Medical Cannabis and Chronic Pain; From Science to Law

Sanford M. Silverman, MD
Comprehensive Pain Medicine
Pompano Beach, FL
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Disclaimer for Sanford M. Silverman, MD

Medical Director: Comprehensive Pain Medicine, Pompano Beach, FL

Member: ASIPP, AAPM, DABPM, FSIPP, DABM, FSAM, FMA, BCMA

Officer/ Board Position: Past President FSIPP, Board Member ASIPP, Board of Governors Broward County Commission on Substance Abuse, Immediate past-President BCMA, Broward County Commission Pain Clinic Task Force

Publications: Articles in Anesthesiology, Canadian Journal of Anesthesia, Pain Physician

Speaker: Pfizer, AstraZeneca, Depomed, Purdue, Endo
NO FINANCIAL INTERESTS FOR THIS LECTURE

Objectives

- Exogenous cannabinoids
- Endogenous cannabinoids
- Neuromodulation v. neurotransmission
- Neurobiological effects
- Receptors
- Medical cannabis
- Dependence
- Cognitive and learning
- Cannabis and the law

History of Cannabis

- **Ancient China – Cannabis was used to make fiber 10,000 years ago and medicinal use started 4,000 year ago**
- **One of the 50 "fundamental" herbs in traditional Chinese Medicine**
- **Used as anesthetic (powdered and mixed with wine), antiemetic, treatment of infectious and parasitic hemorrhaging.**
- **Ancient Egypt – used as early as 1700 BC for hemp and relief of pain from hemorrhoids**

History

Ancient India – used for insomnia, headaches, relieved pain of childbirth and several GI disorders, The ancient Indians recognized its psychoactive properties.

- Ancient Greece – used for human and animal medicine. Used to treat wounds and sores on horses, ear inflammation and pain in human using extract of green Cannabis seeds soaked in wine or water. Dried leaves was used to treat nose bleeds and seeds to expel tapeworms.
- Medieval Islam – Arabic physicians in the 8th to 18th centuries used it as an diuretic, anti-nausea, anti-inflammatory, pain killing and fever reduction.

History

- 19th Century – used as a pain reliever worldwide until Aspirin was invented
- William Brooke 0'Shaughnessy- the father of the medical use of Marijuana in the modern world. In the 1830's he used it for the treatment of muscle spasms, stomach cramps and general pain. He later used it for melancholia, migraines, anti-nausea, anticonvulsant and as a sleeping aid.

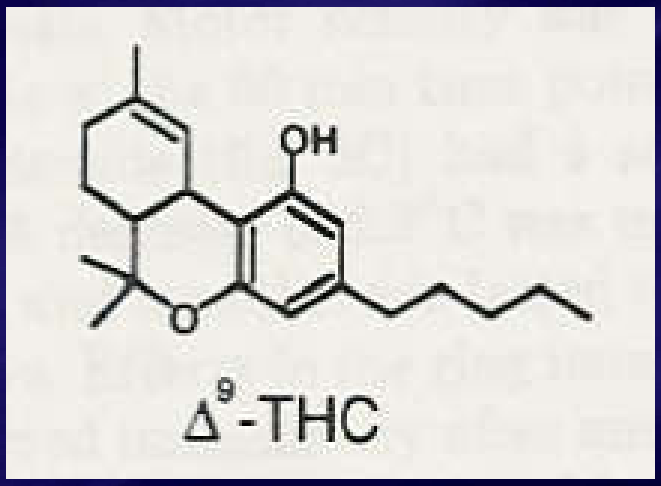
History

- Marijuana was banned in 1937 in the United States in a federal law, the 1937 Marijuana Tax Act.
- Supported by negative stereotypes that the drug was dangerous and altered rational behavior. It was used primarily by Mexicans and African immigrants.
- Marinol, a pill form of synthetic tetrahydrocannabinol (THC) was introduced in the US market in the 1970's as an anti-nausea and appetite stimulating agent.

Cannabinoids

Exogenous Cannabinoid

Mechoulam – 1964, Father of Cannabinoid Chemistry



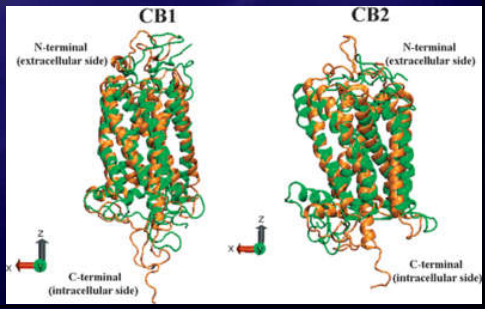
Distribution of Receptor Sites Radiolabeled CP-55,940

CB1 Receptors ; Highly expressed in Nervous system- 1988

- Hippocampus – Memory and Learning
- Amygdala – Novelty, Emotion, Appetite
- Basal Ganglia – Motor
- Cerebellum – Real Time Coordination, Selective Attention and Time Sense
- Nucleus Accumbens - Reward Mechanism (Addiction)
- Cortex (Anterior > Posterior) – Frontal Lobe Executive Functions

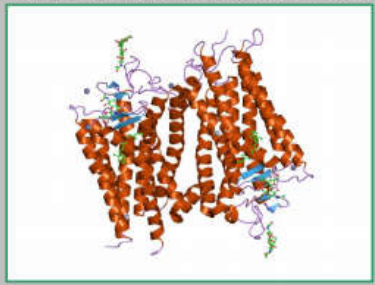
CB2 Receptors ; Immune system B and T cells– 1993

- **CB2B**
  - Spleen, Intestines
- **CB2A (pain)**
  - Brain
  - Testes
  - Leuckocytes, macrophages



Cannabinoid 3 Receptor

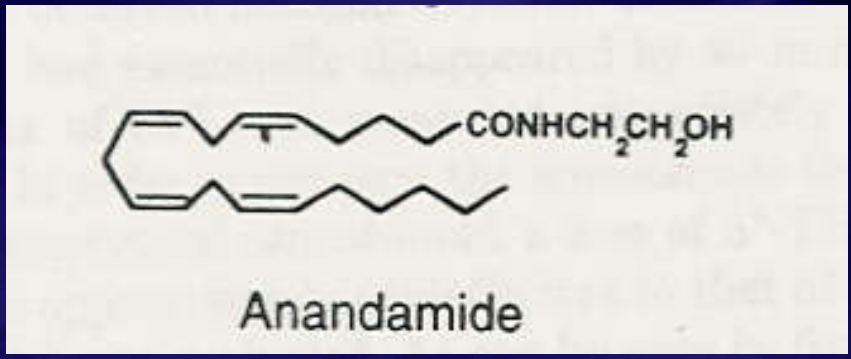
- 2007 GPR55 was established as the CB_3 receptor



Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson NO, Leonova J, Elebring T, Nilsson K, Drmota T, Greasley PJ (2007). "The orphan receptor GPR55 is a novel cannabinoid receptor". *Br. J. Pharmacol.* **152** (7): 1092–101.

Endogenous Cannabinoid

Mechoulam - 1992

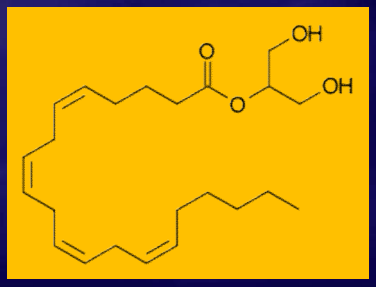


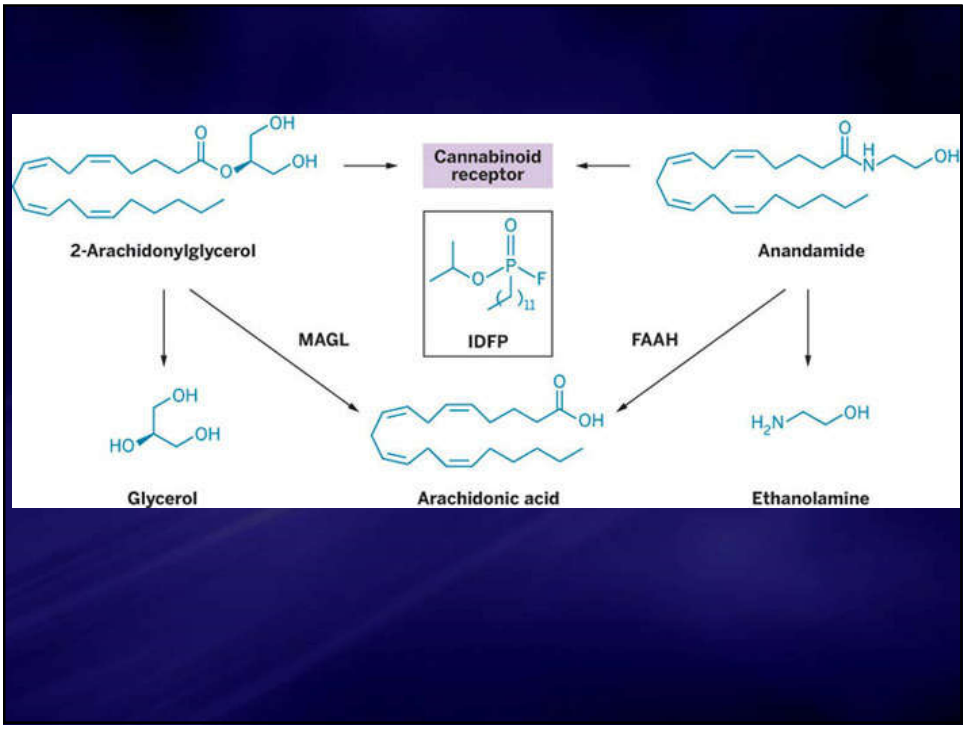
Anandamide

- Anandamide binds to TRPV1 receptors and activates channels in CNS and peripheral nerves
- Partial agonist of the CB1 receptor
- Inactivated by fatty acid amide hydrolase (FAAH)

2 AG - 2-Arachidonoylglycerol

- Endogenous cannabinoid
- Shimon Ben-Shabat, of Ben-Gurion University
- Full Agonist at CB1 and CB2
- Ca dependent channel





