

# Cannabis & Cancer: Practical Steps for Symptom Relief and Anti-Cancer Effects

Dustin Sulak, D.O.

Best Answer for Cancer

May 18<sup>th</sup>, 2018

# Conflicts and Confluences of Interest

- Integr8 Health, owner – medical practices in Falmouth and Manchester, Maine.
- Healer, LLC, equity owner – patient education, industry consulting, extraction and formulation.
- Tested Labs, former equity owner – cannabis analytical laboratory.
- Curio Wellness, paid consultant – cannabis producer in Maryland.
- CliniCann, paid scientific advisory board member – Latin American cannabis specialty clinics.
- Cannabis Expertise, paid course director – medical cannabis CME programs.
- Society of Cannabis Clinicians, unpaid board of directors member – professional society.

# Overview

- Introduction to the endocannabinoid system
- Cannabinoids
  - treat cancer symptoms
  - ameliorate and prevent cancer treatment side effects
  - have antineoplastic properties
  - enhance efficacy of conventional cancer treatments
  - provide palliation in end of life care
- Safety concerns, drug interactions, adverse effects
- Dosing and delivery strategies

# Health Conditions Influenced By Cannabinoids

ADD/ADHD

ALS

Alzheimer's

Anorexia

Anxiety

Asthma

Ataxia

Bipolar

Cachexia

Cancer

Chronic fatigue

Chronic pain

Cramps

Crohn's

Diabetes

Depression

Epilepsy

Fever

Fibromyalgia

Glaucoma

Hepatitis

HIV/AIDS

Incontinence

Insomnia

Migraine

MRSA

Multiple Sclerosis

Nausea

Neuralgia

Neuropathy

Parkinson's

PMS

PTSD

Rheumatoid Arthritis

Seizure disorders

Sickle cell anemia

Spasms

Spinal injury

Stroke

Tourette's

Vomiting

Why does one herb help so many  
different conditions?

The Endocannabinoid System

Endocannabinoid synthesis is an adaptive response to cellular stress, aimed at re-establishing cellular homeostasis.

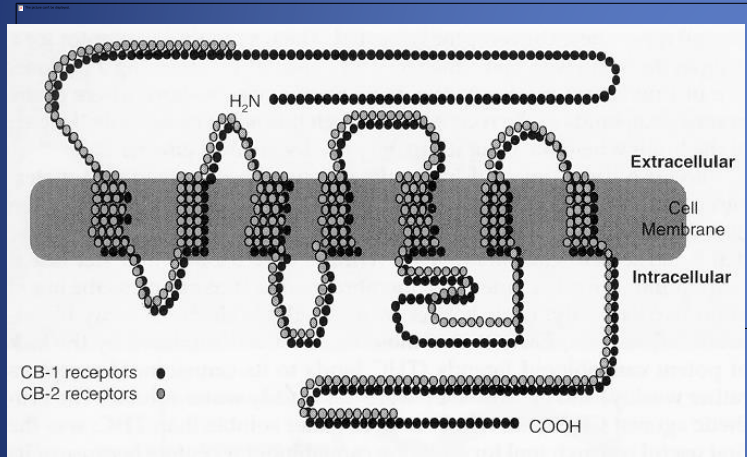
Pubmed search results for “endocannabinoid”

1993: 10 citations

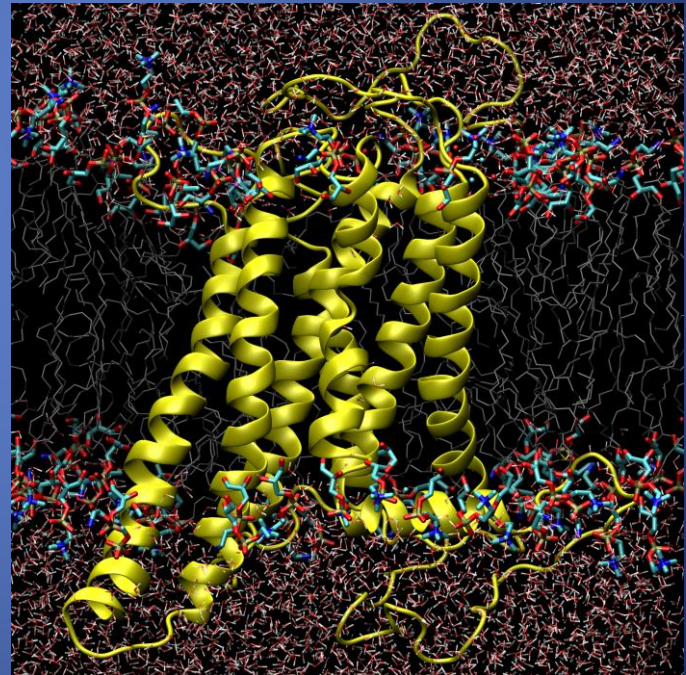
2016: 7,899 citations

# The Cannabinoid Receptors: CB1 and CB2

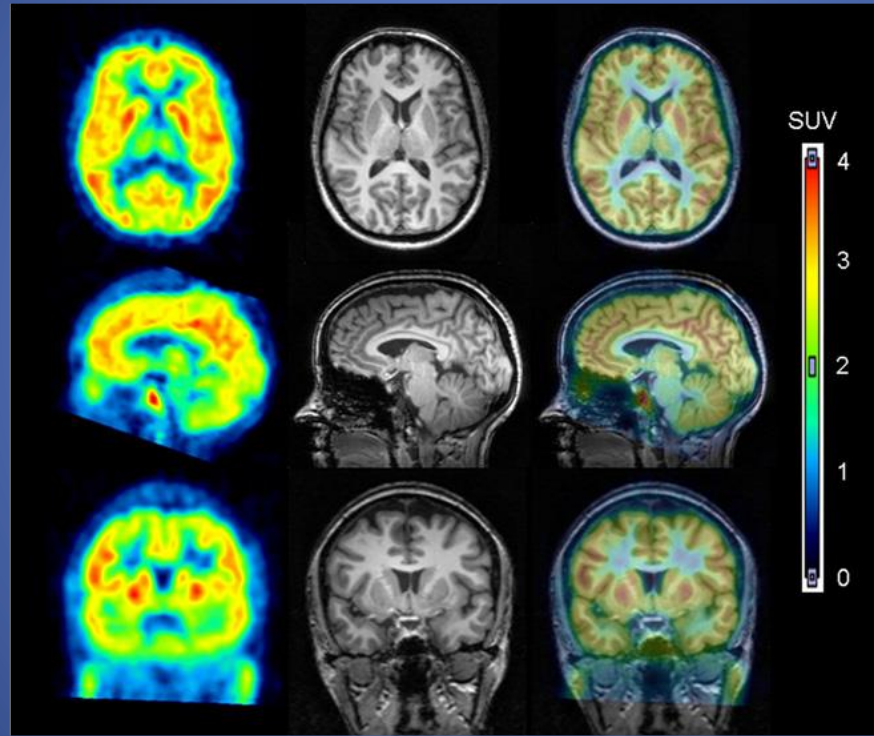
secondary structure



tertiary structure



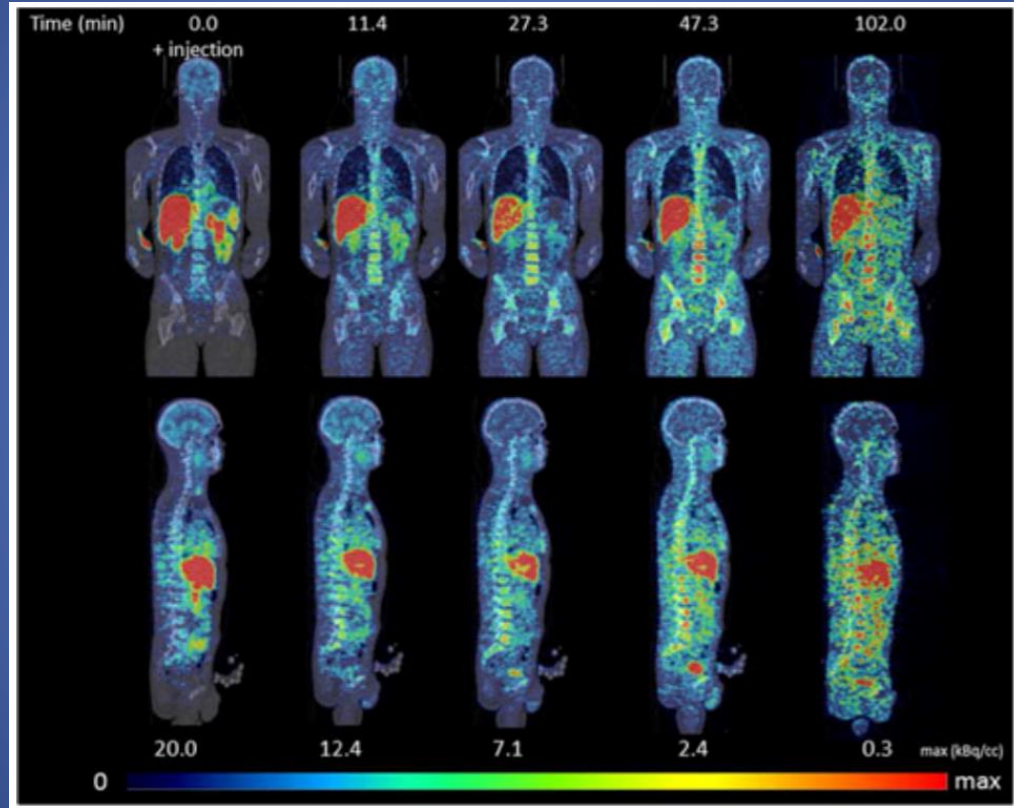
# CB1 Receptor Distribution in Human Brain



