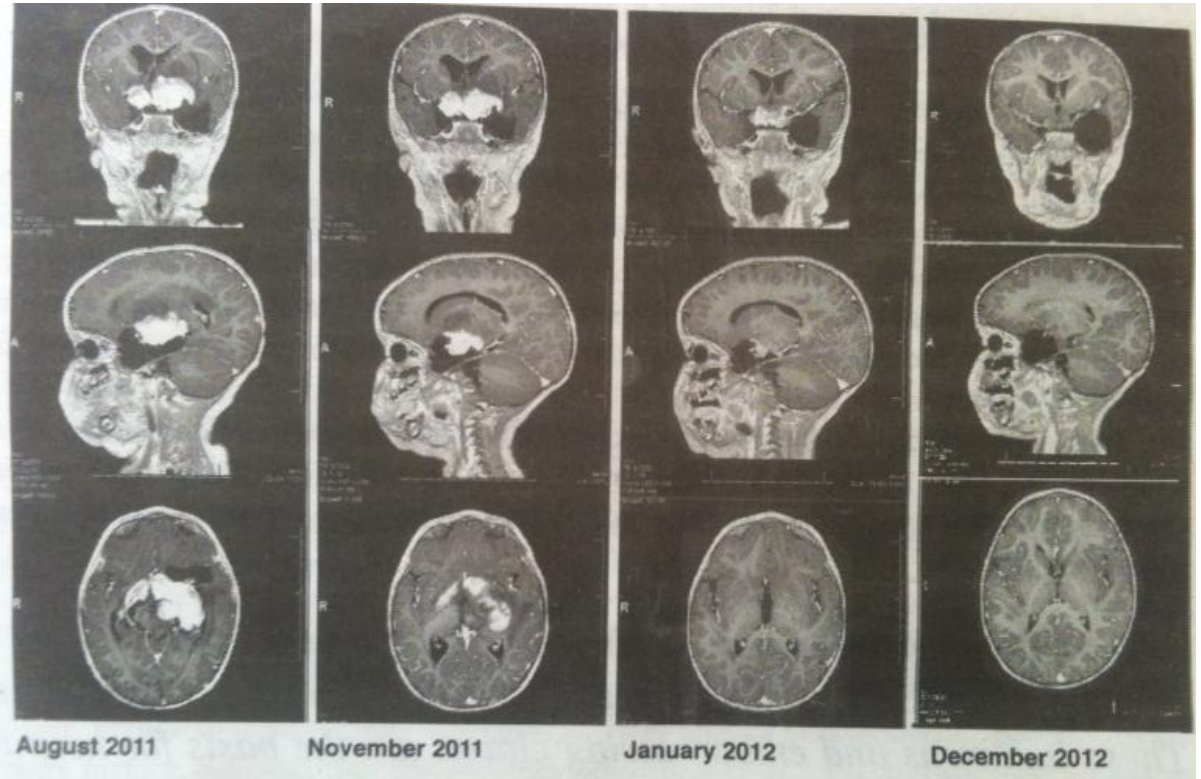
"…cannabinoids could be useful in the treatment of cancer due to their ability to regulate cellular signaling pathways critical for cell growth and survival."





Medical Effects of *Cannabis*

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.

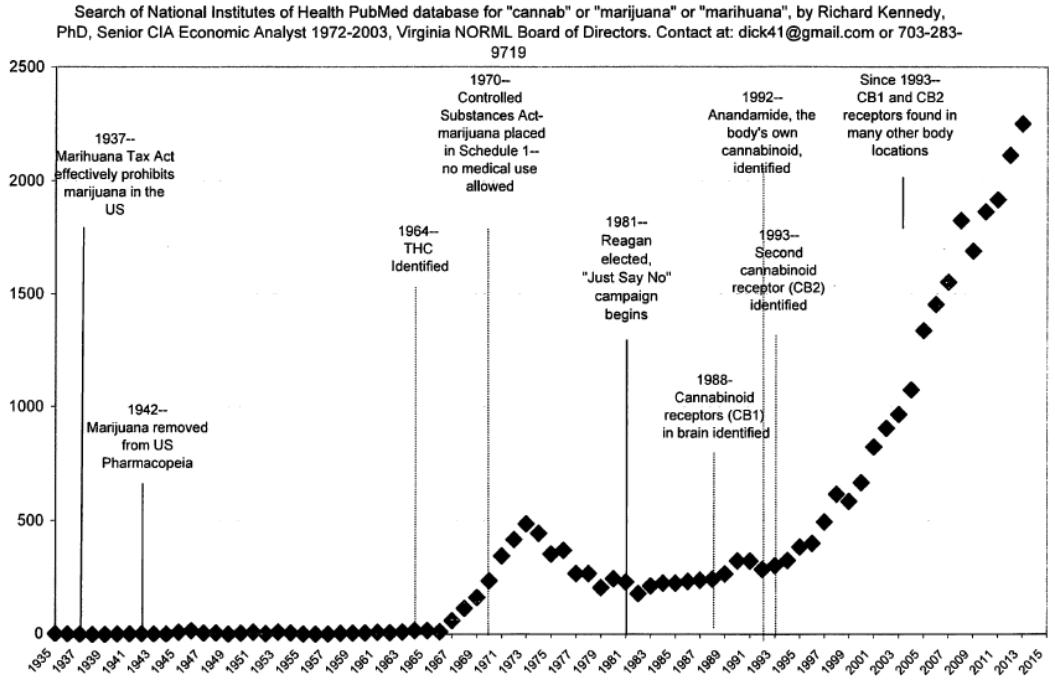
Source: *O'Shaughnessy's* and course attendance.