FAAH inhibitors attractive analgesics

- *FAAH* knockout mice display highly elevated (>15-fold) levels of *N*-acylethanolamines and *N*-acyltaurines in various tissues. Because of their significantly elevated anandamide levels, *FAAH* KOs have an analgesic phenotype, showing reduced pain sensation in the hot plate test, the formalin test, and the tail flick test.[1] Finally, because of their impaired ability to degrade anandamide, *FAAH* KOs also display supersensitivity to exogenous anandamide, a cannabinoid receptor (CB) agonist.[6]
- Due to the ability of FAAH to regulate nociception, it is currently viewed as an attractive drug target for the treatment of pain.[2][3][4]

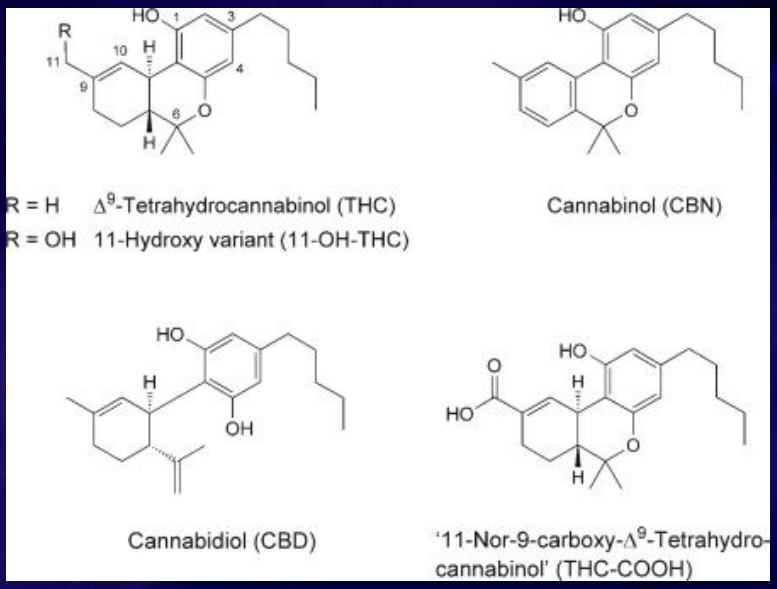
1. Cravatt BF, Lichtman AH (Oct 2004). "The endogenous cannabinoid system and its role in nociceptive behavior". *Journal of Neurobiology* **61** (1): 149–60.doi:10.1002/neu.20080. PMID 15362158.

2. Salaga M, Sobczak M, Fichna J. Inhibition of fatty acid amide hydrolase (FAAH) as a novel therapeutic strategy in the treatment of pain and inflammatory diseases in the gastrointestinal tract. *Eur J Pharm Sci*. 2014 Feb 14;52:173-9. doi: 10.1016/j.ejps.2013.11.012 PMID 24275607

3. Ulugöl A. The endocannabinoid system as a potential therapeutic target for pain modulation. *Balkan Med J*. 2014 Jun;31(2):115-20. doi: 10.5152/balkanmedj.2014.13103 PMID 25207181

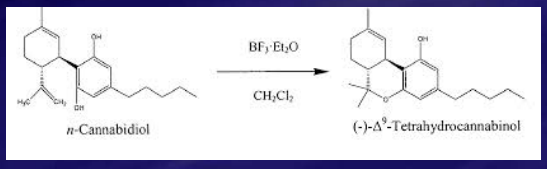
4. Ghosh S, Kinsey SG, Liu QS, Hruba L, McMahon LR, Grim TW, Merritt CR, Wise LE, Abdullah RA, Selley DE, Sim-Selley LJ, Cravatt BF, Lichtman AH. Full Fatty Acid Amide Hydrolase Inhibition Combined with Partial Monoacylglycerol Lipase Inhibition: Augmented and Sustained Antinociceptive Effects with Reduced Cannabimimetic Side Effects in Mice. *J Pharmacol Exp Ther*. 2015 Aug;354(2):111-20. doi: 10.1124/jpet.115.222851 PMID 25998048

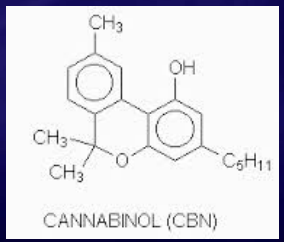
Exogenous Cannabinoids



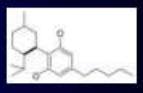
Other Exogenous Cannabinoids

- Cannabidiol (CBD) precursor to THC
- Cannabinol (CBN) degradation product of THC
- CBD and CBN enhance depressant effects of THC while blocking excitatory effects





Cannabidiol (CBD)



- May have different medicinal applications than THC
- Very low affinity for CB1 and CB2
- Minimal psychoactive effect
- 5-HT1A receptor agonist
  - Antidepressant, Anxiolysis
- Allosteric modulator of μ- and δ-opioid receptors
  - Analgesia
- Other: Anti-psychotic, antiepileptic

Side Effects of CBD

- Possible immunosuppressive effects
- Sedation, Feeling heavy
- High concentrations have potential effects on blood sugar
- Overdose (up to 300 mg/kg/IV) in Monkeys – tremors, convulsions, vomiting, sedation to prostration in 30 minutes, cardiac faluire
  - Clinically effective dose around 10 mg/day

CBD Drug Interactions

- Drugs metabolized by CYP450 3A4, 2C19, and 2B subfamilies can be affected
  - May induce or inhibit leading to increased or reduced amounts
- Interacts with THC as THC is metabolized by 3A4 and 2C19

To understand the endogenous cannabinoid system one must understand the endogenous opioid system.

Neurotransmitter v. Neuromodulator

- The endocannabinoid system regulates activity of other neurotransmitters
- "There is barely a physiological system in which endocannabinoids are *not* involved. Hence its importance is far beyond that of THC and marihuana…." - Mechoulam

Old Model ECS

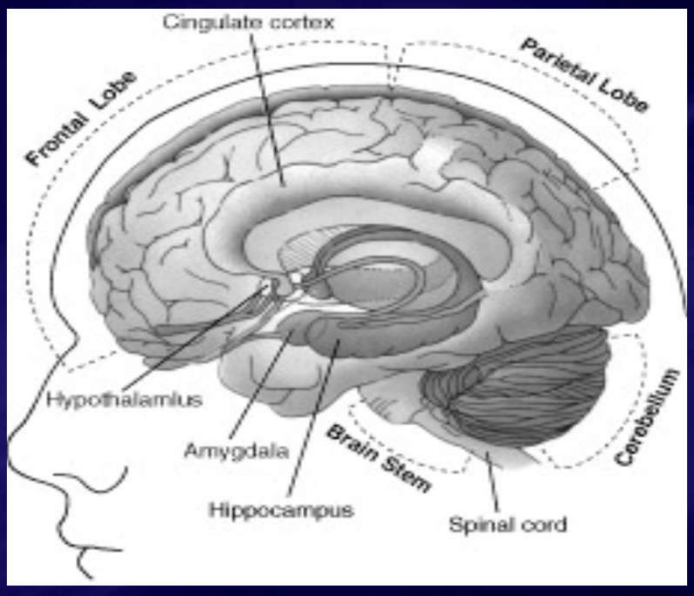
The ECS is comprised of:

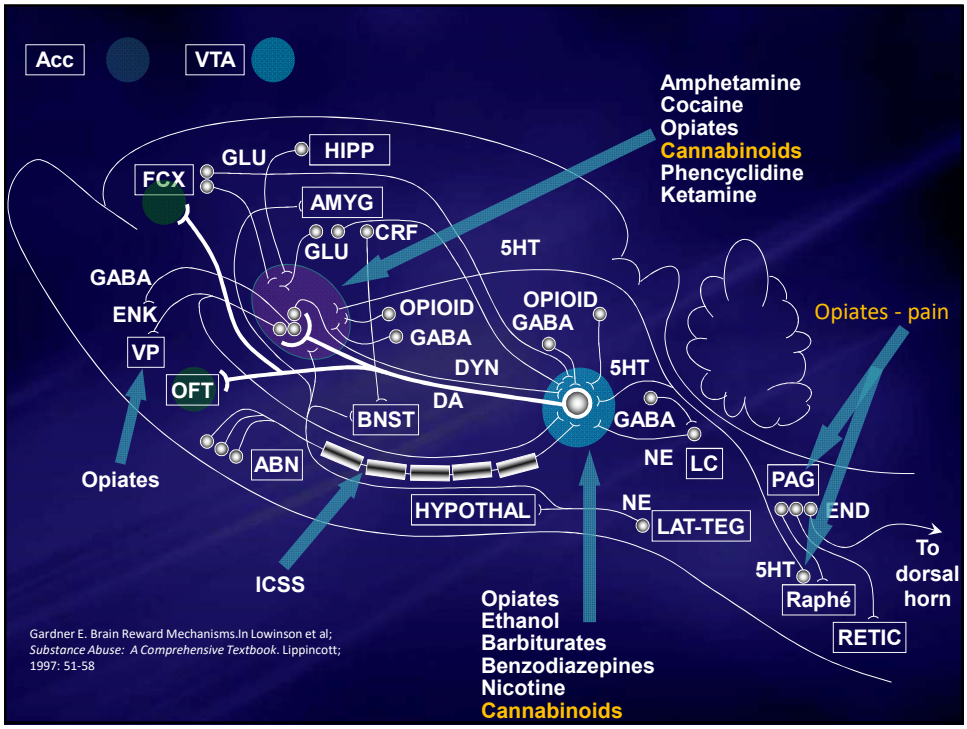
1. The cannabinoid receptors CB1 and CB2
2. The CB1 and CB2 endogenous ligands
   a) anandamide (N-arachidonoyl-ethanolamine, AEA)
   b) 2-arachidonylglycerol (2-AG)
3. A specific and not yet identified cellular uptake mechanism

New Model of the ECS

- ECS +, New Model
  - Putative CB1 antagonist peptides like hemopressins
  - Peroxisome proliferator-activated receptor-α (PPAR-α) and γ (PPAR-γ) ligands
    - oleoylethanolamide (OEA)
    - palmitoylethanolamide (PEA)
  - CB3 receptor
  - TRP receptors
  - N-arachidonoyl-dopamine (NADA)