(Terry et al. 2010)

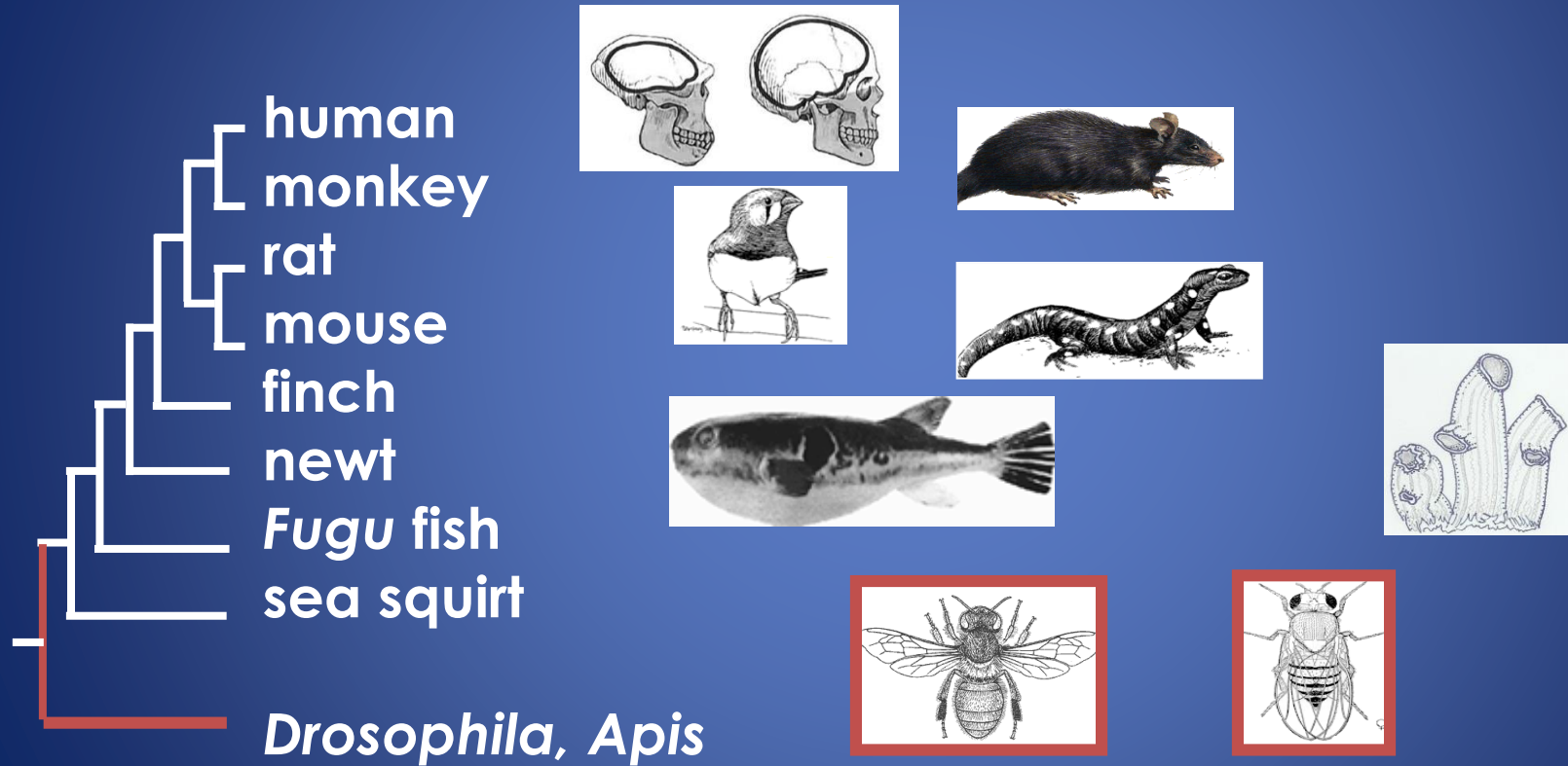


# CB2 Receptor Distribution

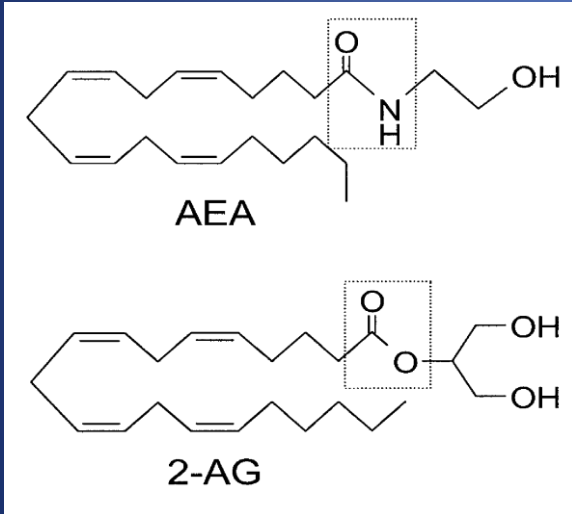


(Ahmad, 2013)

# CB Receptors Evolved 600 Million Years Ago



# Endogenous Cannabinoid Ligands: The Endocannabinoids



## Anandamide (AEA)

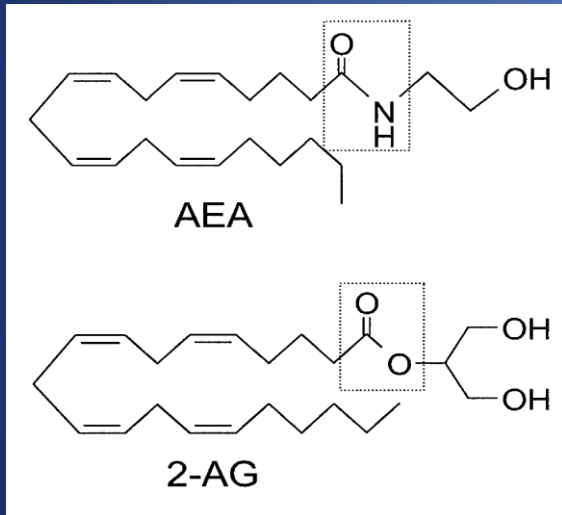
*Devane, Mechoulam et al., 1992*

## 2-arachidonoylglycerol (2-AG)

*Mechoulam et al., 1995*

*Sugiura et al., 1995*

# Endogenous Cannabinoid Ligands: The Endocannabinoids



Anandamide (AEA) and 2-arachidonoylglycerol (2-AG):

- Retrograde messengers in nervous system.
- Autocrine or paracrine mediators elsewhere.
- Synthesized “on demand” from cell membrane precursors (arachidonic acid derivatives) and immediately released.
- Degraded by enzymatic hydrolysis
  - AEA → fatty acid amide hydrolase (FAAH)
  - 2-AG → monoacylglycerol lipase (MAGL)

(McPartland, 2008)

# Cannabis and Cancer

# Symptom Management

Cannabis can be a safe, effective treatment for cancer patients with

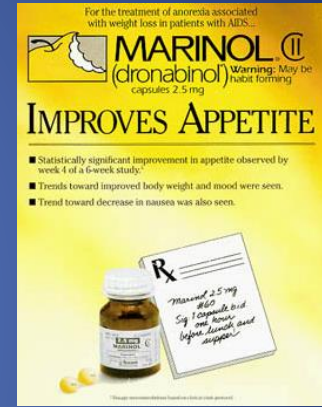
- Nausea and vomiting (Machado Rocha, et al. 2008)
- Chronic pain (Portenoy et al., 2012; reviewed in Tateo, 2016)
- Insomnia (Russo et al., 2007)

Cannabinoids and opioids work synergistically (Cichewicz, 2004)

- Potentiation of analgesia
- Widening of therapeutic index
- Opioid-sparing effects
- Maintenance of efficacy and prevention of tolerance/dose escalation

# FDA-approved Cannabinoids

- Dronabinol, a synthetic THC, was approved as schedule II drug in 1986 and was moved to schedule III in 1999.
- Nabilone, a THC analog, was approved by the FDA in 1985 but not marketed in the US until 2006.
- Both are indicated for chemotherapy-induced nausea/vomiting and as an appetite stimulant for AIDS patients.