Research

Cannabis/Cannabinoid Research Explodes

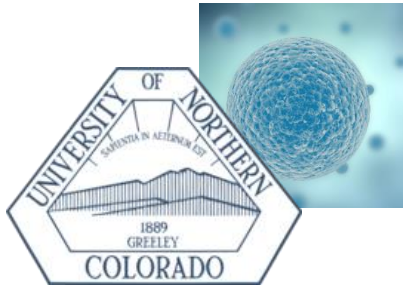
- **PubMed.gov: 37,000+ articles** published in the medical literature; **7,000+ articles on endocannabinoids.**
- **ClinicalTrials.gov: 241 trials** underway.
- **DEA** has authorized **National Institute on Drug Abuse (NIDA)**, the sole federally legal source of research marijuana in the U.S., to significantly 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 Center for Medicinal Cannabis Research University of California

cmcr.ucsd.edu



Cell-in-a-Box® + cannabinoids

Research

Anti-Cancer: Breast

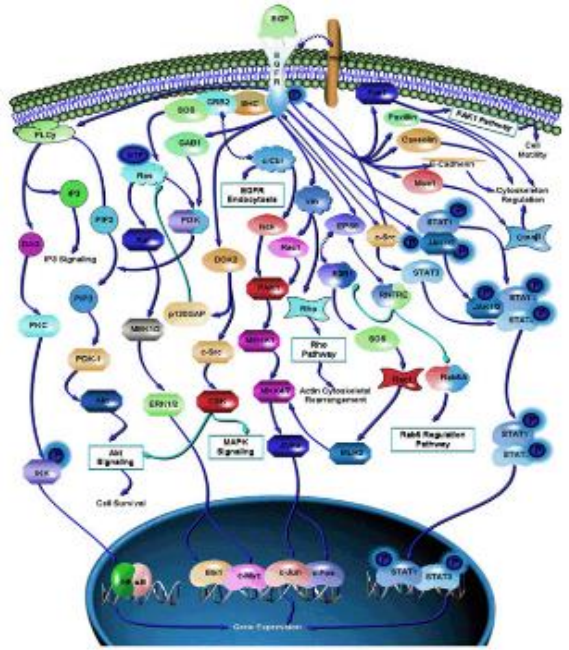
"Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis."

Treatment of mice with breast cancer with lung metastases with CBD showed significant reduction in the primary tumor mass as well as the size and number of lung metastases.

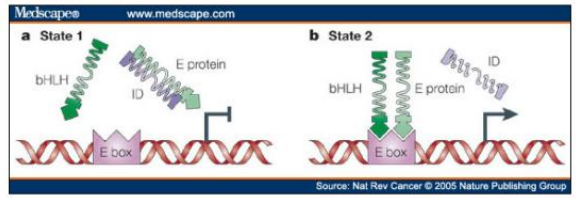
Scientists previously knew: CBD down-regulates Id-1 gene expression in aggressive human breast cancer cells (in culture).
Result → inhibition of proliferation and invasion of tumor cells

This study determined: CBD down-regulates Id-1 gene expression through modulation of ERK and ROS pathways

California Pacific Medical Center Research Institute, San Francisco.
McAllister SD, et al. *Breast Cancer Research and Treatment*. 2011; 29(1):37-47.



Id-1



- a protein (transcription factor inhibitor)
- regulates the metastatic potential of breast cancer

Research

Anti-Cancer: Brain

"Cannabidiol enhances the inhibitory effects of Δ9-THC on human glioblastoma cell proliferation and survival."

THC has been shown to be a broad-range cancer inhibitor in cell cultures and animal studies. The addition of CBD to THC may improve the overall effectiveness of THC in the treatment of glioblastoma (brain cancer) patients.

Specific Findings:

- THC and CBD inhibit the growth of multiple glioblastoma cell lines
- CBD enhances the inhibitory effects of THC on glioblastoma cell growth
- The combination treatment of THC and CBD leads to modulation of specific mitogen-activated protein kinases
- The combination treatment of THC and CBD inhibits cell cycle and induces apoptosis
- The inhibitory effects of the combination treatment are the result of CB2 receptor activation and production of ROS

Marcu, et al. *Molecular Cancer Therapeutics.* 2010;9(1):180-9.