Hippocampal Cannabinoid Receptors




Acc
VTA
Amphetamine
Cocaine
Opiates
Cannabinoids
Phencyclidine
Ketamine
GLU
HIPP
FCX
AMYG
CRF
GLU
5HT
GABA
ENK
VP
OPIOID
GABA
OPIOID
GABA
DYN
5HT
OFT
DA
BNST
GABA
Opiates - pain
Opiates
ABN
NE
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HYPOTHAL
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LAT-TEG
END
To
dorsal
horn
5HT
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ICSS
RETIC
Opiates
Ethanol
Barbiturates
Benzodiazepines
Nicotine
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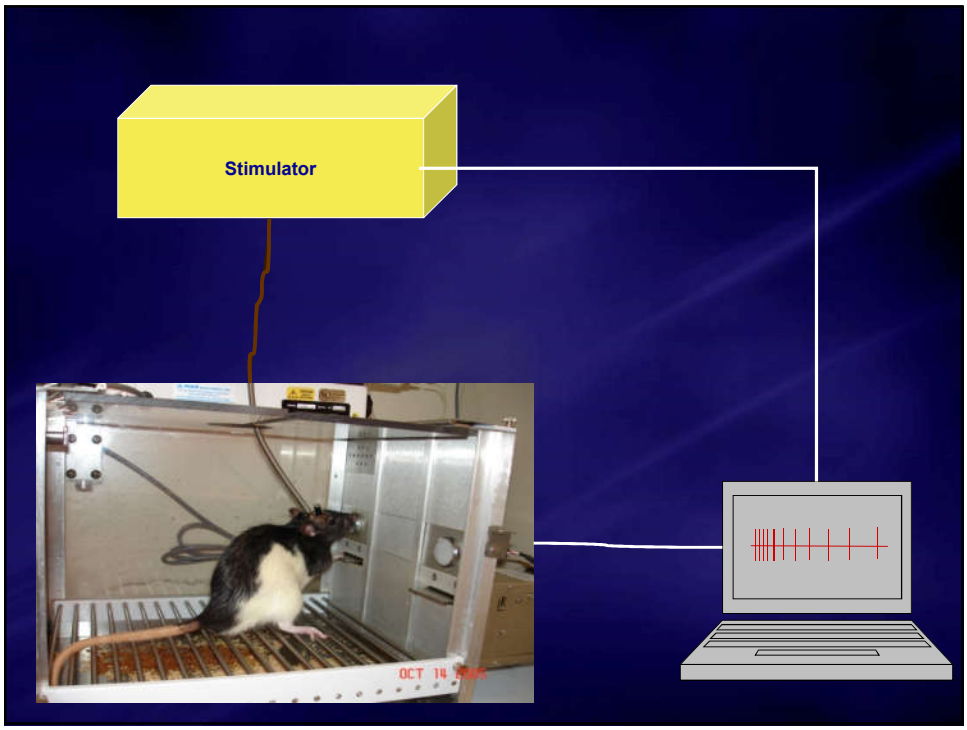

Stimulator

Cannabinoids and Opioids

Opioid interactions

- Parallel yet interactive systems
- CB1 knockout mice are bred WITHOUT CB1 receptors
- CB1 knockout mice will NOT self administer morphine
- Naloxone blocks effects of CB1 receptor agonists (cannabinoid)

Survival

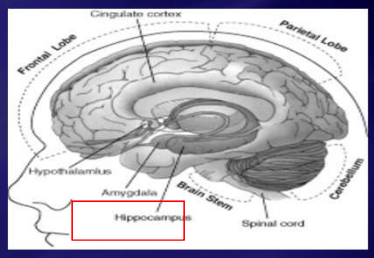
- CB1 knockout
- Survive and reproduce
  - Increased morbidity and premature mortality
  - Show greater aggression
  - Anxiogenic-like behavior
  - Depressive-like behavior
  - Anhedonia
  - Increased memory and decreased forgetting of aversive memories

    Marsicano et al, *Nature*, 418(6897):530-4, Aug 1,2002
  - Hypomotility, especially in exploration

    Zimmer et al., *Proc. Natl. Acad. Sci. USA*: Vol. 96, #10, 5780-85, May 11, 1999

The Role of Cannabinoids in the Hippocampus

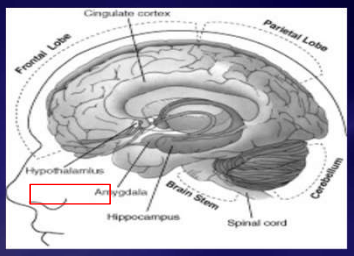
Modulating Working Memory



Hippocampal Effects of Marijuana

- Memory
- Memory and Learning
- Acute Short-term Memory Effect
- Social Recognition Research
  - Rats snout sniffing recognition routine
  - Given THC snout sniffing is repeated and does not last long
  - Given cannabinoid antagonist, then increase recognition less time for snout sniffing

The Role of Cannabinoids in the Amygdala



- Registration of Novelty
- Determination of Emotional Relevance
- Forgetting of Aversive Memories
- Regulation of Appetites
- Regulation of Pain Threshold
- Regulation of Anxiety/Fear
- Global Characteristics of Consciousness

Virtual Novelty

The Impact of THC on the Amygdala

- Sensory Effects – Dishabituation
- Attentional Effects – Increased Field Size
- "Motivational" Effects – Novelty
- Numinosity – The Sense of Awe

- Result: Roller Coaster Dynamic

Amygdalar Endocannabinoid Effects on Appetite and Bonding

- Cannabinoid stimulation increases appetite and blockers decrease appetite
- Clinical trial of 20 mg of the CB1 antagonist rimonabant showed an average 20 pound weight loss (and a positive impact on smoking cessation)
- The cannabinoid blocker SR141716A given to rat pups within 24 hours of birth stops suckling and causes death in 4-8 days

Fride et al, "Critical role of the endogenous cannabinoid system in mouse pup suckling and growth," *European J of Pharmacology* 419(2001) 207-214

Endocannabinoids in the Basal Ganglia and Cerebellum

- Substantia Nigra and Globus Pallidus have highest levels in the brain
- Levels are comparable to dopamine
- The endogenous cannabinergic system exerts a major modulatory action in the basal ganglia by its ability to block both the major excitatory and inhibitory inputs to the Substantia Nigra and Globus Pallidus

Motor Effects of Cannabinoids

- Cannabinoid Agonists
  - Reduce spontaneous activity – catalepsy
  - Incoordination
- Cerebellar "Flow" (Related to Distortions in Time Sense?)
- Driving Research
- Flight Simulator Research

Yesavage et al., Carry-over effects of marijuana intoxication on aircraft pilotperformance: a preliminary report, *Am J Psychiatry*, 1985

Functions Regulated by Tonic Endocannabinoid Activity -Summary

- Modulating size of working memory and aversive memory
- Modulating pain threshold
- Modulating threshold of novelty/familiarity
- Modulating attentional scope (narrow Vs. widened focus)
- Modulating level of spontaneous motor activity
- Modulating fear, anxiety and stress responses
- Modulating appetite(s)/bonding
- Modulating global characteristics of consciousness

Medical Cannabis

Rationale for Potential Cannabinoid Medications

- Pain
- Motor disorders – Spasticity
- Seizure disorders
- Appetite(s)/N&V/bonding disorders
- Memory disorders
- Fear and anxiety disorders
- Novelty/familiarity and Attentional disorders - Boredom (?)

Cannabinoids and Opiates

Brain researchers now see the endogenous opioid and cannabinoid systems in the CNS as two independent but parallel and overlapping physiological regulatory systems. Both are involved in controlling our sensitivity to pain, and both may be involved in some way in the reward mechanisms of the brain.

Cannabinoids and Pain

- Chronic pain involve multiple mechanisms
- Neuronal threshold decreases – hyperalgesia and allodynia
- Multiple neurochemical changes
  - Glutamate
  - AMPA
  - NO
  - interleukin-1β
  - TNF-α
- Non-neuronal microglial proliferation
- CB2A receptors modulate anti-inflammatory response which may reduce glial proliferation
- Independent mechanism from mu receptor activation

Wilkerson et al: The Central Role of Glia in Pathological Pain and the Potential of Targeting the Cannabinoid 2 Receptor for Pain Relief; ISRN Anesthesiol. ; 2011(2011)

Neuroprotective Antioxidants from Marijuana[a]

A.J. HAMPSON,[b,c] M. GRIMALDI,[d] M. LOLIC,[e] D. WINK,[f] R. ROSENTHAL,[e] AND J. AXELROD[b]

[b]*Laboratory of Cellular and Molecular Regulation, NIMH, Bethesda, Maryland 20892, USA*

[d]*Laboratory of Adaptive Systems, NINDS, Bethesda, Maryland 20892, USA*

[e]*Department of Emergency Medicine, George Washington University, Washington DC 20052, USA*