# Cannabinoids & Cancer

- Cannabis can help patients tolerate conventional cancer treatment, such as chemotherapy and radiation (reviewed in Bowles et al, 2011)
- Low likelihood of drug interaction. (Stout, 2014)
- For patients with terminal cancer, cannabis offers numerous benefits in palliative care at the end of life. (Green, 2010)



# Cannabinoids Prevent and Treat Chemotherapy-Induced Neuropathy

BJP

British Journal of  
Pharmacology



BRITISH  
PHARMACOLOGICAL  
SOCIETY

BJP British Journal  
of Pharmacology

Activation of cannabinoid  
nociception evoked by

E J Rahn<sup>1</sup>, A Makriyannis<sup>2</sup> and  
Hohmann<sup>1,\*</sup>

Article first published online: 2012

DOI: 10.1038/sj.bjp.0707333

2007 British Pharmacological Society

RESEARCH PAPER

Cannabidiol inhibits  
receptors without  
efficacy

Sara Jane Ward<sup>1,\*</sup>,  
Rumi Kawamura<sup>2</sup>,  
Harshini Neelakantam

Article first published

DOI: 10.1111/bph.124

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The Journal of Neuroscience, May 16, 2012 • 32(20):7091–7101 • 7091

Neurobiology of Disease

## Cannabinoid Type-1 Receptor Reduces Pain and Neurotoxicity Produced by Chemotherapy

Iryna A. Khasabova,<sup>1</sup> Sergey Khasabov,<sup>1</sup> Justin Paz,<sup>3</sup> Catherine Harding-Rose,<sup>1</sup> Donald A. Simone,<sup>1</sup>  
and Virginia S. Seybold<sup>2</sup>

Departments of <sup>1</sup>Diagnostic and Biological Sciences and <sup>2</sup>Neuroscience, University of Minnesota, Minneapolis, Minnesota 55455, and <sup>3</sup>College of Biological Sciences, University of Minnesota, St. Paul, Minnesota 55108

# Neuropathic Pain: Clinical Trials

- HIV neuropathy, smoked cannabis, 3.6% THC: 34% reduction in daily pain vs. 17% in placebo group (Abrams *et al.* 2007)
- HIV neuropathy, smoked cannabis, 8% THC: 30% pain relief (Ellis *et al.* 2009).
- MS, Cannador extract: decreased pain, *no* beneficial effect on spasticity (Zajicek *et al.* 2003)
- Mostly MS or spinal cord injury, Sativex: decreased pain and muscle spasm (Wade *et al.* 2003)

# Neuropathic Pain: Clinical Trials

- Mostly MS or spinal cord injury, Sativex: decreased pain, improved sleep (Notcutt *et al.* 2004)
- MS, oral THC 10 mg: decreased pain (Svendsen *et al.* 2004)
- MS, Sativex: decreased pain (Rog *et al.* 2005)
- Brachial plexus avulsion, Sativex: decreased pain, improved sleep (Berman *et al.* 2004)

# Antineoplastic Effects - Preclinical

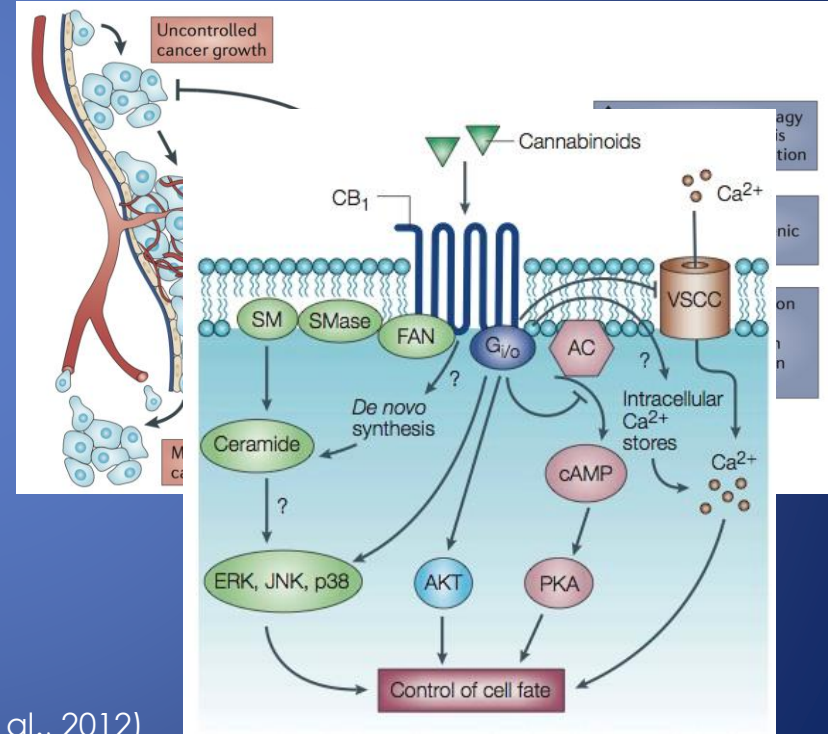
Cannabinoids inhibit tumor growth in multiple cell lines:

- Biliary Tract Cancer
- Breast Carcinoma
- Cervical Carcinoma
- Colorectal Carcinoma
- Gastric Adenocarcinoma
- Glioma and other CNS tumors
- Hepatocellular Carcinoma
- Leukemia
- Lung Carcinoma
- Lymphoma
- Melanoma
- Oral Cancer
- Pancreatic Adenocarcinoma
- Prostate Carcinoma
- Skin Carcinoma
- Thyroid Epithelioma
- Uterine Carcinoma

(Reviewed in Landin et al., 2016)

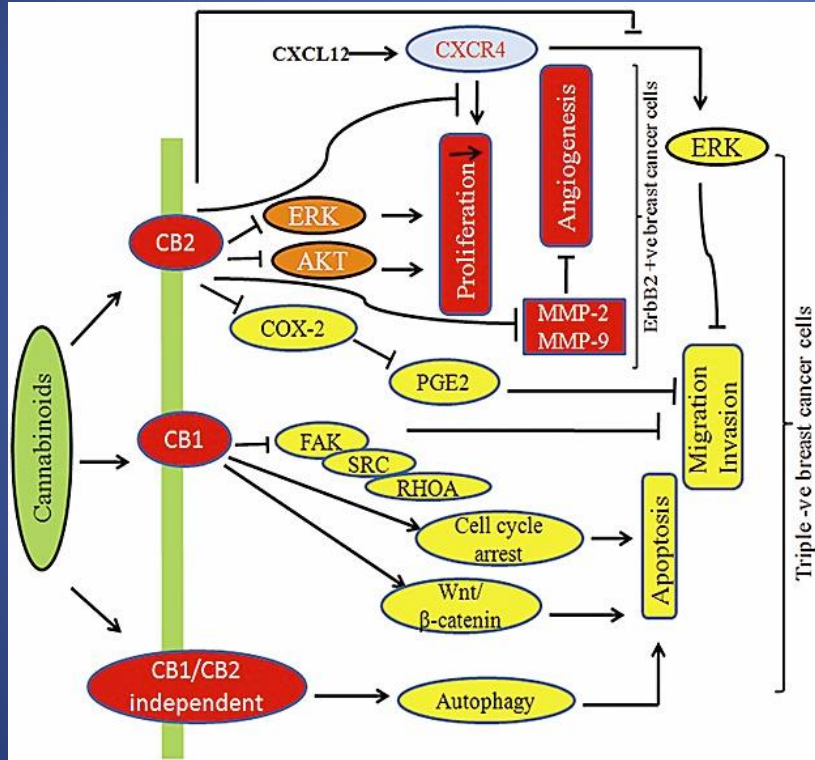
# Antineoplastic Effects – Multiple Mechanisms

