Welcome to the 2-Hour Medical Cannabis Certification Course ESA102
Hosted by Cannabis Expertise

CANNABIS EXPERTISE

EXTRA STEP integr8 1

CANNABIS EXPERTISE

This course is a national accredited CME event for Healthcare Professionals. For Ohio Healthcare Providers, to be certified to recommend medical marijuana to patients, all applicants must hold an active, unrestricted MD or DO license from the State Medical Board of Ohio. Additionally, applicants will need to complete at least two hours of continuing medical education that will assist in diagnosing qualifying conditions, treating those conditions with medical marijuana and possible drug interactions. The contents of this course is designed to assist Physicians per Ohio Revised Code Section 4731.301 Certificate to Recommend Medical Use of Marijuana

EXTRA STEP integr8 2

Break: *Please take this time to submit questions*

CANNABIS EXPERTISE

Break: *Please take this time to submit questions*

Questions are Welcome and we will have a question and answer period at the end of the Medical slides.

Please submit all questions through the Chat (chat) functionality at the top, right hand side of your webinar window and our team will make sure they get answered.
**If Attending a live event please utilize the Q&A form found on your table, Cannabis Expertise Staff will collect at the Break.*

EXTRA STEP integr8 3

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Speaker Information

- Background
- Disclosure
- Information

EXTRA STEP integr8 4

Overview

- Brief history of medical cannabis
- Endocannabinoid physiology
- Cannabinoid pharmacology
- Recommending cannabis as a medicine: dosing and delivery
- Toxicology, side effects, addiction potential
- Clinical indications: Pain, opioid addiction, PTSD

EXTRA STEP integr8 5

Medical Cannabis History

EXTRA STEP integr8 6

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Emperor Shên-Nung
Pên-tsao Ching, 2700 BCE

Ma Fen [Herba Cannabis Sativae] is acrid and balanced. ---Taking much of it may make one behold ghosts and frenetically run about. Protracted taking may enable one to communicate with the spirit light and make the body light. --- It mainly supplements the center and boosts the qi. **Protracted taking may make one fat, strong, and never senile.**

Shou-zhong, Y. 1997. The divine farmer's materia medica: A translation of the *Shen Nong Ben Cao Jing.* Boulder, CO: Blue Poppy Press.

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William O'Shaughnessy, 1839

ON THE PREPARATIONS
OF THE
INDIAN HEMP, OR GUNJAH

The narcotic effects of Hemp are popularly known in the south of Africa, South America, Turkey, Egypt, Asia Minor, India, and the adjacent territories of the Malays, Burmese, and Siamese. In all these countries Hemp is used in various forms, by the dissipated and depraved, as the ready agent of a pleasing intoxication. In the popular medicine of these nations, we find it extensively employed for a multitude of affections. But in Western Europe, its use either as a stimulant or as a remedy, is equally unknown. With the exception of the trial, as a *bolus*, of the Egyptian "Hasheesh," by a few youths in Marseilles, and of the clinical use of the wine of Hemp by Mahncmann, as shewn in a subsequent extract, I have been unable to trace any notice of the employment of this drug in Europe.

Much difference of opinion exists on the question, whether the Hemp so abundant in Europe, even in

Irish physician stationed in India, introduced medical cannabis to England

8

William B. O'Shaughnessy, 1839

Hudson Benjamin, Christies Images, 1999.

O'Shaughnessy essayed Indian hemp in three cases of tetanus, all of whom survived the acute disorder, but with one succumbing to gangrene after refusing amputation. Frequent dosing relaxed spasmodic paroxysms, allowing nutrition/hydration until recovery ensued, sometimes weeks later.

O'Shaughnessy, W. B. (1838-1840). On the preparations of the Indian hemp, or gunjah *(Cannabis indica)*. *Transactions of the Medical and Physical Society of Bengal*, 71-102, 421-461.

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Bernhard Fronmüller

"Of all anaesthetics ever proposed, Indian hemp is the one which produced a narcotism most closely resembling the natural sleep without causing any extraordinary excitement of the vessels, or any particular suspension of secretions, or without fear of a dangerous reaction, and consecutive paralysis."

J. of Materia Medica 2:474, 1860.

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Bernhard Fronmüller

In 1000 patients with sleep disturbance, Indian hemp produced cures in 53%, partial cure in 21.5%, and little or no effects in 25.5%.

Fronmüller, B. 1869. Klinische Studien über die schlafmachende Wirkung der narkotischen Arzneimittel [Clinical studies on the sleep inducing effects of narcotic medicines]. Erlangen.