[f]*Radiation Biology Branch, NCI, Bethesda, Maryland 20892, USA*

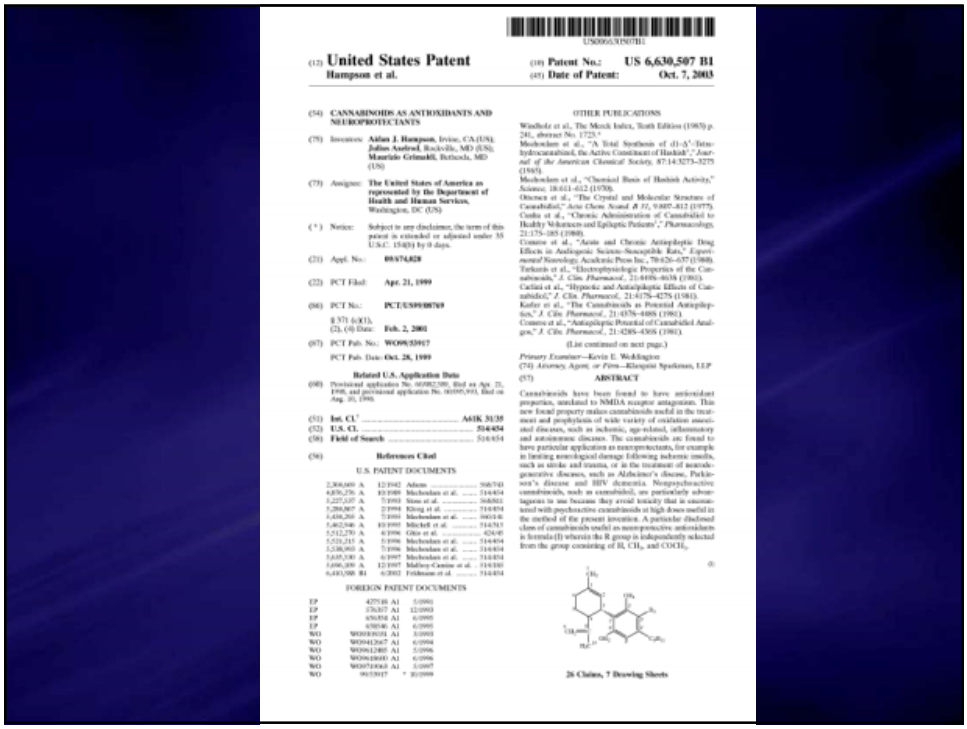
ABSTRACT: **Cannabidiol and other cannabinoids were examined as neuroprotectants in rat cortical neuron cultures exposed to toxic levels of the neurotransmitter, glutamate. The psychotropic cannabinoid receptor agonist Δ⁹-tetrahydrocannabinol (THC) and cannabidiol, (a non-psychoactive constituent of marijuana), both reduced NMDA, AMPA and kainate receptor mediated neurotoxicities. Neuroprotection was not affected by cannabinoid receptor antagonist, indicating a (cannabinoid) receptor-independent mechanism of action. Glutamate toxicity can be reduced by antioxidants. Using cyclic voltammetry and a fenton reaction based system, it was demonstrated that Cannabidiol, THC and other cannabinoids are potent antioxidants. As evidence that cannabinoids can act as an antioxidants in neuronal cultures, cannabidiol was demonstrated to reduce hydroperoxide toxicity in neurons. In a head to head trial of the abilities of various antioxidants to prevent glutamate toxicity, cannabidiol was superior to both α-tocopherol and ascorbate in protective capacity. Recent preliminary studies in a rat model of focal cerebral ischemia suggest that cannabidiol may be at least as effective *in vivo* as seen in these *in vitro* studies.**

INTRODUCTION

Cannabinoid components of marijuana are known to exert behavioral and psychotropic effects but also possess therapeutic properties including analgesia,[1] ocular hypotension,[2] and antiemesis.[3] This report examines another potential therapeutic role for cannabinoids as neuroprotectants and describes their mechanism of action in rat cortical neuronal cultures. During an ischemic episode, large quantities of the excitatory neurotransmitter, glutamate, are released in the brain. This event causes neuronal death by over-stimulation of NMDA[4] (NMDAr), AMPA and kainate type receptors, which massively increase intracellular calcium, resulting in metabolic

[a]*In vitro* data presented in this paper and FIGURES 1–6 were first published in Proceedings of the National Academy of Sciences (July 1998, **95**: 8268–8273).

[c]Address for correspondence: Dr. Aidan Hampson, Cortex Pharmaceuticals, Inc., 15231 Barranca Parkway, Irvine, CA 92618.
e-mail: aidan@codon.nih.gov



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.: **09/674,828**

(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

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(51) **Int. Cl.**[7] **A61K 31/35**
(52) **U.S. Cl.** **514/454**
(58) **Field of Search** 514/454

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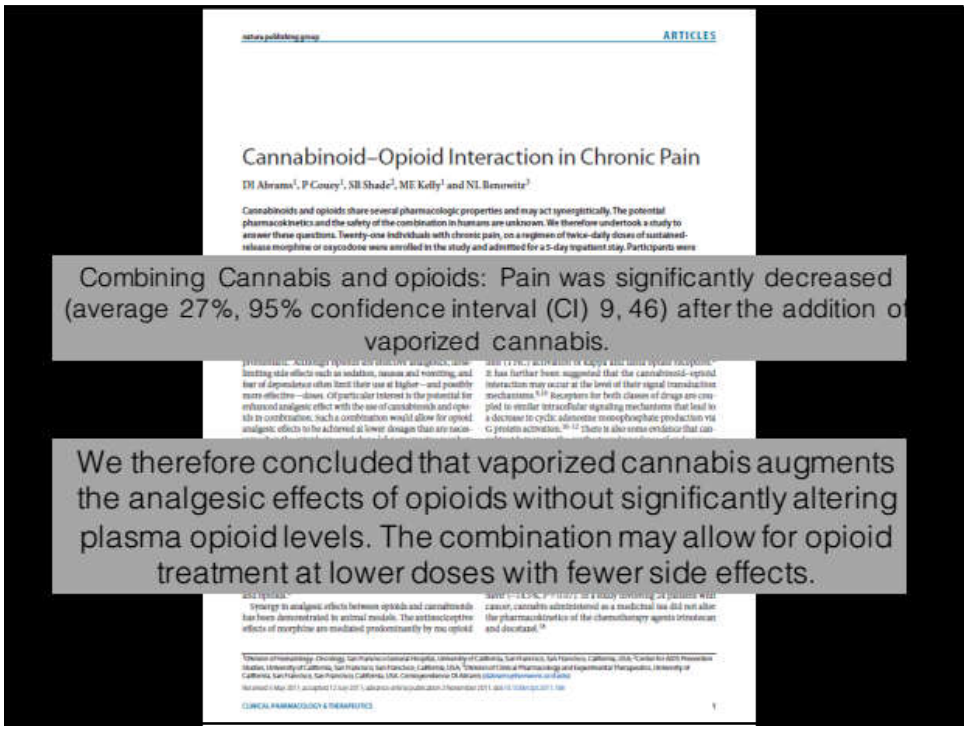
(List continued on next page.)

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 new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidative associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia. Nonpsychoactive cannabinoids, such as cannabidiol, are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present invention. A particular disclosed class of cannabinoids useful as neuroprotective antioxidants is formula (I) wherein the R group is independently selected from the group consisting of H, CH_3, and $COCH_3$.

26 Claims, 7 Drawing Sheets



nature publishing group — ARTICLES

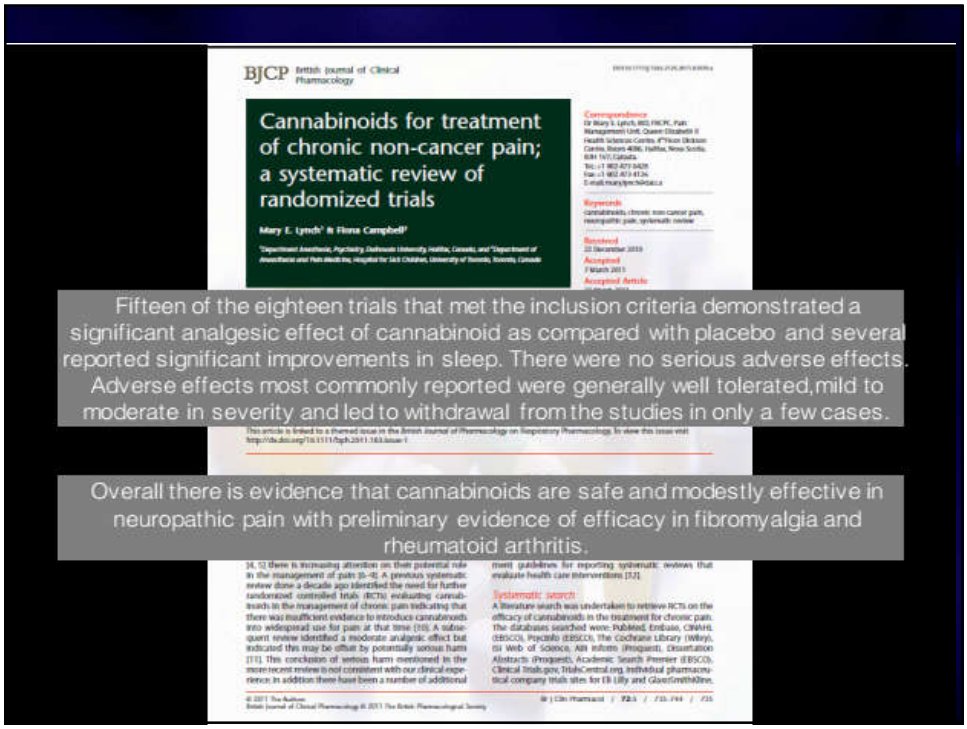
Cannabinoid–Opioid Interaction in Chronic Pain

DI Abrams[1], P Couey[1], SB Shade[2], ME Kelly[1] and NL Benowitz[3]

Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions. Twenty-one individuals with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone were enrolled in the study and admitted for a 5-day inpatient stay. Participants were

Combining Cannabis and opioids: Pain was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis.

We therefore concluded that 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.



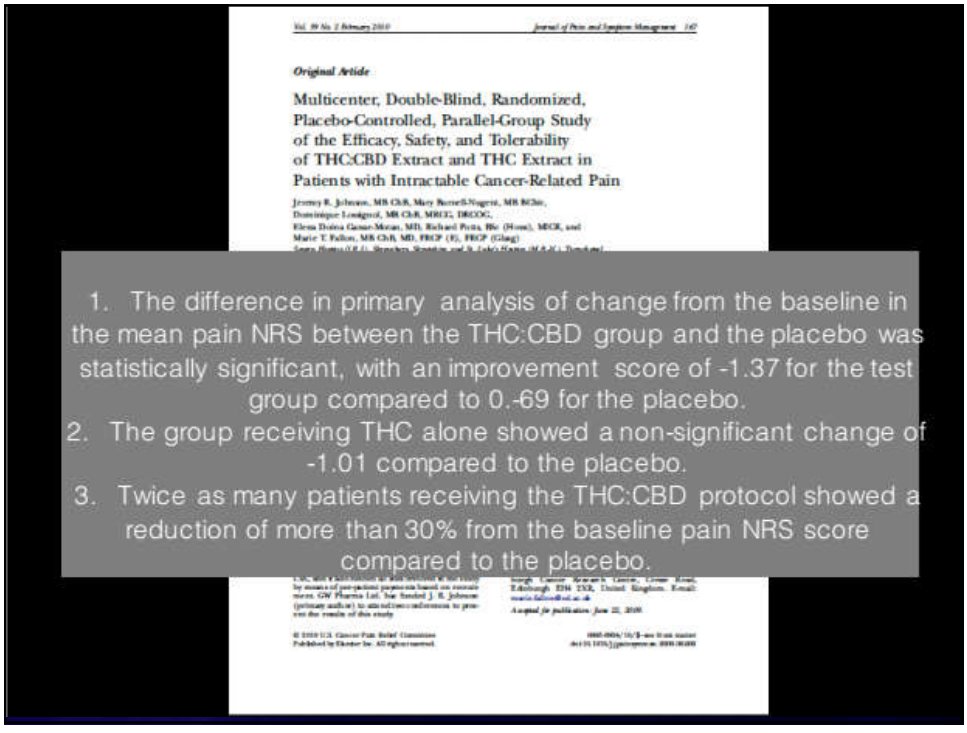
BJCP British Journal of Clinical Pharmacology

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

Mary E. Lynch & Fiona Campbell

Fifteen of the eighteen trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo and several reported significant improvements in sleep. There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases.

Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.

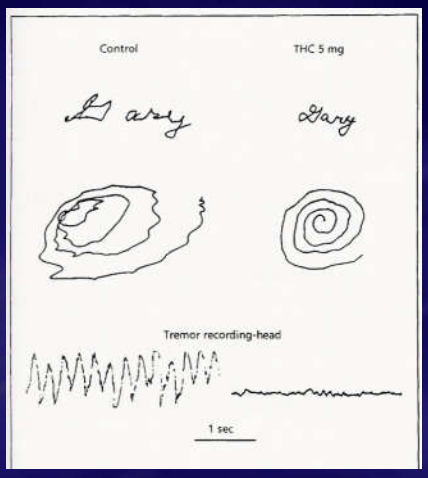


Original Article

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain

1. The difference in primary analysis of change from the baseline in the mean pain NRS between the THC:CBD group and the placebo was statistically significant, with an improvement score of -1.37 for the test group compared to 0.-69 for the placebo.
2. The group receiving THC alone showed a non-significant change of -1.01 compared to the placebo.
3. Twice as many patients receiving the THC:CBD protocol showed a reduction of more than 30% from the baseline pain NRS score compared to the placebo.

THC Effect on MS



British Medical Association, *Therapeutic Uses of Cannabis*, UK: Harwood Academic Publishers, 1997

Most Common Medical Uses of Cannabis

- Anorexia, N/V, Diarrhea
- Insomnia/Depression
- Anxiety/Panic Attacks
- AIDS Related Illnesses
- Arthritic/Chronic Pain
- Muscle Spasm
- Harm Reduction
- Epilepsy

Marijuana vs. Tobacco

Chemical	Marijuana	Tobacco
THC	820.0 mcg	-----
Nicotine	-----	2850.0 mcg
Phenol	76.8 mcg	138.5 mcg
Naphthalene	3.0 mcg	1.2 mcg
Benzanthracene	75.0 ng	43.0 ng
Benzpyrene	31.0 ng	21.1 ng
Total	22.7 mg	39.0 mg

Marijuana vs. Tobacco

Chemical	Marijuana	Tobacco
Carbon Monoxide	17.6 mg	20.2 mg
Ammonia	0.3 mg	0.2 mg
Hydrogen Cyanide	532.0 mcg	498.0 mcg
Acetaldehyde	1200.0 mcg	980.0 mcg
Acetone	443.0 mcg	578.0 mcg
Benzene	76.0 mcg	67.0 mcg
Toluene	112.0 mcg	108.0 mcg

Impact of Marijuana Smoke on the Respiratory System

- Acute and Chronic Bronchitis
- Local Immunological Impairment
- Precancerous Changes

Compared to Tobacco Smoke, Each Inhalation of Marijuana Smoke is typically

- 2/3 larger
- Inhaled 1/3 deeper
- Held 4 times longer
- 50% higher in tar

Therefore,

3-4 marijuana cigarettes are roughly equivalent to 20+ tobacco cigarettes.

Can CBD decrease cancer pain

- Most Research done with THC
- Drawback with CBD
  - Low bioavailability
  - Narrow therapeutic window when given PO
- Beneficial for sleep and anxiety

Epilepsy

- Four controlled studies in 1970's examined effect of CBD on siezures
- 2 studies found limited improvements

Condition	Dose	Duration	Results	Citation
Epilepsy (1): Nine patients with temporal lobe epilepsy, treatment resistant assigned to receive CBD (n=4) or placebo (n=5)	200 -300 mg per day	3 months	2 of 4 patients became seizure free. 1 of 4 patients improved. 1 patient remained unchanged. Placebo group (5) all remained unchanged	Mechoulam & Carlini. (1978) Naturwissenschaften 65, 174-179
Epilepsy (2): CBD in capsules vs placebo. CBD (n = 8) or placebo (n=7)	200 -300 mg per day	4.5 months	15 epileptic patients refractory to standard anti-epileptic drugs. 4 of 8 CBD patients nearly seizure free. 3 patients with partial improvement. 1 patient with no improvement. Placebo group - only 1 of 7 showed improvement	Cuhna et al. (Mechoulam as senior author) (1980). "Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients". Pharmacology 21:175-185
Epilepsy (3): Letter to the editor (not complete report) - 12 institutionalized epileptic patients with refractory seizures, randomly assigned to CBD or placebo	300 mg for 2 weeks followed by 200 mg for 3 weeks	5 weeks total	No difference in seizure frequency between groups	Ames and Cridland. Letter to the Editor: Journal Samt Deel 69, p 14 (1986)

Condition	Dose	Duration	Results	Citation
Seizures (4): 12 patients with medication resistant seizures treated with CBD or placebo	300 mg	24 weeks	Slight Benefit in CBD treated patients but no statistics provided	Tremblay and Sherman "Double-Blind Clinical Study of Cannabidiol as a Secondary Anticonvulsant" (1990). Presented at "Conference on Cannabis and Cannabinoids, Kolympari/Crete, July 1990", cited according to: Consroe P, Sandyk R. Potential Role of Cannabinoids for therapy of neurological disorders. In: Murphy L, Bartke A, eds. Marijuana/Cannabinoids, Neurobiology and Neurophysiology. Boca Raton: CRC Press 1992, 459-524
Dystonia (5): Open label study of CBD in 5 patients with Dystonia	100 to 600 mg	6 weeks	Dose related improvement in dystonia was observed in all patients and ranged from 20% to 50%	Consroe P et al., Open label evaluation of cannabidiol in dystonic movement disorders. Int J Neurosci. 1986 Nov;30(4):277-82
Huntington's Disease (6): Class III Crossover study in 15 patients	10mg / kg (in 2 divided doses)	?	No difference in CBD vs Placebo, but study was underpowered to detect differences	Consroe P et al., Controlled clinical trail of cannabidiol in Huntington's Disease. Pharmacol Biochem Behav 1991;40:701-708

Muscle Spasm

- Use of Sativex spray to treat spasm from MS associated with increased incidence of falls
- There have been no studies of pure CBD on muscle spasm
- CBD may supplement anti-spastic effect of THC

Cancer

- Effects of CBD on cancer cells
  - Reduction in invasiveness ,metastasis and apoptosis of cancer cells
  - Maybe due to down regulation of helix-loop-hellix transcript ion factor inhibition of DNA binding
- Combined CBD and THC enhances anticancer effect of THC in vitro and reduces the dose of THC required to reduce tumor growth
- To date NO CLINICAL HUMAN trials of pure CBD in cancer trials

CBD and BTP

- Protective against neurotoxicity of chemotx (paclitaxel)
- Intranasal would be better for BTP while transdermal for continuous pain
- TRPV1-2 and 5HT1A receptor agonist

AM1241

A Novel Cannabinoid

- CB2 agonist only
- Provides pain relief equal to opioids in rat studies of neuropathic and inflammatory pain
- No sedative effects

Ibrahim, NM et al, "Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain," *Proceedings of the National Academy of Sciences*, 100(18):10529-33, 2003

Quartilho, A, et al, "Inhibition of inflammatory hyperalgesia by activation of peripheral CB2 cannabinoid receptors," *Anesthesiology, 99(4):955-60, 2003*

Rimonabant (Acomplia)

CB1 Endocannabinoid Receptor Antagonist

- 20 pound weight loss after 2 years treatment
  (Those switched to placebo during year two regained their weight)
- Smoking cessation aid (36% vs 20% 10 week success rate) with less weight gain (subjects who successfully quit smoking without rimonabant gained 84% more weight)
- 1 in 8 stopped due to side effects: nausea, diarrhea, depression, dizziness, anxiety, and amnesia

Sativex Spray

- **Nabiximols** (USAN,[1] trade name **Sativex**) is a patented cannabinoid oromucosal mouth spray developed by the UK companyGW Pharmaceuticals for multiple sclerosis (MS) patients, who can use it to alleviate neuropathic pain, spasticity, overactive bladder, and other symptoms.[2] Nabiximols is distinct from all other pharmaceutically produced cannabinoids currently available because it is a mixture of compounds derived from *Cannabis* plants, rather than a mono-molecular synthetic product. The drug is a pharmaceutical product standardised in composition, formulation, and dose, although it is still effectively a tincture of the cannabis plant. Its principal active cannabinoid components are the cannabinoids: tetrahydrocannabinol (THC) and cannabidiol(CBD). The product is formulated as an oromucosal spray which is administered by spraying into the mouth. Each spray delivers a near 1:1 ratio of CBD to THC, with a fixed dose of 2.7 mg THC and 2.5 mg CBD. Nabiximols is also being developed in Phase III trials as a potential treatment to alleviate pain due to cancer. It has also been researched in various models of peripheral and central neuropathic pain.