Research

Anti-Cancer: Prostate

"Inhibition of human tumor prostate PC-3 cell growth by cannabinoids R(+)-Methandamide (MET) and JWH-015: Involvement of CB2."

The cannabinoid receptor CB2 was involved in the inhibition of prostate cancer cell growth in cell culture and mouse experimental models. Conclusion: CB2 agonists have potential in the therapeutic treatment of prostate cancer.

Specific Findings:

- MET (anandamide analog) and MET (synthetic CB2 agonist) exert anti-proliferative effects in PC-3 cells
- Downregulation of CB2 expression reversed the effects of JWH-015, confirming the involvement of CB2 in the pro-apoptotic effect of cannabinoids
- In vivo treatment with JWH-015 caused a significant reduction in tumor growth in mice

Olea-Herrero N, et al. *British Journal of Cancer*. 2009; 15;101(6):940-5.

Research

Anti-Cancer: Intestines

"Loss of Cannabinoid Receptor 1 Accelerates Intestinal Tumor Growth."

Colon cancer tumors in mice shrunk when injected with cannabinoids. In particular, the CB1 receptor (which preferentially binds THC) was found to slow cancer growth when activated.

Research Highlights:

- CB1 expression is lost in most colorectal cancers, allowing a cancer-promoting protein free to inhibit cell death
- CB1 expression can be restored with an existing drug, decitabine (demethylating agent)
- The researchers found that mice prone to developing intestinal tumors, that also have functioning CB1 receptors, develop smaller tumors when the receptors are stimulated
- DuBois: "Turning CB1 back on and then treating with a cannabinoid agonist could provide a new approach to colorectal cancer treatment or prevention."

Wang D, et al. *Cancer Research*. 2008; 68(15):6468-76.

Research

Anti-Cancer: Liver

"Overexpression of cannabinoid receptors CB1 and CB2 correlates with improved prognosis of patients with hepatocellular carcinoma."

Higher numbers of CB1 and CB2 receptors correlates with improved prognosis in patients with hepatocellular carcinoma (liver cancer). The authors conclude: "Our results suggest…possible beneficial effects of cannabinoids on prognosis of patients with HCC."

Research Highlights:

- Receptor expression was analyzed in tumor vs. matched nontumor tissue taken from human hepatocellular carcinoma (HCC) samples
- Disease-free survival was significantly better in HCC patients with high levels of CB1 and CB2 expression
- CB1 and CB2 have potential as prognostic indicators
- Liver cirrhosis patients who had higher numbers of these receptors also showed an improved prognosis.

Xu X, et al. *Cancer Genetics and Cytogenetics*. 2006; 171(1):31-38.

Research

Anti-Cancer: Pancreas

"Gemcitabine (GEM)/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism."

Cell Culture: GEM/cannabinoid combined treatments synergistically inhibited pancreatic adenocarcinoma cell growth.

Mouse Model: GEM/cannabinoids combo "strongly s growth of human pancreatic tumor cells xenografted in nude mice without apparent toxic effects."

Research Highlights:

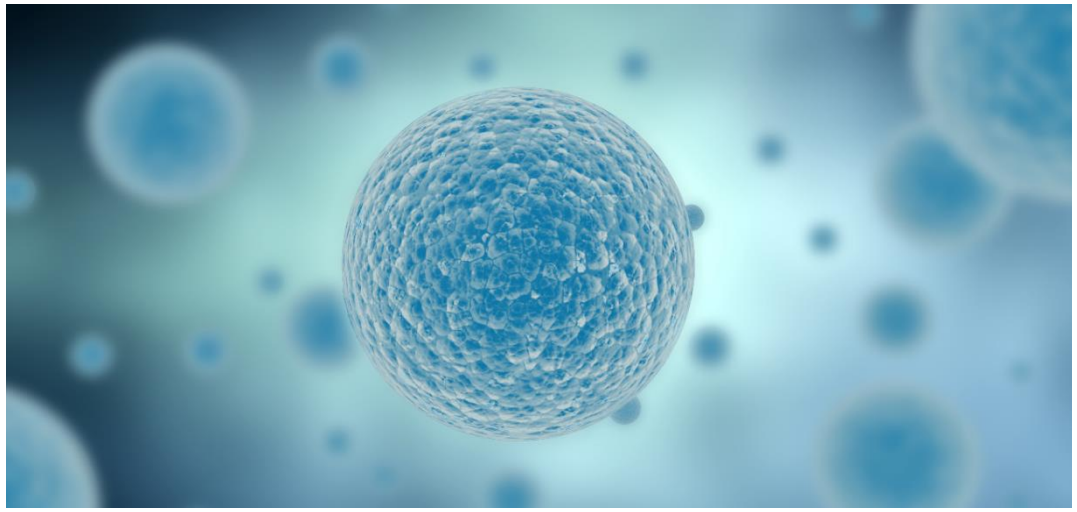
- ROS (Reactive Oxygen Species) have recently emerged as promising targets for anticancer drug discovery.
- GEM/cannabinoid combined treatments enhance intracellular ROS production.
- Cannabinoid-based therapy may activate cell death predominately in tumor cells.
- Other studies have also shown cannabinoids to have inhibitory activity for pancreatic cancer: Dando, 2013; Michalski, 2008; Carracedo, 2006.