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Cannabis enters *The Dispensatory of the United States of America* in 1854

Sir William Osler, on migraine:

"*Cannabis indica* is probably the most satisfactory remedy."

The Principles and Practice of Medicine, 1915 12

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Empirical Medicine of the 19th and early 20th Century

EXTRA STEP integr8 13

EXTRA STEP integr8 14

Empirical Medicine of the 19th Century

- Combined morphine, cannabis, and capsicum
- Provided a phyto-opioid, phytocannabinoid, and phytovanilloid in one preparation
- Affected the 3 known endogenous biochemical systems mediating pain: endorphin/enkephalin, endocannabinoid, vanilloid
- Arguably may have provided better outpatient pain relief than is currently available in the 21st century
- 19th century physicians noted ability of cannabis to produce opiate sparing, reduce morbidity, and treat opiate withdrawal

EXTRA STEP integr8 EBR Slide adapted from Ethan Russo w/ permission 15

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Endocannabinoid Physiology

Overview

- Cannabinoid receptors
- Endogenous cannabinoids
- Function and regulation of the endocannabinoid system in various tissues
- Exogenous cannabinoids and their effects on the ECS
- Common drug, herbal, and non-pharmacologic influences on the ECS

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

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Why does one herb help so many different conditions?

The Endocannabinoid System

19

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

Pubmed search results for "endocannabinoid"
1993: 10 citations
2017: 7,969 citations

20

Discovery Of The Endocannabinoid System Has Lagged Behind The Endorphin System

Endorphin system	Endocannabinoid system
4000 BC Sumerians described opiates	2000 BC Chinese described cannabis
1801 morphine isolated from opium	1964 THC isolated from cannabis
1973 opioid receptor	1988 cannabinoid receptor
1976 endogenous opioids - enkephalins, endorphins	1992 endogenous cannabinoids - anandamide, 2-AG

21

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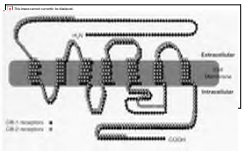
Cannabinoid Receptors

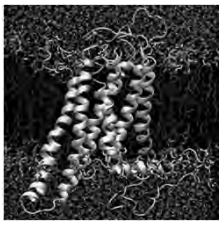
22

The Cannabinoid Receptors: CB1 and CB2

secondary structure



tertiary structure



23

Cannabinoid Receptors

CB1 located in:

- CNS
- Testes, uterus
- Adipose tissue
- Connective tissue
- Endocrine glands
- Exocrine glands
- Leukocytes
- Spleen
- Heart
- GI tract
- Liver

CB2 located in:

- Monocytes
- Macrophages
- B-cells
- T-cells
- Liver
- Spleen
- Tonsils
- CNS
- Enteric nervous system

(reviewed in McPartland, 2008) 24

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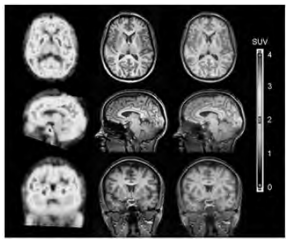
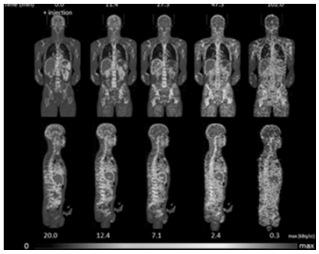
CB1 Receptor Distribution in Human Brain



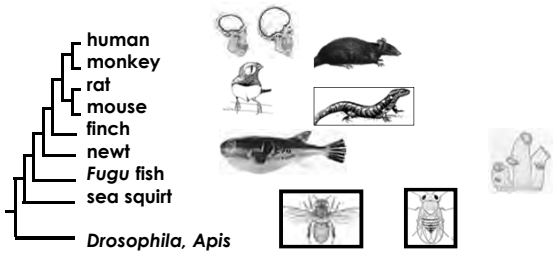
(Terry et al. 2010) 25

CB2 Receptor Distribution



(Ahmad, 2013) 26

CB Receptors Evolved 600 Million Years Ago



McPartland, 2006 27

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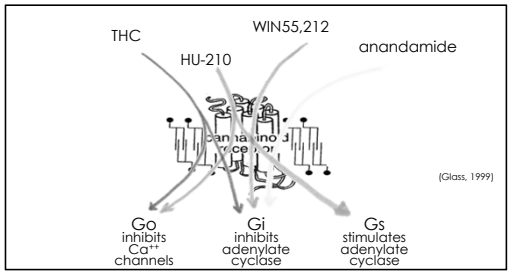
Cannabinoid Receptors Can Activate Different G Protein Subtypes