Synthetic Cannabinoids – The Top Ten

- Dronabinol (Marinol) nausea, vomiting, anorexia; Schedule III
- Nabilone (Cesamet) Schedule II
- Sativex Oral Spray (GW pharmaceuticals) Neuropathic pain (outside US) contains THC and CBD natural extracts from plant
- Rimonabant(sanofi- Aventis) CB1 inverse agonist; smoking cessation; obesity
- Dexanabinol (Solvay , Acquired by Abbott) Synthetic cannabinoid use after cardiac surgery, regain memory, use after TBI
- Ajulemic Acid (Indevus Pharmaceuticals), antiinflammatory, neuropathic pain
- Cannabinor (pharmos)- CB2 receptor agonist – antiinflammatory, neuropathic pain
- Taranabant (Merck) CB1 inverse agonist, suppresses appetitie
- HU 308 (Pharmos) Brain CB2 agonist – Hypertension; antiinflammatory
- HU 331 (Cayman Chemical) Central CB1, peripheral CB2, and non CB receptor pharmacology; memory, weight loss, appetite

Medical Cannabis States

Cannabis Addiction/Dependence

The Question of Marijuana Addiction

"There is no question marijuana can be addictive; that argument is over. The most important thing right now is to understand the vulnerability of young, developing brains to these increased concentrations of cannabis"

Dr. Nora Volkow, NIDA Director, *Los Angelos Times, 4/26/04*

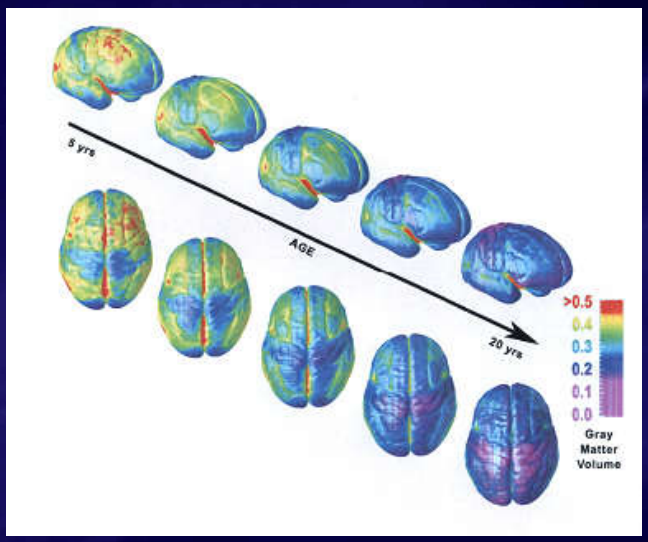
Rates of Cannabis Dependence

- 10% for anyone 18 years and older who ever experiments
- 27 % for age< 18
- 9 % for age> 18
- 3 times more likely to lead to dependency for those who first smoke before 18 years old

Why are dependence rates different

- Brain continues to grow up until age 24 (Prefrontal area development)
- Executive decision making functions not fully developed
- During puberty endocannabanoid system changes
- Exposure to exogenous cannabinoids during adolescence has been to alter neural systems (endorphin, glutamate, GABA, serotonin, catecholamines)

Brain matures from posterior to anterior



Early Reactions to Cannabis Predict Later Dependence

- Positive Subjective Responses:
  - Got Really High
  - Felt Happy
  - Felt Relaxed
  - Did Silly Things
  - Laughed a Lot
- 5 Positive responses to initial marijuana use increased odds of later dependence by 28.5 times
- Negative responses were unrelated to later dependence:
  - Felt ill, dizzy
  - Felt Frightened
  - Passed Out

- Fergusson, et al., *Archives of General Psychiatry*, Vol. 60, October 2003 pp. 1033-1039

Cannabis Withdrawal Syndrome Criteria
(Common Symptoms)

- Anger or Aggression
- Decreased Appetite / Wt. Loss
- Irritability
- Nervousness / Anxiety
- Restlessness
- Sleep Difficulties / Strange Dreams

- Alan Budney, et. al., "Review of the Validity and Significance of Cannabis Withdrawal Syndrome," *Am. J. Psychiatry*, 161:11, November, 2004, pp. 1967-77

Special Risks for Adolescents
Seduction vs. Addiction

- Marijuana as self medication (esp. with ADHD)
- Marijuana as a vehicle for independence and affiliation
- Marijuana are an antidote to boredom
- Marijuana as a palliative to the demands of adolescent development

Cannabis and Cognition

- "The weight of the available evidence suggests that long-term heavy use of cannabis does not produce any severe or grossly debilitating impairment of cognitive function."

Nadia Solowij, *Cannabis and Cognitive Functioning*, Cambridge University Press, 1998

Cannabis and Cognition, cont.

- "Nonetheless, studies indicate that the long-term use of cannabis may produce subtle cognitive impairment in the higher cognitive functions of memory, attention and the organization and integration of complex information." – after as little as 3-5 years of use
- Longer duration of use decreases ability to reject complex irrelevant information (large processing negativity, PN, at an early stage of processing = difficulty focusing attn)
- Greater frequency of use slows detection and use of relevant stimuli (delayed P300) = decreased executive function
- "Preliminary work suggests that there may be only partial recovery of function."
- Impairments only demonstrated under full scale IQ of ~120

Nadia Solowij, *Cannabis and Cognitive Functioning*, Cambridge University Press, 1998

Cannabis and Psychosis

- Cannabis use is associated with a dose dependent increased risk of developing schizophrenia

  Zammit et al, "Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study," BMJ, 2002 November 23; 325 (7374): 1199

- There is a strong association between use of cannabis and earlier age at first psychotic episode in male schizophrenics.

  Veen et al, "Cannabis Use and Age at Onset of Schizophrenia," *Am J Psychiatry* 2004; 161:501-505

Castle and Murray, Ed. *Marijuana and Madness, Cambridge Univ. Press, 2004*

High Risk Populations

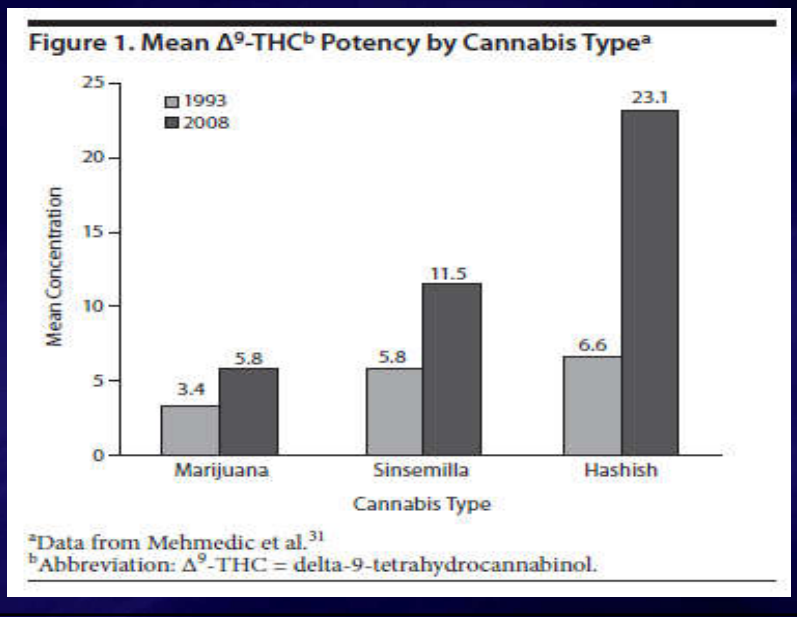
- Children and Adolescents
- The Fetus
- Pre-existing Chemical Dependence and Family History + for CD
- Pre-existing or latent Psychiatric Illness

Pregnancy

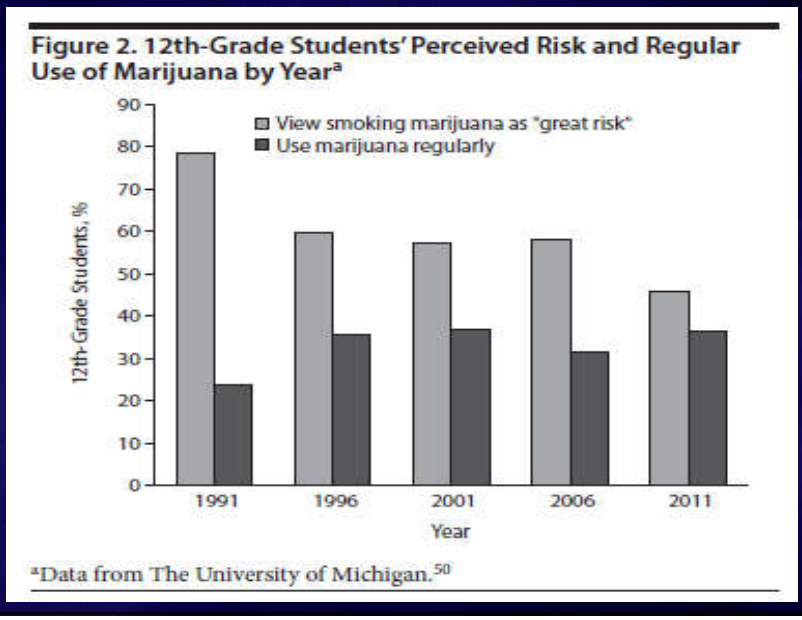
There is no known safe dose of cannabis during pregnancy. Smoking marijuana causes the same problems as smoking tobacco (prematurity and low birth weight).

The Effects of Chronic Marijuana Use

Today's Pot is not your father's Pot



Perception is Realty



Safety studies

- **Marijuana carry-over effects on aircraft pilot performance.**Leirer VO[1], Yesavage JA, Morrow DGAviat Space Environ Med. 1991 Mar;62(3):221-7.. The results support our preliminary study and suggest that very complex human/machine performance can be impaired as long as 24 h after smoking a moderate social dose of marijuana, and that the user may be unaware of the drug's influence.
- HUMAN PSYCHOPHARMACOLOGY Hum. Psychopharmacol. Clin. Exp. 15, 551±558 (2000) Marijuana, Alcohol and Actual Driving Performance J. G. RAMAEKERS*, H. W. J. ROBBE AND J. F. O'HANLON Low doses of THC moderately impair driving performance when given alone but severely impair driving performance in combination with a low dose of alcohol
- 29 March 2006Clinical Research High-Potency Marijuana Impairs Executive Function and Inhibitory Motor Control Johannes G Ramaekers[1], **These data suggest that high potency marijuana consistently impairs executive function and motor control. Use of higher doses of THC in controlled studies may offer a reliable indication of THC induced impairment as compared to lower doses of THC that have traditionally been used in performance studies.**

Schizophrenia

- Connection with cannabis use and schizophrenia outcomes, esp. adolescent users
- Schizophrenia affects 2.4 million Americans
- Typical onset between 18 and 25 years
- Schizophrenia is highly heritable, about 80% of the liability is attributable to genetic factors

Genetic Predisposition

- Evidence suggests that having a family history of schizophrenia, “psychosis prone”, or paranoid personality disorder increases risk
- Caspi et al. in 2005 that carriers of the MET allele of the COMT gene were especially likely to develop psychosis if they used in adolescence
- More recent, AKT1 gene interacts with cannabis in provoking psychosis

Heavy Cannabis Use in Adolescents

- Early, heavy cannabis use seems to be associated with the greatest risk for developing schizophrenia
- About 9% of people who use cannabis become addicted
- Early cannabis use does appear to predispose people to a greater risk for psychosis than later risk