Donadelli M, et al. *Cell Death and Disease*. 2011;2:e152-164.

Research

Cell-in-a-Box®

PHARMACYTE BIOTECH



PharmaCyte Biotech (PMCB) is a clinical stage biotech company developing targeted treatments for cancer and diabetes.

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

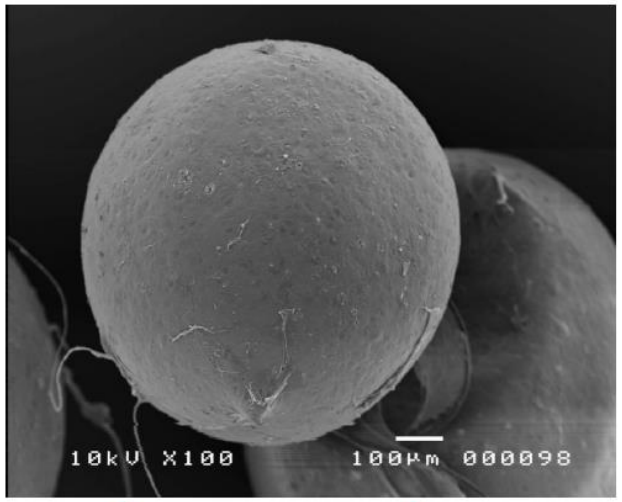
In addition to its other areas of research and product development, **PMCB** is currently developing treatments for cancer utilizing the constituents of *Cannabis* known as cannabinoids.