- G_o –
- G_i –
- G_s –

- Depends on which agonist activates the receptor: "agonist trafficking"
- An assortment of keys opens the same lock, but the door opens into different rooms

(Glass, 1999) 28

Agonist Trafficking



29

Endogenous Cannabinoids

30

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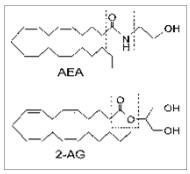
Endogenous Cannabinoid Ligands: The Endocannabinoids

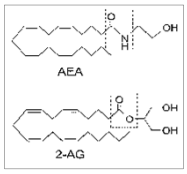


Anandamide (AEA)
Devane, Mechoulam *et al.,* 1992

2-arachidonoylglycerol (2-AG)
Mechoulam *et al.,* 1995
Sugiura *et al.,* 1995

31

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 -> (FAAH)
  - 2-AG -> (MAGL)

(McPArtland, 2008)

32

Other Endocannabinoid Targets

- GPR55 (Ryberg, 2007) (Staton, 2008)
- TRPV1 "capsaicin receptor" (Ross, 2003)
- PPARs: Peroxisome proliferator-activated receptors (O'sullivan, 2007)
- Voltage-gated ion channels
  - Ca2+, Na+, and various types of K+ channels
- Ligand-gated ion channels
  - 5-HT3 and nicotinic ACh receptors. (Oz, 2006)

33

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Endocannabinoid Basics: Summary

- CB1 and CB2 receptors found throughout the body
- Anadamide (AEA) and 2-AG synthesized on-demand for homeostatic functions
- Complex effects of cannabinoids due to agonist trafficking and overlap with other systems

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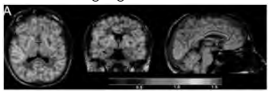
Function And Regulation Of The Endocannabinoid System

- Nervous System
- Connective Tissues
- Immune System
- Neoplasm
- Embryology
- Digestive System
- Hunger and Feeding

EXTRA STEP integr8 35

CB1 Receptor Distribution in CNS

- Most common G protein coupled receptor in the brain
- Highest densities:
  - hippocampus
  - cerebral cortex
  - cerebellum
  - amygdaloid nucleus
  - basal ganglia



- Accounts for effects:
  - short-term memory
  - cognition
  - mood and emotion
  - motor function
  - nociception.
- Virtually absent in brainstem cardiorespiratory centers – no lethal overdose

Glass, 1997
Burns, 2007

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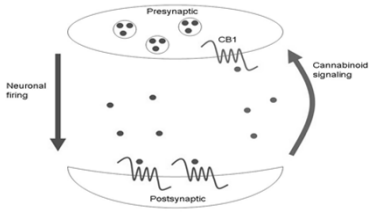
Cannabinoid Activity in the Synapse: Retrograde Signaling

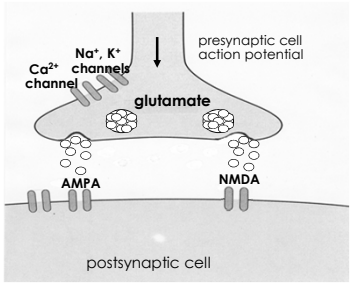


37

Depolarization-Induced Suppression of Excitation

- Action potential from depolarized neuron arrives at axon terminal and opens voltage-gated calcium channels.
- Ca^{2+} influx releases glutamate vesicles, glutamate diffuses across synaptic cleft to activate receptors in postsynaptic cell.

(Wilson & Nicholl, 2002)

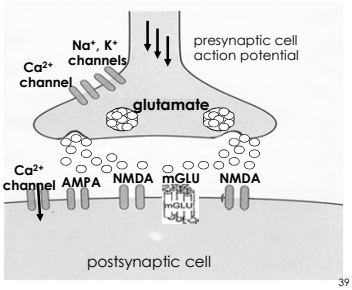


38

Depolarization-Induced Suppression of Excitation

- *Strong stimulus* of presynaptic cell increases glutamate release, which upregulates other glutamate receptors in the post-synaptic cell.
- Upregulated glutamate receptors open Ca^{2+} channels in the post-synaptic cell.