Early Use and Psychosis

- 25 year longitudinal study by Fergusson et al studied 1,055 participants at ages 18, 21, and 25.
- The researchers found that cannabis users at age 18 had higher rates of psychotic symptoms than nonusers at 21 and 25 years, reverse not true
- Causality suggested from cannabis use to psychotic symptoms

Worsens Psychoses Symptoms

- 4 year follow-up study of patients (Grech et al., 2005) with recent onset of psychosis, those who stopped using cannabis had fewer positive symptoms and less continuous illness course; negative symptoms not different
- Another study (Gonzales-Pinto et al., 2011) - reduction in negative symptoms and a better functional outcome over 8 years for those with first-episode psychosis who stopped using cannabis vs. those with continued use

Bipolar and Cannabis

- As in schizophrenia, prevalence of substance use is high with cannabis as the most commonly used substance
- Recent evidence suggests a causal role with cannabis use and onset of bipolar disorder
- Studies have indicated a relationship between cannabis use and earlier onsets in bipolar I and II with and without psychosis

Bipolar and Cannabis

- Lagerberg and al. study hypothesize that:
  - Cannabis use is associated with earlier onsets of both hypo(manic)/mixed and depressive episodes in bipolar disorder
  - There is an inverse dose-response relationship between cannabis use and age at onset (i.e. higher level of cannabis use, lower age at onset)
  - This association is not limited to psychotic bipolar disorder

Bipolar and Cannabis

- There was a significant association indicating a dose-response relationship between cannabis use and age at onset
- The relationship remained statistically significant when controlling for possible confounders
- There were no interaction effects between cannabis use and presenting polarity or presence of psychosis
- Doses of cannabis used may affect the age at onset of bipolar disorder

Cannabis Use and age at onset

- Decrease in age at onset of bipolar illness
  - 23.2 years (+/- 9.7) for patients who never used cannabis or used < 10 times during one month lifetime
  - 20.5 years (+/- 7.3) for patients who used > 10 times during one month lifetime
  - 18.6 years (+/- 5.0) for patients with a lifetime cannabis use disorder (abuse or dependence)

Cannabis and Driving

- Alcohol and cannabis are the 2 most commonly used psychoactive drugs, often used in combination
- According to recent studies (Drummer et al., 2004) the number drivers being killed or injured with THC in their blood stream is increasing
- Accident culpability of drivers increased with rising THC in blood when detected in combination with ETOH (Drummer et al.)

Cannabis and Driving

- In controlled studies of cognitive performance and mood, interaction between drugs have shown mostly an additive effect (Bramness et al., 2010; Ramaekers et al., 2004)
- Specific to driving, performance has generally been found to affected by THC and ETOH consumption in a dose-dependent manner (Berghaus et al., 1995)
- Reaction time, tracking, psychomotor skills, visual functions, attention

Cannabis and Driving

- Various authors suggest that individual's history of cannabis use may influence the subjective effects after consumption
- Several studies have suggested the effect of THC consumption on driving may be greater for non-regular users of THC than for regular users (Wright and Terry, 2002, Papafotiou, 2001)
- Several studies indicate that driving-related psychomotor skills may be less impaired for regular THC users than non-regular users following consumption of THC and/or alcohol

Cannabis and Driving

Fed study: Booze impact greater than pot on driving

By René Marsh, CNN transportation and government regulation correspondent
Updated 9:07 AM ET, Thu June 25, 2015

(CNN)A new study, funded in part by the federal government, suggests alcohol has a more extreme impact on drivers than marijuana.

Researchers said alcohol "significantly increased lane departures/minimum and maximum lateral acceleration; these measures were not sensitive to cannabis." Researchers also concluded Cannabis-influenced drivers "may attempt to drive more cautiously to compensate for impairing effects, whereas alcohol-influenced drivers often underestimate their impairment and take more risk."

Results

- Driving simulator performance significantly compromised in the THC and alcohol combined conditions, esp. for night-time conditions.
- Addition of alcohol to both the low and high doses of THC produced additive decrement in driving impairment scores of 21% (low) and 17% (high)
- Generally, regular users displayed more driving errors than non-regular users
- Blood results of study show that level of THC detected in blood is higher after the consumption of THC in combo with ETOH than THC without (consistent with past studies)

Results

- Results reveal that under the influence of THC, many driving errors are observed whether alcohol is present or not (similar to previous project, Papafotiou et al.)
- Study supports previous studies that show THC:
  - Impairs car control
  - Increases the standard deviation of the lateral position of a vehicle
  - Impairs tracking ability
  - Increases the number of sideway movements of a vehicle and percentage of time outside of a lane

Neurocognitive Decline

- Meier et al. 2012 study done to:
  - test association between persistent cannabis use and neuropsychological decline
  - Determine if decline is concentrated among adolescent-onset users
- Prospective study of a birth cohort of 1037 individuals followed from birth to age 38.
- Neuropsychological testing done at age 13 (prior to onset of cannabis) and again at age 38 after a pattern of persistent cannabis use developed

Neurocognitive Decline

- Persistent cannabis use associated with neuropsychological decline broadly across all domains of functioning
- Informants reported more noticing more cognitive problems for persistent cannabis users
- Impairment was concentrated among adolescent-onset cannabis users-more persistent use associated with greater decline
- Cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset users

Evidence of Cognitive Decline

- Study members with more persistent cannabis dependence (up to 3 or more diagnoses of dependence over the assessments) showed greater IQ decline with -0.38 SD units corresponding to a loss of 6 IQ points.
- Adolescent-onset users tended to become more persistent users with greater use showing more significant IQ decline. Adult-onset users did not show IQ decline with persistent use.
- Authors concluded that persistent marijuana use over 20 years was associated with neurocognitive decline in adolescent onset users

Educational Achievement

- Early use more damaging than later onset of use
- Lower GPA's, negative attitudes toward, and reduced satisfaction with school, increased absenteeism, expulsions, suspensions, dropouts and unemployment
- Those who have smoked more than 100 times:
  - Rates of leaving school - 5.8 times higher
  - Rates of entering college - 3.3 times lower
  - Rates of college degree - 4.5 time lower

Fergusson, Horwood and Beutrais: "Cannabis and educational achievement," *Addiction*, 98, 1681-1693, 2003

Developmental Vulnerability

- Adolescent onset users diagnosed before age 18 tended to become more persistent users
- After comparing adolescent and adult-onset users on total number of cannabis-dependence diagnoses, adolescent-onset users showed greater IQ decline
- Adult-onset cannabis users did not appear to experience IQ decline as a function of persistence cannabis use

Developmental Vulnerability

- Examined the cessation effect separately within adolescent and adult-onset cannabis users
- Among adolescent-onset persistent users, within-person IQ decline was apparent whether cannabis was used infrequently or frequently in the year before testing
- Within IQ decline was not apparent among adult-onset persistent cannabis users who used cannabis infrequently or frequently in the year before testing

Regulatory

Florida Legislation – Medical Marijuana

- Constitutional amendment
- Medical marijuana bill "Charlotte's Web"
  - HB 843
  - SB 1030
  - Must have 0.8 % or less of THC and 10% or more of CBD
  - Non smoked form
  - Terminal Illness (can use any cannabis not just low THC)
  - FL statute 893.02 (3)
    - "Cannabis" means all parts of any plant of the genus *Cannabis*, whether growing or not; the seeds thereof; the resin extracted from any part of the plant; and every compound, manufacture, salt, derivative, mixture, or preparation of the plant or its seeds or resin. The term does not include "low-THC cannabis," as defined in s. 381.986, if manufactured, possessed, sold, purchased, delivered, distributed, or dispensed, in conformance with s. 381.986.

Current FL legislation

- Must register with DOH dept. compassionate use
- Must be certified by online course by FMA
- Must be treating patient for 90 days PRIOR to ordering low THC high CBD cannabis
- Must have failed all other options
- Informed consent must state that tx is experimental and NOT covered by insurance

Florida Constitutional Amendment

- Allows medical use of marijuana for individuals with debilitating medical conditions as determined by a licensed Florida physician. Allows caregivers to assist patients' medical use of marijuana. The Department of Health shall register and regulate centers that produce and distribute marijuana for medical purposes and shall issue identification cards to patients and caregivers. Applies only to Florida law. Does not immunize violations of federal law or any non-medical use, possession or production of marijuana.
- "Debilitating Medical Condition" means cancer, epilepsy, glaucoma, positive status for human immunodeficiency virus (HIV), acquired immune deficiency syndrome (AIDS), post-traumatic stress disorder (PTSD), amyotrophic lateral sclerosis (ALS), Crohn's disease, Parkinson's disease, multiple sclerosis, or other debilitating medical conditions of the same kind or class as or comparable to those enumerated, and for which a physician believes that the medical use of marijuana would likely outweigh the potential health risks for a patient.
- "Marijuana" has the meaning given cannabis in Section 893.02(3), Florida Statutes (2014), and, in addition, "Low-THC cannabis" as defined in Section 381.986(1)(b), Florida Statutes (2014), shall also be included in the meaning of the term "marijuana."

2002 9th circuit court of appeals

- Upheld a permanent injunction enjoining the government from revoking a physician's license to prescribe controlled substances based solely on the physician's professional recommendation of the use of medical marijuana, and also from conducting an investigation of a physician based on the same impermissible motive.
- Court recognized "physician speech is entitled to first amendment protection because of the doctor-patient relationship"
- "only that the government may not initiate an investigation of a physician solely on the basis of a recommendation of marijuana within a bona fide doctor-patient relationship, unless the government in good faith believes it has substantial evidence of criminal conduct."

2002 9th circuit court of appeals

The court found that the Physician's recommendation itself was not illegal conduct, but noted that "if, in making the recommendation, the Physician intends for the patient to use it as the means for obtaining marijuana, as a prescription is used as a means for a patient to obtain a controlled substance, then a Physician would be guilty of aiding and abetting the violation of Federal law."