PharmaCyteBiotech.com
OTCQB: PMCB

Research

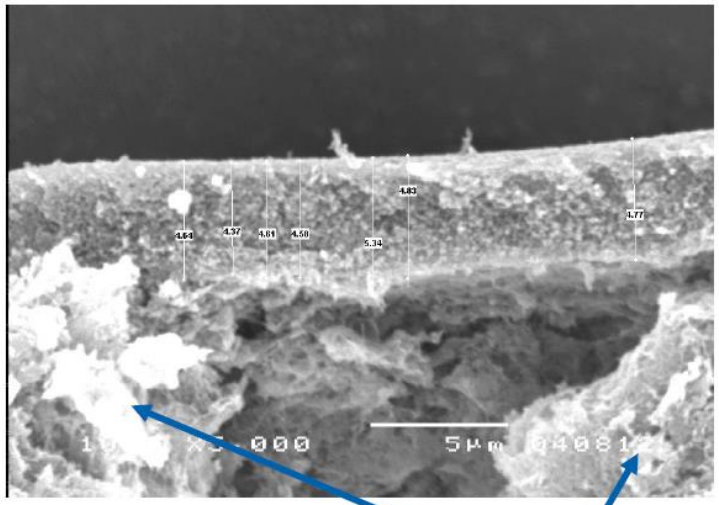
PHARMACYTE BIOTECH

Cell-in-a-Box® Capsules: Microscopy



0.7 mm

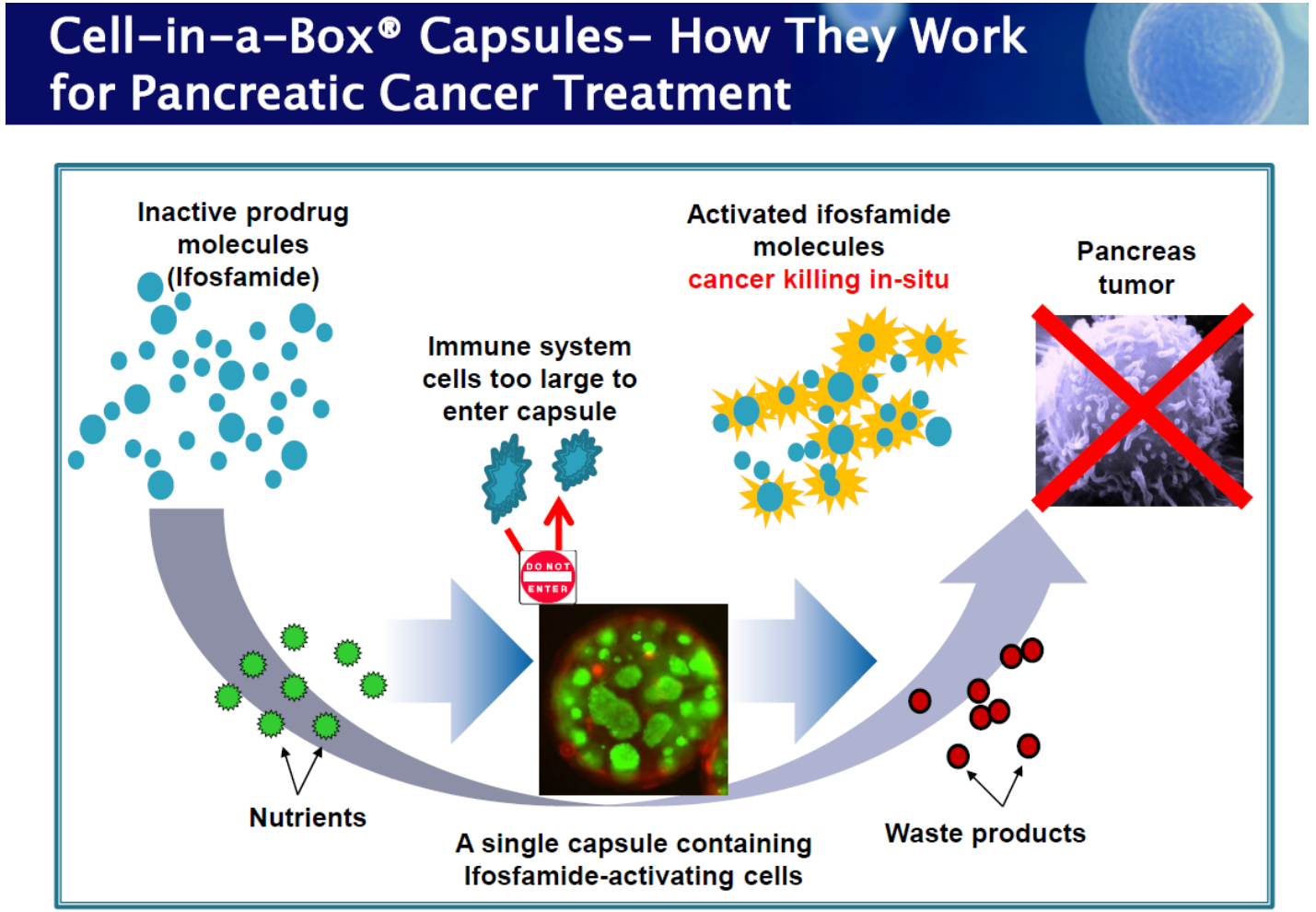
View of a Single Capsule



Capsule Cross Section Showing Cancer Prodrug-activating Cells

Research

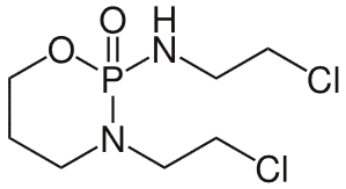
PHARMACYTE BIOTECH



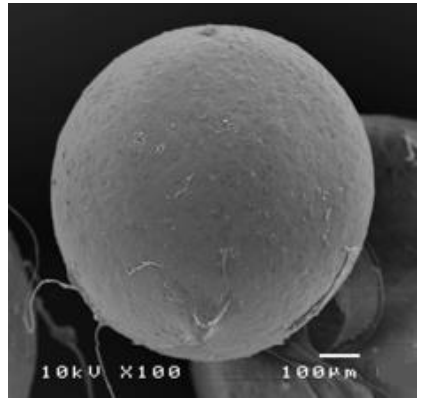
Research

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

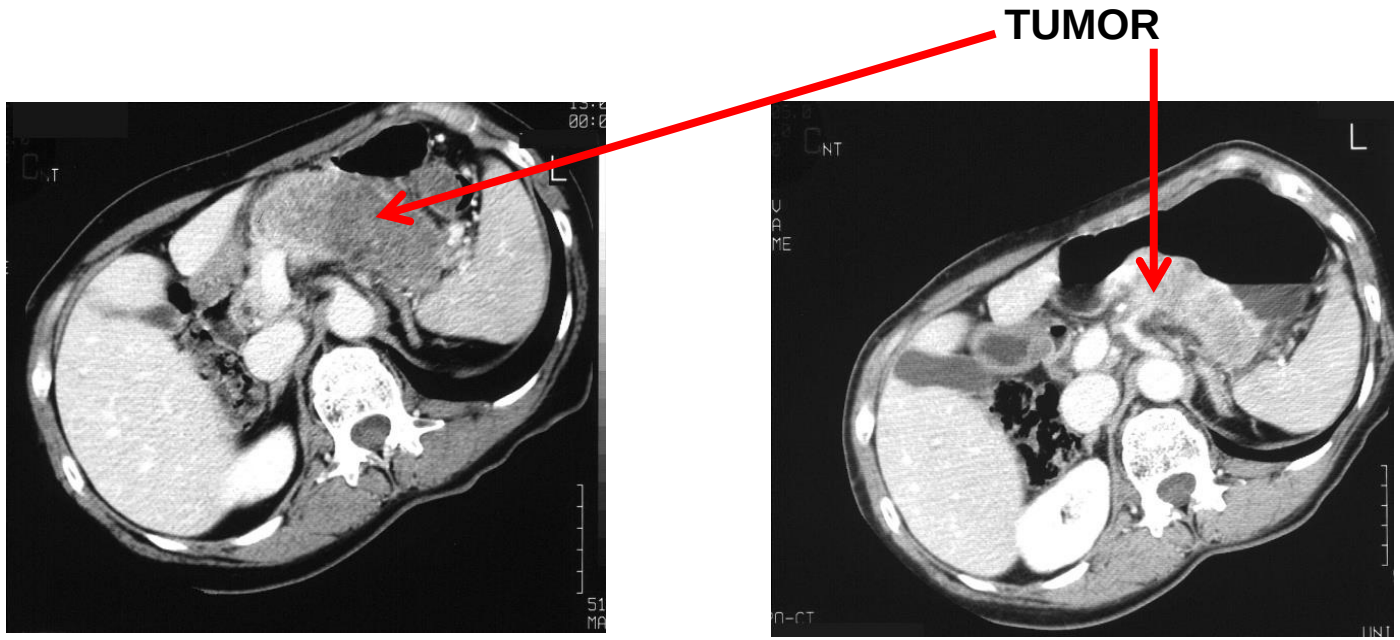


diam. = 0.7mm

Research

Phase 1/2 Pancreatic Cancer Trial

CT Scans of Pancreatic Cancer



Before treatment

20 weeks post-treatment

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.

Research

PHARMACYTE BIOTECH

Pipeline

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

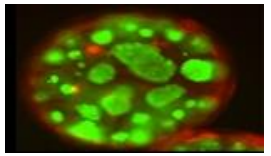
Diabetes:

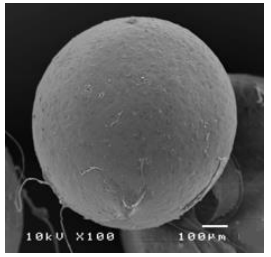