- Induce apoptosis via a CB1-mediated ceramide-caspase pathway.
- Multiple non-receptor dependent MOAs: ↑apoptosis and autophagy
- Suppress tumor angiogenesis
- Inhibit cancer adhesion and migration
- Selective antitumor compounds that kill cancer cells without injuring healthy cells



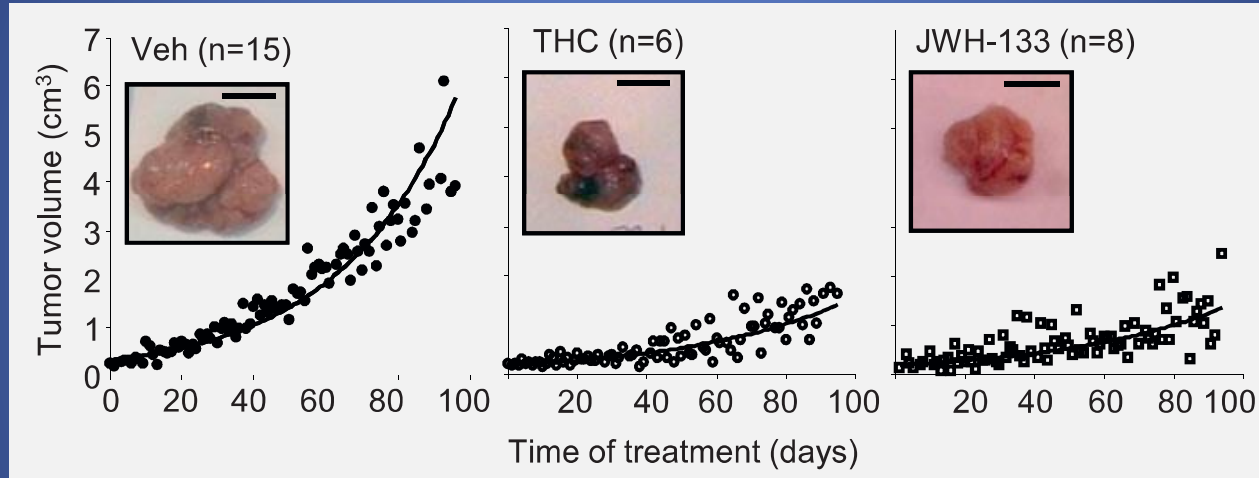
(Guzmán, 2003; Bifulco, 2006; Sarfaraz, 2008, Velasco et al., 2012)

# Breast Cancer: Multiple MOAs



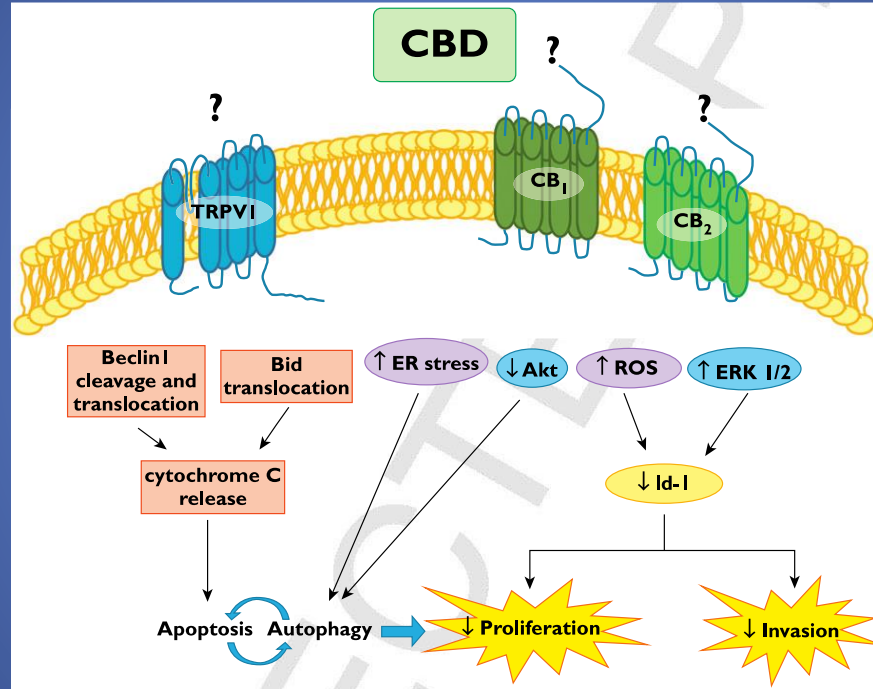
Chakravarti et al., 2014

# Breast Cancer Xenografts



Caffarel, María M., et al. "Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition." *Mol Cancer* 9.1 (2010): 196.

# Breast Cancer: CBD MOAs



Massi et al, 2012

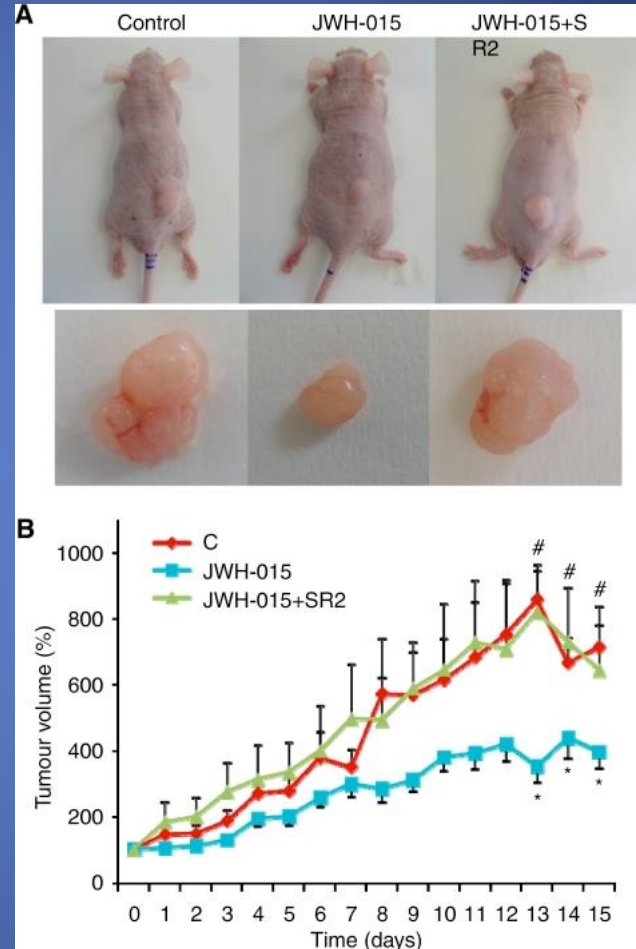


# CBD Prevents Chemotherapy-Induced Neuropathy

- Paclitaxel dosage is limited by development of peripheral neuropathy
- Adding CBD (5mg/kg and 10mg/kg) to mice treated with paclitaxel completely prevented the development cold and mechanical allodynia.
- No latent neuropathy emerged after the cessation of CBD treatment. (Ward et al, 2011)

# Prostate Cancer Xenografts

Olea-Herrero, N., et al. "Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: Involvement of CB2." *British journal of cancer* 101.6 (2009): 940-950.