(Wilson & Nicholl, 2002)



39

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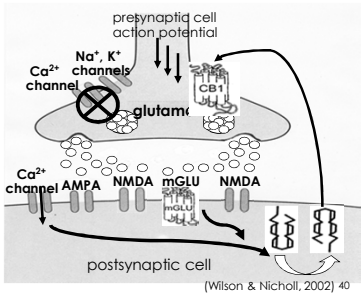
Depolarization-Induced Suppression of Excitation

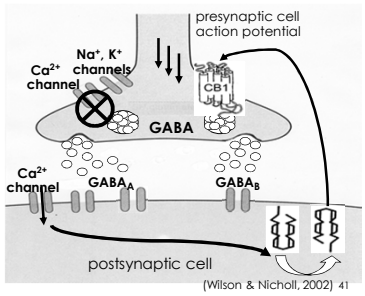
- Ca^{2+} influx into post-synaptic cell stimulates the synthesis and release of 2-AG.
- 2-AG diffuses retrograde to presynaptic CB1, which closes pre-synaptic Ca^{2+} channels and stops vesicle release.



(Wilson & Nicholl, 2002) 40

Depolarization-Induced Suppression of *Inhibition*

- Ca^{2+} influx into post-synaptic cell stimulates the synthesis and release of 2-AG.
- 2-AG diffuses retrograde to presynaptic CB1, which closes pre-synaptic Ca^{2+} channels and stops vesicle release



(Wilson & Nicholl, 2002) 41

Mechanisms By Which Cannabinoids Modulate Neural Plasticity

- Neurogenesis
  - pCREB: phosphorylated cAMP response element-binding protein
  - BDNF: brain-derived neurotrophic factor
- (DSE)
- (DSI)
- (LTP)
- (LTD)

(Fishbein, 2012)
(Lovinger, 2008) 42

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Neural Protection

- AEA and 2-AG are endogenous neuroprotective agents produced by the nervous system upon both chemical and mechanical trauma. (Mechoulam, 2002)
- Δ9-THC, CBD, AEA, 2-AG, and HU-210 all decrease glutamate excitotoxicity. (Baker, 2003)
  - Reduce seizure activity
  - Limit infarct size post-stroke
- Cannabinoids effective at reducing and preventing perinatal brain injury (reviewed in Fernández-López et al., 2013)

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Federal Patent

US006630507B1

(12) **United States Patent**
Hampson et al.

(10) **Patent No.: US 6,630,507 B1**
(45) **Date of Patent: Oct. 7, 2003**

(54) **CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS**

(75) Inventors: **Aidan J. Hampson**, Irvine, CA (US); **Julius Axelrod**, Rockville, MD (US); **Maurizio Grimaldi**, Bethesda, MD (US)

(73) Assignee: **The United States of America as represented by the Department of Health and Human Services**, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/674,028**

(22) PCT Filed: **Apr. 21, 1999**

OTHER PUBLICATIONS

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Mechoulam et al., "A Total Synthesis of d1-Δ1-Tetrahydrocannabinol, the Active Constituent of Hashish*," *Journal of the American Chemical Society*, 87:14:3273–3275 (1965).
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Ottersen et al., "The Crystal and Molecular Structure of Cannabidiol," *Acta Chem. Scand. B 31*, 9:807–812 (1977).
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Turkanis et al., "Electrophysiologic Properties of Cannabinoids," *J. Clin. Pharmacol.*, 21:449S–463S (1981).
Carlini et al., "Hypnotic and Antielpileptic Effects of Can-

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Autonomic Tone

- Sympathetic Nervous System: CB1
  - Inhibits norepinephrine release
  - Dampens sympathetically mediated pain
  - Modulates hypothalamic–pituitary–adrenal (HPA) axis and hypothalamic-locus coeruleus-norepinephrine (HLN) axis
- Parasympathetic Nervous System: CB1
  - Reduces elevated activity

EXTRA STEP integr8 (Pertwee, 2005) 45

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Autonomic Tone – Vascular and Cardiac

- Myocardial CB1 activation:
- Vascular tissue CB1 activation:
- Antihypertensive effects in humans
- Protective role in myocardial ischemia has been suggested in rodent studies.

(Pacher, 2006) 46

Endocannabinoid System and Pain

Pre-clinical models show ECS activation causes antinociceptive effects in
- Acute Pain
- Persistent Inflammatory Pain
- Neuropathic Pain

Cannabimimetic tetrad test:
- Hypomotility
- Catalepsy
- Hypothermia
- **Analgesia**

Guindon, 2009 47

Antinociceptive Effects Of Cannabinoids Involve Many Mechanisms

- Brain
- Spinal Cord
- Peripheral Nervous System

(Guindon, 2009) 48

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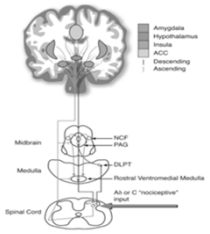
Descending Pain Inhibitory Pathway

- Midbrain
- Rostral ventromedial medulla
- Spinal cord

Cannabinoids suppress GABA-releasing interneurons that inhibit neurons in the descending pathway.