Encapsulated live cells produce, store and secrete insulin on demand

Research

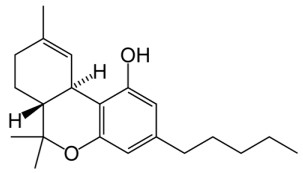
Objective: Safe and Effective Cannabinoid-Based Treatments

- 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 biosustaianble.
- Pre-clinical investigations are underway at the **University of Northern Colorado** under a **Schedule I license** granted by the **DEA**.

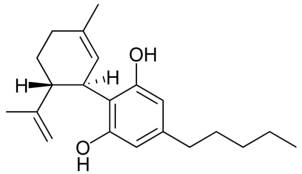




UNIVERSITY OF NORTHERN COLORADO
1889 GREELEY



THC

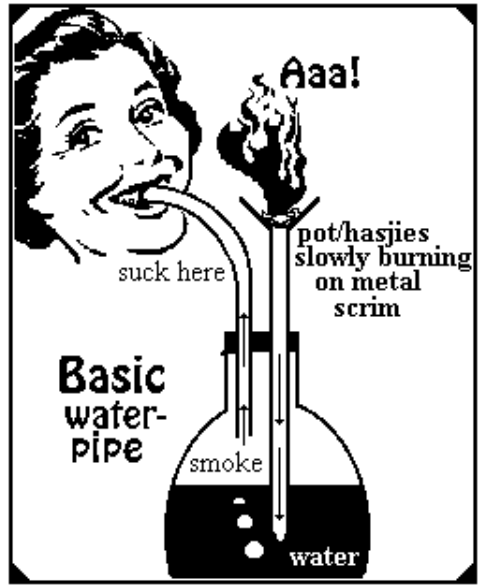


CBD

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.

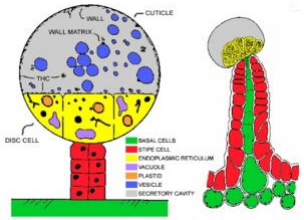


Cannabinoid Delivery Systems

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

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

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

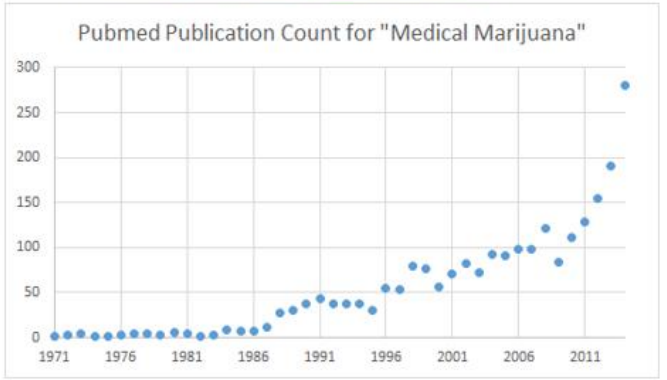
“Rick Simpson Oil”