# Glioblastoma Multiforme Xenografts

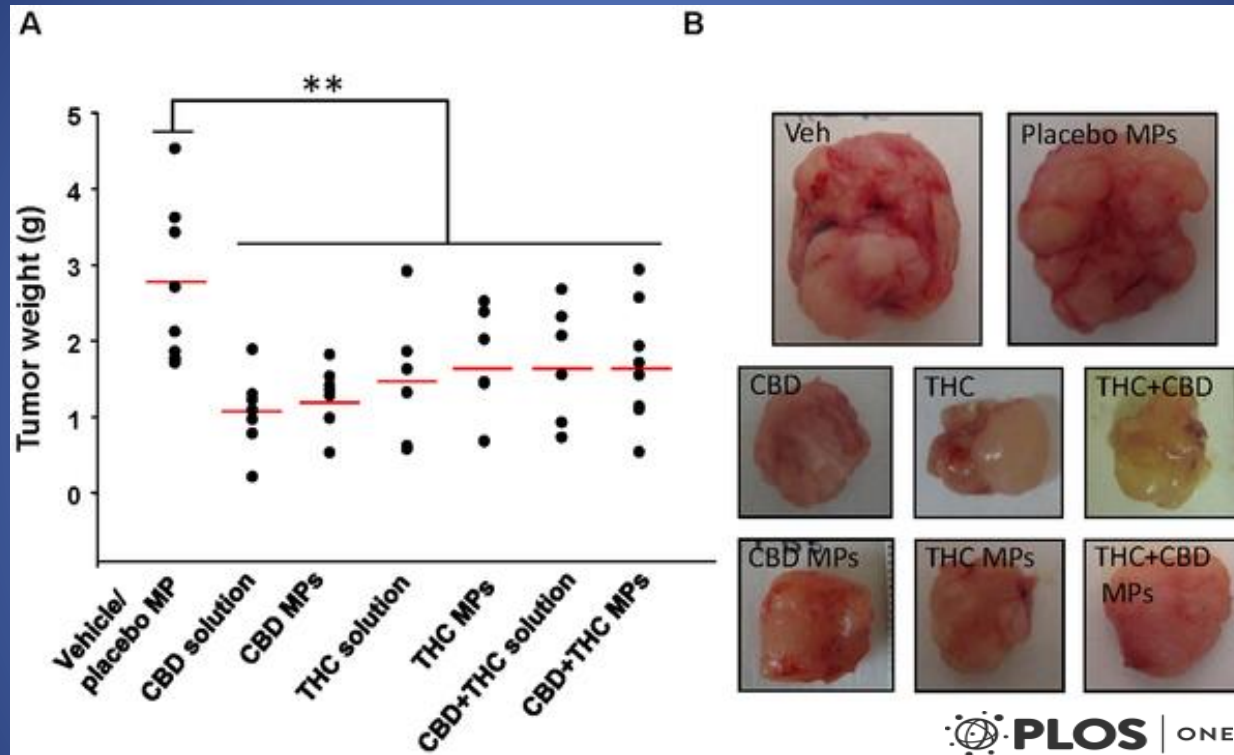


Figure 3. Cannabinoid-loaded microparticles reduce the weight of U87MG cell-derived tumour xenografts.

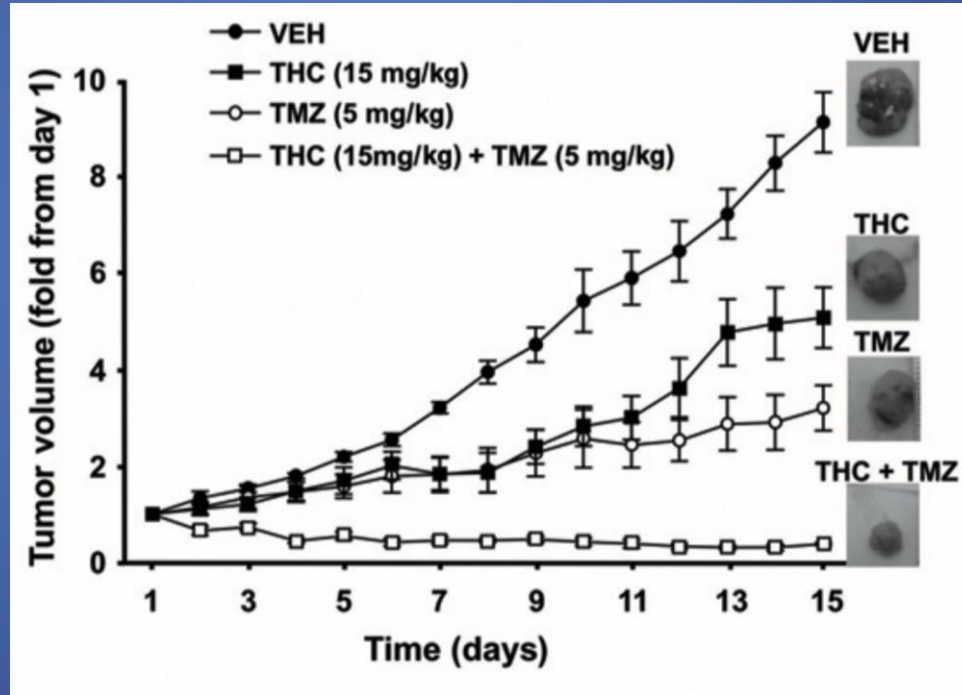
Hernán Pérez de la Ossa D, Lorente M, Gil-Alegre ME, Torres S, et al. (2013) Local Delivery of Cannabinoid-Loaded Microparticles Inhibits Tumor Growth in a Murine Xenograft Model of Glioblastoma Multiforme. PLoS ONE 8(1): e54795. doi:10.1371/journal.pone.0054795

# Adjunct to Standard Care?

- Cannabinoids can potentially enhance the effectiveness of standard cancer treatments. (Torres, 2011; Scott et al., 2014)
- Cannabinoids possess synergistic anti-cancer properties - a combination of the plant's constituents is often superior to isolated compounds. (Marcu et al, 2010)

# Glioma Xenografts – Synergy with Chemotherapy

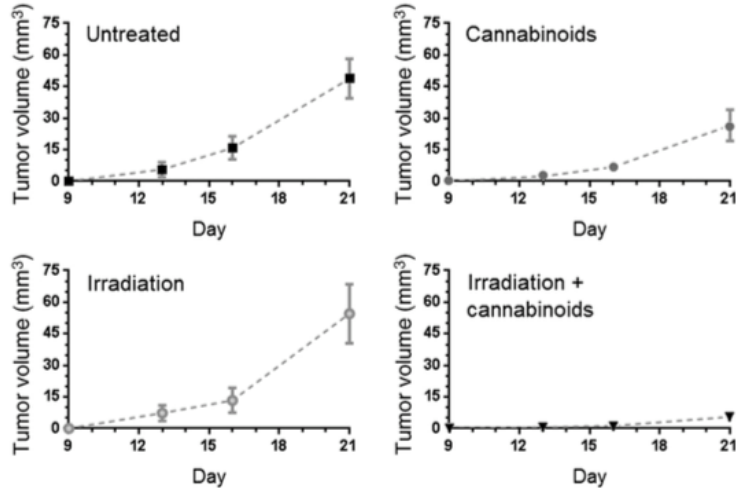
Torres et al., 2011



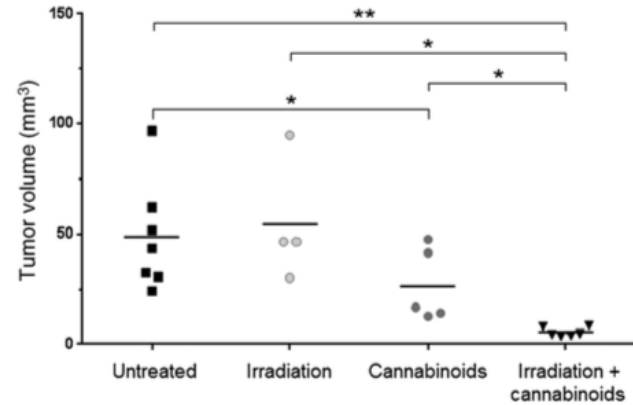
## The Combination of Cannabidiol and $\Delta^9$ -Tetrahydrocannabinol Enhances the Anticancer Effects of Radiation in an Orthotopic Murine Glioma Model

Katherine A. Scott, Angus G. Dalgleish, and Wai M. Liu

**B**



**C**



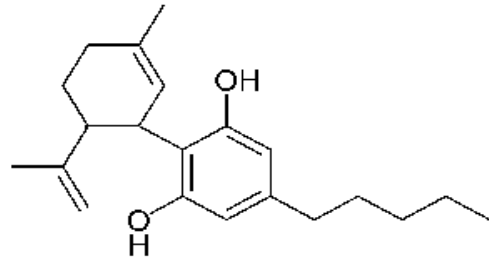
\*P < 0.05 \*\*P < 0.01

# The Plant *Cannabis sativa*

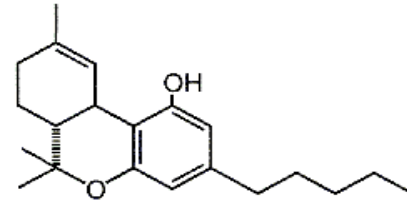
- Herb (female flower): long history of medicinal and spiritual uses
  - Sinsemilla = without Seeds
  - More oils, more potent
- Hemp = same species
  - Fiber (stalk) – textiles, fiberboard, paper
  - Hurd – concrete
  - Seed – high quality food, oil
  - Recently: hemp-derived non-THC cannabinoid products



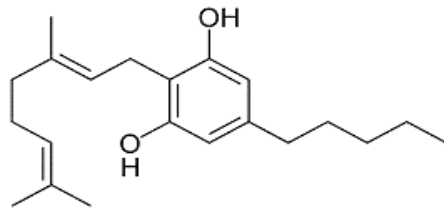
# Phytocannabinoids



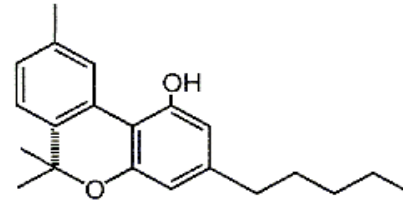
cannabidiol (CBD)