2002 9th circuit court of appeals

- Both California's compassionate use act and Florida's act require the involvement of the Physician before a patient is able to legally (under state) law procure cannabis.
- Instead, the requirement is a three months doctor-patient relationship prior to the procurement or ordering of medical cannabis.
- The ninth circuit court opinion affords California Physicians a measure of protection from federal prosecution and investigation because the California statute only requires a "recommendation" from a Physician, not a prescription.
- Florida's act requires a Physician "order" in order for the patient to obtain low-THC cannabis

Memorandum: Deputy Attorney General David Ogden; October 19, 2009

- The memorandum provides clarification to federal prosecutors in States that have enacted medical cannabis use.
- Prosecution of illegal drug trafficking and manufacturing is a priority for the DOJ. However, there should NOT be focus on individuals whose actions are in clear and unambiguous compliance with existing state laws.
- The following represent clear non-compliance with state laws:
  - Unlawful possession of unlawful use of firearms
  - Violence
  - Sales to minors
  - Financial and marketing activities inconsistent with the terms, conditions, or purposes of state law, including evidence of money laundering activity and slash or financial gains were excessive amounts of cash and inconsistent with the purported compliance with state or local law
  - Amounts of marijuana inconsistent with purported compliance with state or local law
  - Illegal possession or sale of other controlled substances
  - Ties to other criminal enterprises

Ogden memorandum continued

- The memorandum makes it clear that the Atty. General's office is specifically NOT doing the following
  - Legalizing marijuana or providing legal defense to a violation of Federal law
  - Creating any privileges, benefits, or rights, substance use or procedural, enforceable by any individual, party or witness in any administrative, civil, or criminal matter
  - Creating a legal defense to a violation of the controlled substances act
  - Precluding an investigation were prosecutions where there is reasonable basis to believe that compliance with state law is being invoked as a pretext for the production or distribution of marijuana for purposes not authorized by state law
  - Precluding an investigation or prosecution, even when there is clear and unambiguous compliance with existing state law, in particular circumstances where investigation or prosecution otherwise search important Federal interests.

DEA position statement on marijuana

Marijuana is properly categorized under schedule 1 of the controlled substances act (CSA), 21 USC 801, Et.SEQ. *The clear weight of the currently available evidence supports this classification, including evidence that smoked marijuana as a high potential for abuse, as no excepted medicinal value in treatment in the United States, and evidence that there is a general lack of accepted safety for its use even under medical supervision.*

DEA

"while some people have interpreted these guidelines to mean that the Federal government as relaxed its policy on "medical" marijuana, that is not the case. Investigations and prosecutions of violations our state and Federal law will continue."

DEA targets doctors linked to medical marijuana

By Kay Lazar and Shelley Murphy GLOBE STAFF JUNE 06, 2014

US Drug Enforcement Administration investigators have visited the homes and offices of Massachusetts physicians involved with medical marijuana dispensaries and delivered an ultimatum: sever all ties to marijuana companies, or relinquish federal licenses to prescribe certain medications, according to several physicians and their attorneys

The Cole Memorandum: 2/14/2014

- The DOJ on 8/29/2013 issued guidance of several prosecutors concerning marijuana enforcement under the CSA
- Prosecution would commence against the following
  - Preventing the distribution of marijuana to minors
  - Presenting revenue from the sale of marijuana from going to criminal enterprises, gangs, and cartels
  - Preventing the diversion of marijuana from states where it is legal under state law in some form to other states
  - Presenting state-authorized marijuana activity from being used as a cover or pretext for the trafficking of other illegal drugs or other illegal activity
  - Preventing violence and the use of firearms and the cultivation and distribution of marijuana
  - Preventing drunk driving and the exacerbation of other adverse public health consequences associated with marijuana use
  - Preventing the growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands
  - Preventing marijuana possession or used on Federal property

Cole Memorandum

- Financial transactions involving proceeds generated by marijuana-related conduct 10 former a basis for prosecution under the money laundering statutes.
- Transactions by or three money transmitting business involving climbs “derives from” marijuana-related on top can also serve as a predicate for prosecution under 18 USC 1960.
- The DOJ is committed to using its limited investigative and prosecutorial resources to address the most significant marijuana-related cases.
- For example, if a financial institution or individual provides banking services to a marijuana-related business knowing that the business is diverting marijuana from a state where marijuana sales are regulated to one is where such sales or illegal under state law, or is being used by a criminal organization to conduct financial transactions or its criminal goals, such as the concealment of funds derived from other illegal activity or the use of marijuana proceeds to support other illegal activity

Medical Marijuana and taxes

- Marijuana Legalization and Taxes: The Impact of Section 280E
  - 26 U.S.C. § 280E denies the deduction of business expenses to those selling drugs on Schedules I and II of the Controlled Substances Act
  - Section 280E singles out legal marijuana retailers for a significantly higher income tax burden relative to other types of legal businesses
  - Section 280E causes hugely disproportionate tax bills for these businesses authorized by state law but treated as criminal by the IRS.
  - Section 280E was not written with state-legal marijuana in mind, and modernizing
  - it would restore neutrality to the tax code and level the playing field.
  - Congress has several options for modernizing Section 280E

More Federal Actions

- Medical Marijuana in Omnibus bill section 538:
  - None of the funds made available in this Act to the Department of Ju□ tice may be u□ed, with respect to the states of Alabama, Alaska, Arizona,California, [every other medical marijuana state], to prevent such states from implementing their own state laws that authorize the use, distribution, possession, or cultivation of medical marijuana.
- Major victory for marijuana dispensary in federal court

By David Downs on October 19, 2015 at 7:23 PM

  - United States District Judge Charles R. Breyer ordered the lifting of an injunction against oneof California's oldest lawful dispensaries, the Marin Alliance for Medical Marijuana.
    Judge Breyer ruled t hat newly enacted Congressional law — the RohrabacherFarr Amendment — prevents the government from prosecuting the Fairfaxbased Marin Alliance for Medical Marijuana, and its founder Lynette Shaw

Nevada Board of Medical Examiners

- " participating as a shareholder, officer or managing member of any medical marijuana cultivation facility, dispensary or other establishment or entity authorized under (see Nevada law) currently a violation a Federal law under the controlled substances act, 28 USC 801 et a seq., because marijuana:
  - Is classified as a schedule 1 drug
  - Has not been fully evaluated an approved by the food and drug administration for medicinal purposes, i.e. contraindications, dosages, potency, quantity and side-effects
  - Lacks accepted safety standards for use
  - As a high potential for abuse of

Summary

- There is some but limited evidence that cannabis has some additional benefit
- There is abundant evidence that cannabis has addictive properties and has a disproportionate effect on the use, specifically under age 18
- Cannabis is a schedule 1 of substance and is considered an illegal substance per Federal law
- Physicians violate Federal law when writing an order for medical cannabis. They can be prosecuted
- Physicians who serve as a medical director for a dispensing organization will probably NOT be investigated or prosecuted , by may receive unwelcome attention from the DEA.
- Physicians should be "safe from prosecution" if they meticulously follow state law
- Per Federal memoranda, medical cannabis businesses CANNOT use banking or other traditional forms of transactions
- Cannabis growers can be prosecuted under Federal Law for growing and dispensing cannabis

Summary

- Cannabinoids may have medicinal and beneficial effects
- SMOKING MARIJUANA IS BAD!!!
- The adolescent brain is susceptible to significant negative effects of marijuana
- Cannabidiol is NONEUPHORIGENIC
- Marijuana demonstrates neurocognitive effects in young persons which may be irreversible
- Dependency is 3 X greater < 18 years

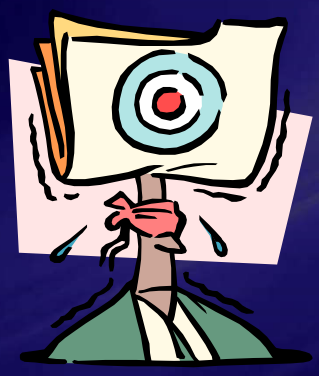
American Medical Marijuana Physicians Association

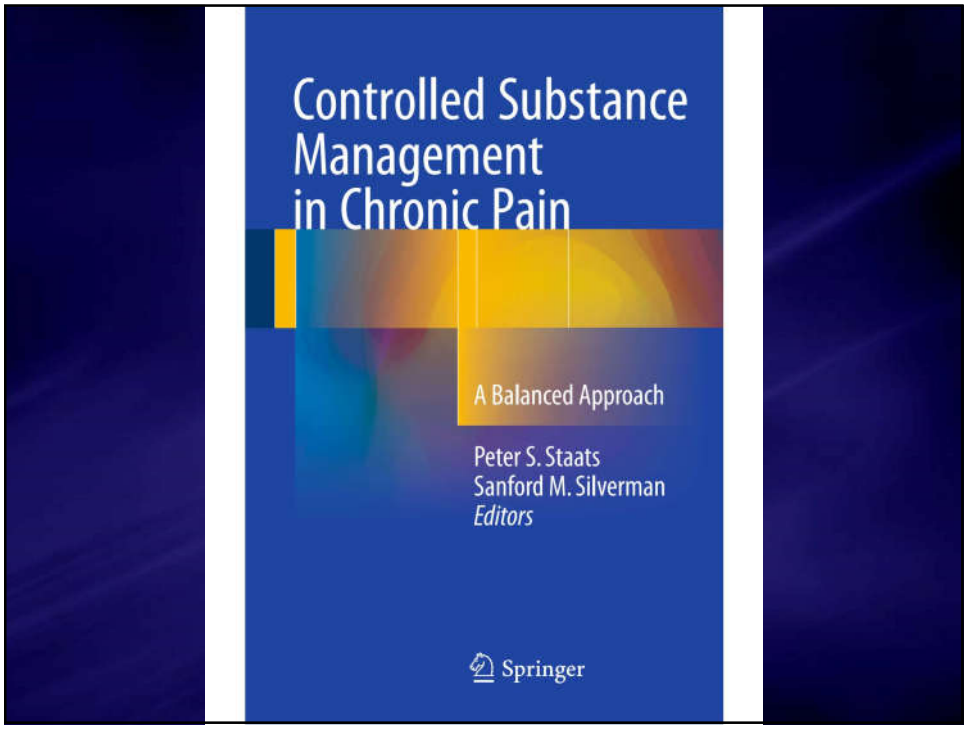
http://ammpa.net

Thank You

Sanford M. Silverman, MD
Comprehensive Pain Medicine
100 East Sample Rd, Suite 200
Pompano Beach, Florida 33064
Phone: 954-545-0106

Questions & Discussion




Controlled Substance Management in Chronic Pain
A Balanced Approach
Peter S. Staats
Sanford M. Silverman
Editors
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