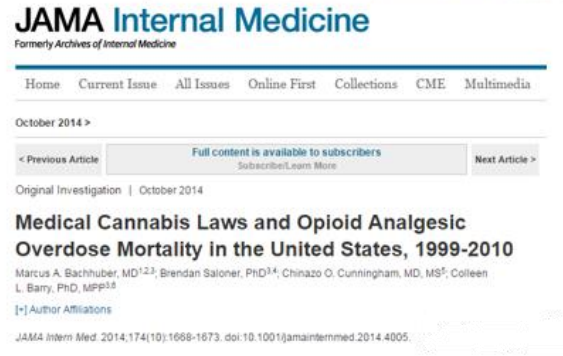
- Rick Simpson maintains that he used an alcohol (ethanol) extract of cannabinoids to cure his prostate cancer.
- The end-product of using the century’s-old technique of **herbal alcohol extraction** has become known as “Rick Simpson Oil.”
- Such concentrates contain **75-80%+ cannabinoids**.
- “Rick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

Practitioners: Integrating Medical *Cannabis*

Medical Marijuana in the Spotlight

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





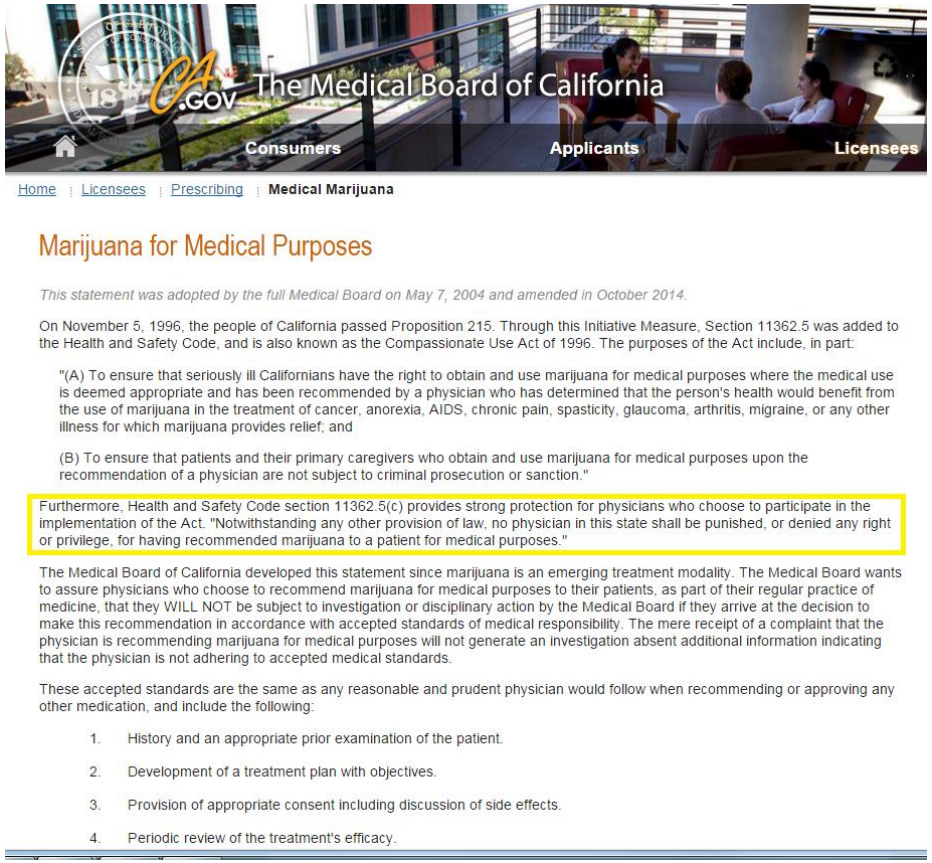
Practitioners: Integrating Medical *Cannabis*

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



Practitioners: Integrating Medical *Cannabis*

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."

MBOC

The Medical Board of California

Consumers | Applicants | Licensees

Home | Licensees | Prescribing | **Medical Marijuana**

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.
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

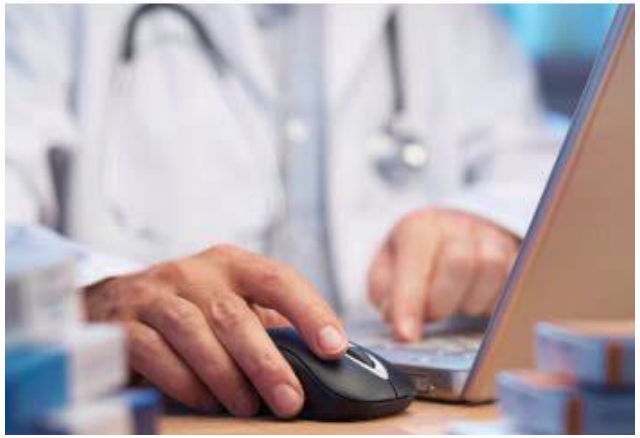
Practitioners: Integrating Medical *Cannabis*

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.