Δ-9-tetrahydrocannabinol (THC)



cannabigerol (CBG)



cannabinol (CBN)



# Other Active Phytochemicals

- 100+ cannabinoids including THC, CBN, CBD, CBC, CBG, THCV and other minor cannabinoids.
- Terpenoids and Flavonoids also have therapeutic properties.
- Acidic (raw) cannabinoids have different properties and mechanisms of action.
- Antioxidant and antimicrobial properties

# $\Delta^9$ -THC Mechanism of Action in the Endocannabinoid System

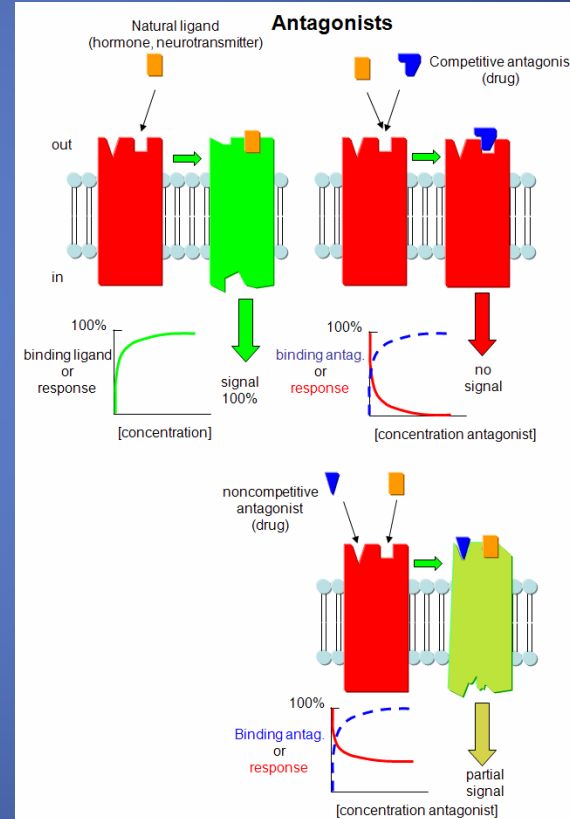
- THC mimics AEA and 2-AG by acting as a partial agonist at CB1 and CB2.
- Antagonism more likely at CB2, and in CB1 when ECS is down-regulated.

(Pertwee, 2008)

# CBD Mechanism of Action

- Very low affinity for CB1 and CB2 receptors
- Antagonizes CB1 & CB2 agonists
- Allosteric modulation of CB1
- Non-competitive inverse agonist

(Zhornitsky & Potvin, 2012; Laprairie et al. 2015; Morales et al., 2016)



# CBD Mechanisms of Action

- Antagonizes
  - GPR55
  - alpha-1 adrenergic
  - $\mu$ -opioid receptors
  - Adenosine receptors
- Activates
  - 5-HT<sub>1A</sub> serotonergic
  - TRPV1–2 vanilloid receptors
- Inhibits uptake
  - noradrenaline
  - dopamine
  - serotonin
  - GABA
- anandamide
- Inhibits activity of fatty amide hydrolase (FAAH) and numerous other enzymes
- Acts on mitochondria Ca<sup>2</sup> stores
- May block low-voltage-activated (T-type) Ca<sup>2</sup> channels
- May stimulate activity of the inhibitory glycine-receptor

(reviewed in Zhornitsky, 2012)

# THC & CBD Synergism

## Cannabidiol (CBD)

- Antagonizes undesirable effects of THC such as intoxication, sedation and tachycardia
- Enhances the analgesic, anti-emetic, and anti-carcinogenic properties of THC.  
(Russo & Guy, 2006)

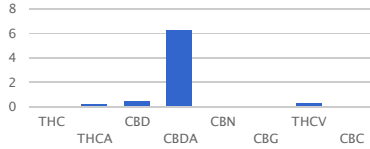
# TESTED LABS

## Cannabis Potency Results

Date: 03-Nov-15, 15:58:54  
 Client:   
 Sample: Coops CBD  
 Type: Flower  
 Notes:

www.TestedLabs.com 207-618-9333  
 (http://www.TestedLabs.com)

Cannabinoid	Result
THC	0.07 %
THCA	0.3 %
CBD	0.48 %
CBDA	6.3 %
CBN	0.04 %
CBG	0 %
THCV	0.32 %
CBC	0.04 %
<hr/>	
<b>Total CBD (CBD+CBDA)</b>	<b>6.78 %</b>
<b>Max CBD *</b>	<b>6.01 %</b>
<b>Total THC (THC + THCA)</b>	<b>0.37 %</b>
<b>Max THC *</b>	<b>0.33 %</b>
<b>Total Cannabinoid Results</b>	<b>7.55 %</b>



# TESTED LABS

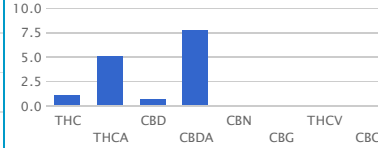
## Cannabis Potency Results

Date: 03-Nov-15, 15:20:16  
 Client:   
 Sample: Daliyah  
 Type:   
 Notes:

207-618-9333

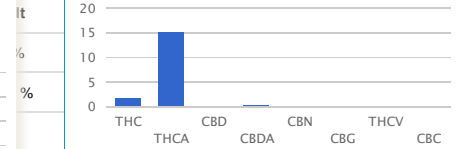
### Result

1.25 %  
 5.14 %  
 0.76 %  
 7.79 %  
 0.05 %  
 0.04 %  
 0.14 %  
 0.04 %  
 8.55 %  
 7.59 %  
 6.39 %  
 5.76 %  
**Results** 15.21 %



## Cannabis Potency Results

Date: 03-Nov-15, 15:28:00  
 Client:   
 Sample: Mob Sue-Mae  
 Type: Flower  
 Notes:



# Cannabis Safety

“Except for the harms associated with smoking, the adverse effects of marijuana use are within the range tolerated for other medications.”

“There is no conclusive evidence that marijuana causes cancer in humans, including cancers usually related to tobacco use.”

National Academy of Sciences, Institute of Medicine. 1999.  
Marijuana and Medicine: Assessing the Science Base

# Cannabis Smoking in Respiratory Tract and Lung Cancer

- 1,212 incident cancer cases and 1,040 cancer-free controls matched to cases on age, gender, and neighborhood.
- No positive associations were observed when adjusting for several confounders including cigarette smoking.
- The adjusted odds ratio estimate (and 95% confidence limits) for  $\geq 60$  versus 0 joint-years:
  - oral cancer 1.1 (0.56, 2.1)
  - laryngeal cancer 0.84 (0.28, 2.5)
  - lung cancer 0.62 (0.32, 1.2)

Hashibe et al., 2006



# Medical Cannabis Side Effects

- Dizziness
- Dry mouth
- Nausea
- Fatigue
- Sleepiness
- Euphoria
- Depression
- Vomiting
- Diarrhea
- Disorientation
- Anxiety
- Confusion
- Impaired balance
- Hallucination
- Paranoia

Whiting, Penny F., et al. "Cannabinoids for Medical Use: A Systematic Review and Meta-analysis." *JAMA* 313.24 (2015): 2456-2473.

# Cannabis Withdrawal

- Common cannabis withdrawal symptoms
  - Anger or aggression
  - Decreased appetite or weight loss Irritability
  - Nervousness/anxiety
  - Restlessness
  - Sleep difficulties, including strange dreams
- Symptoms appear 1-2 days after cessation and resolve in 1-2 weeks

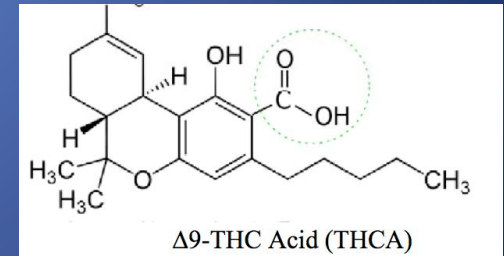
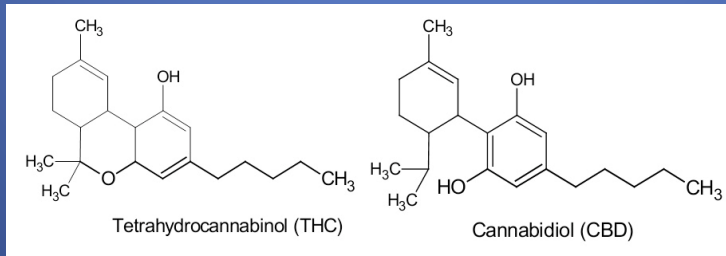
Reviewed in Budney et al. 2004

# Drug Interactions

- THC - CYPs 2C9, 3A4
- CBD - CYPs 2C19, 3A4
- CBN - CYPs 2C9, 3A4

“Studies of THC, CBD, and CBN inhibition and induction of major human CYP-450 isoforms generally reflect a low risk of clinically significant drug interactions with most use, but specific human data are lacking.”

# Clinical Dosing Terminology



# Dosing By The Milligram

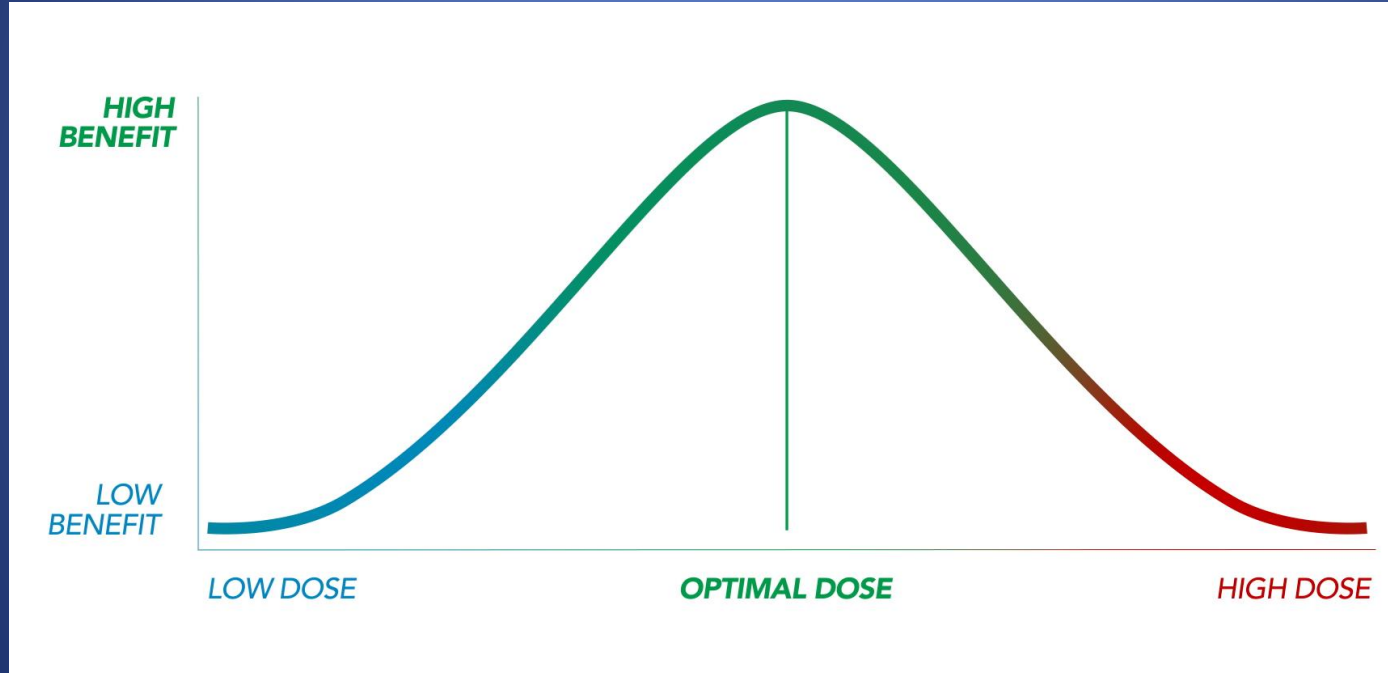
Oral dosing range effective in our practice:

0.015mg/kg/day – 30mg/kg/day

(e.g. 1mg - 2,100mg daily for 70kg adult)

Monkeys treated with oral THC at 9,000mg/kg  
survived (Rosenkrantz et al., 1975)

# Biphasic Dose-Response



# Multiphasic Dose-Response

Example: THC &  
Locomotor activity in rats

(Sañudo-Peña et al, 2000)

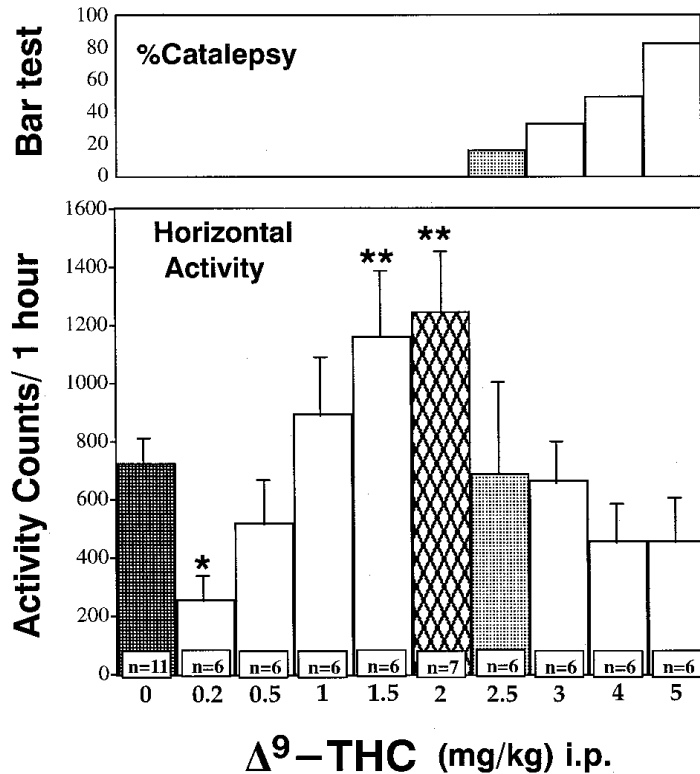
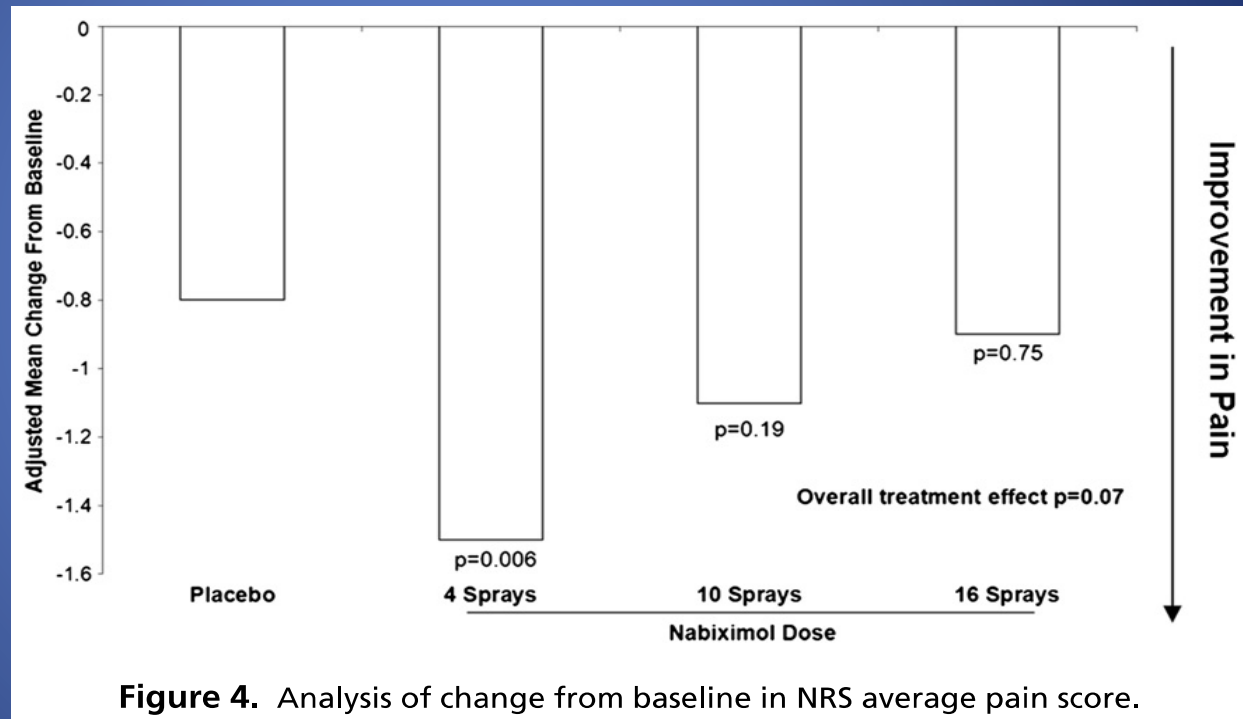


Fig. 1. Dose-curve of systemic administration of  $\Delta^9$ -tetrahydrocannabinol effects on horizontal activity in rats. There is an increase in activity with relatively low doses (1–2 mg/kg) of the cannabinoid receptor agonist.