Practitioners: Integrating Medical *Cannabis*

Green Medical Solutions™



Practitioners: Integrating Medical *Cannabis*

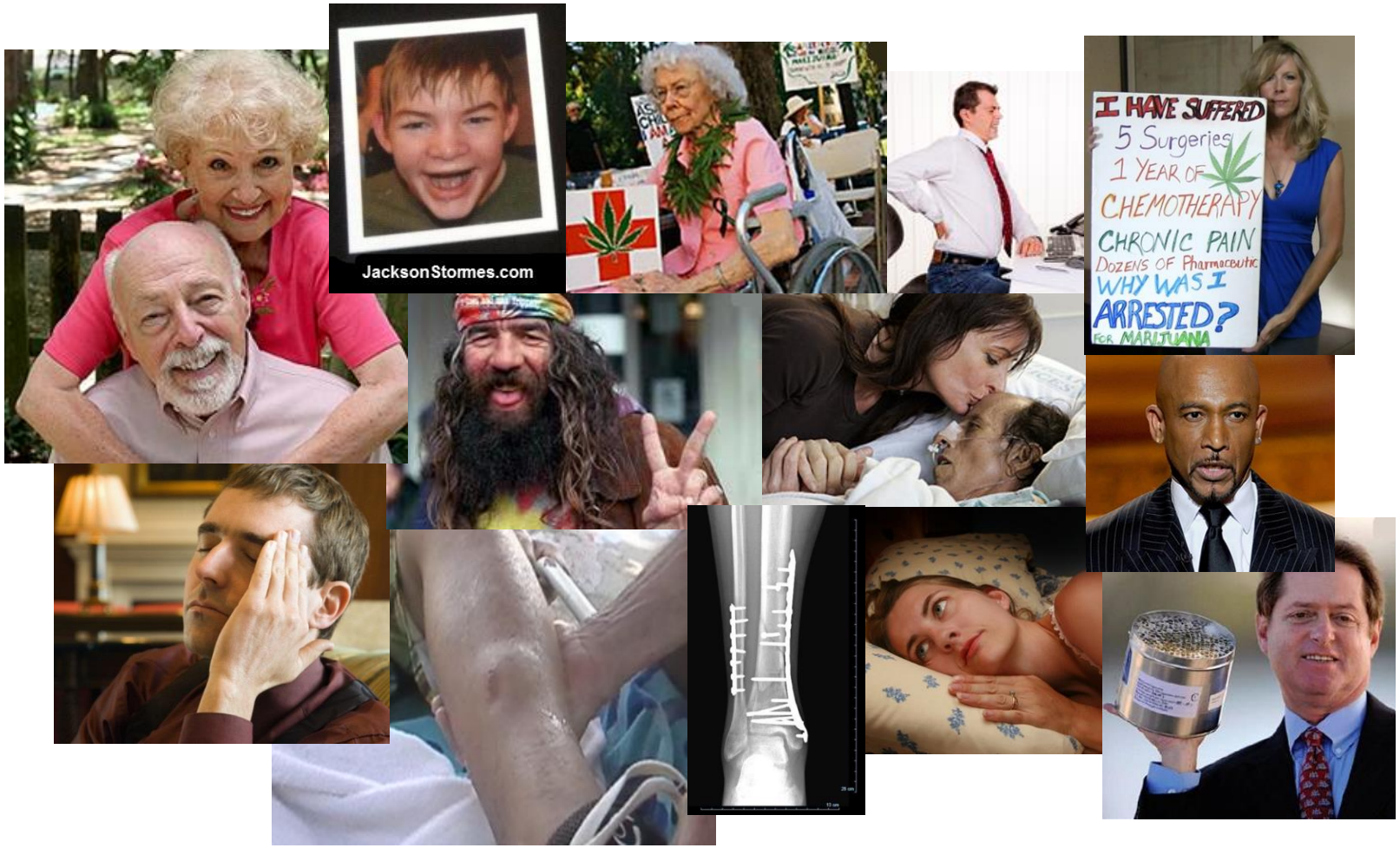
Benefits of Integrating Medical *Cannabis* into Your Practice

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**

Green Medical Solutions™

Parting Thoughts…



Marijuana should be regulated, not scheduled.

<u>Medical</u> marijuana should not be taxed.

Resources

Centric Wellness

- www.CentricWellness.com

Medical Marijuana Education Center

- www.MMJ-U.com

CBD (cannabidiol) Information

- www.ProjectCBD.org

Clinical Trials (a service of NIH)

- www.ClinicalTrials.gov

National Cancer Institute (at the NIH)

- www.Cancer.gov (search: “cannabis, cannabinoids”)

U.S. National Library of Medicine/National Institutes of Health

- www.PubMed.gov

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Center for Medicinal Cannabis Research (UCSD) website: **http://cmcr.ucsd.edu/**

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