# Nabiximols for Opioid-Treated Cancer Patients With Poorly Controlled Chronic Pain

Randomized, placebo-controlled, graded-dose trial, n=263, 9 weeks. (Portenoy et al, 2012)



**Figure 4.** Analysis of change from baseline in NRS average pain score.

20.8mg

52mg

83.2mg



# Delivery Methods: Oromucosal and Enteral



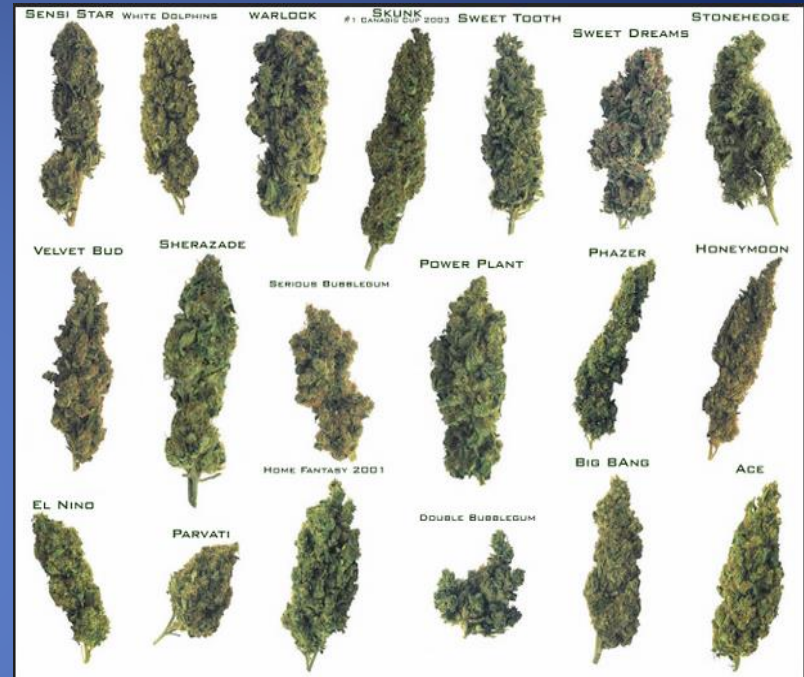
# Delivery Methods: Inhalation



# Chemovars (strains)

Common terms (usually inaccurate):

- Sativa
  - Taller plant
  - More energetic, “cerebral” effects – “High”
- Indica
  - Shorter, easier for indoor growing
  - More relaxing, “body” effects – “Stoned”
- Most strains are a hybrid, each has a unique ratio of cannabinoids and mix of terpenoids
- Laboratory testing is essential for specific dosing



What's important?

- CBD vs THC
- Stimulating vs Sedating
- Patient-specific response

# Clinical Cannabinoid Medicine:



# Clinical Considerations: Cancer

1. Understand the diagnosis and prognosis. Assess the patient's understanding of this information.
2. Is patient seeking cannabis as adjunct or alternative to conventional treatment? Where is this decision coming from?
3. Work with patient to determine appropriate goals of treatment for palliation, improvement in quality of life, and healing.
4. Assess patient's comfort with his or her own mortality.

# Low-Dose Treatment

- 0.1-1 mg/kg/day
- Always start here for cannabis-naïve
- Develop a relationship with cannabis
- Gently build tolerance to common initial side effects
- Relieve death anxiety and make better medical choices.

# Low-Dose Treatment

- Consider CBD-dominant strain during daytime to reduce psychoactivity, if aligned with patient preference.
- Use THC dominant in the evening and encourage patient to explore the healing aspects of cannabis consciousness while relaxing in a comfortable environment before bed.

# Low-Dose Treatment

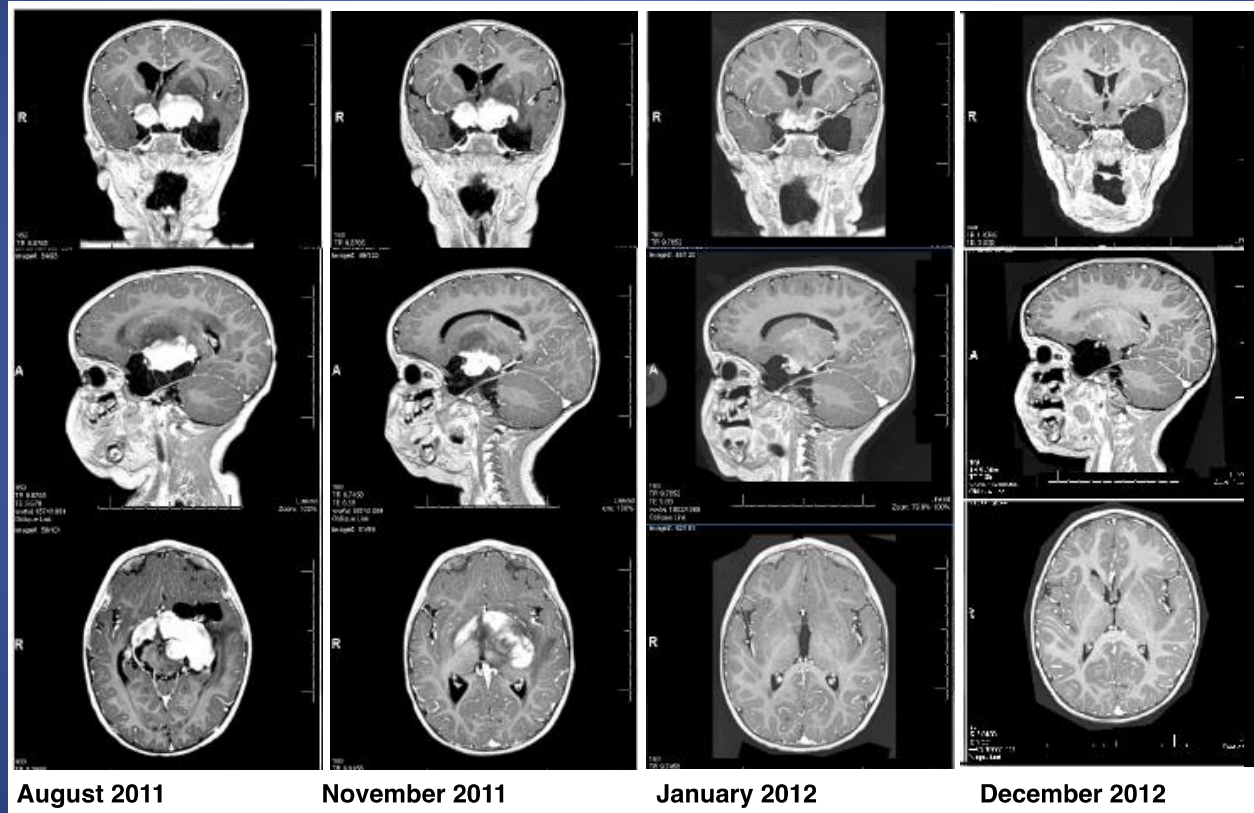
- Address sleep with higher PO dose if needed. Be sure to choose a sedating strain.
- Emphasize the importance of prophylaxis with low dose cannabis during chemo and radiation treatments to prevent neuropathy, reduce inflammation, and potentially enhance efficacy.



# High-Dose Treatment

- Goal is 5-25mg/kg/day total cannabinoids, titration phase 1-4 weeks followed by maintenance phase.
- CBD dominant during day, THC during night works well for most patients

# Optic Pathway Glioma – Cannabis Monotherapy



# Cannabis Helps With End of Life Care

- Pain
- Anxiety & agitation
- Polypharmacy
  - Broad therapeutic spectrum, able to replace multiple medications
- Decreased appetite/anorexia
  - Cannabis stimulates appetite (only antiemetic known to do so).
- Dysphagia
  - Wide range of delivery methods
- Secretions
  - Dries without the adverse effects of anticholinergic drugs



Thank You!

Dustin Sulak, D.O.