(Walker, 2005) 49

Homeostasis of Activators and Sensitizers

- At the site of an injury, activators and sensitizers cause peripheral sensitization, including hyperalgesia and allodynia.
  - damaged tissue (K+ and H+ ions, bradykinins, adenosine triphosphates)
  - leukocytes (histamines, prostaglandins, leukotrienes, proinflammatory cytokines),
  - leukocyte-activated platelets (5-hydroxytryptamine)
  - neighboring autonomic nerves (norepinephrine)
  - the nociceptor itself (substance P and calcitonin gene-related peptide).
- Peripheral sensitization elicits a homeostatic response by the endocannabinoid system.

(Walker, 2005) 50

Homeostasis of Activators and Sensitizers

Functioning of the endocannabinoid system at the peripheral terminal of the nociceptor provides the "first line of defense against pain."

CB1 signaling
- Decreases the release of activators and sensitizers around the site of tissue injury
- opens K+ channels in the nociceptor cell membrane, so the nerve becomes hyperpolarized and less likely to fire.

CB2 signaling decreases release of activators and sensitizers from neighboring mast cells and macrophages.

(Walker, 2005) 51

Illustration Of A Polymodal C-fiber Nociceptor

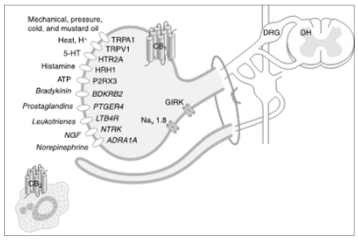
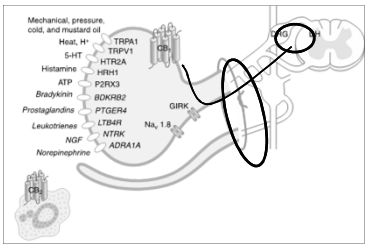
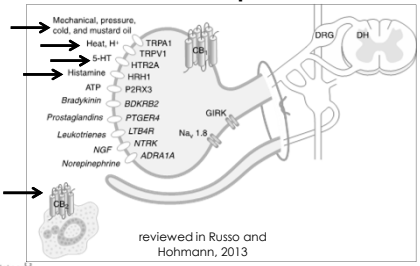


Illustration Of A Polymodal C-fiber Nociceptor



Cannabinoids And Terpenoids In Cannabis Decrease Nociceptor Activators



reviewed in Russo and Hohmann, 2013

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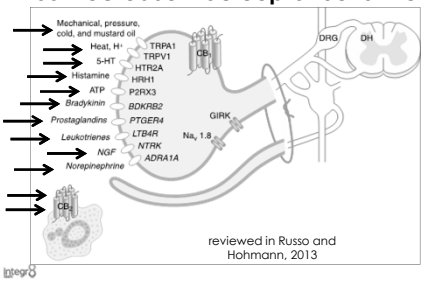
Cannabinoids And Terpenoids In Cannabis Also Decrease Nociceptor Sensitizers



reviewed in Russo and Hohmann, 2013

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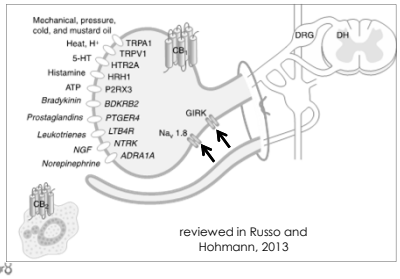
Cannabinoids And Terpenoids In Cannabis Also Hyperpolarize The Nociceptor



reviewed in Russo and Hohmann, 2013

56

Cannabinoid-Opioid Synergy

- Opioid and cannabinoid receptors are both present in pain signaling regions of the brain and spinal cord.
- Opioid and cannabinoid signaling pathways interact with each other.
- Administering cannabinoids with opioids results in
  - Potentiation of anti-nociceptive effect
  - Avoidance of tolerance to the opioid with retention of the antinociceptive effect

reviewed in Cichewicz, 2004 57

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Opioid-sparing Effect of Cannabinoids: A Systematic Review and Meta-analysis

- 17 of 19 pre-clinical studies demonstrated synergistic effects from opioid-cannabinoid co-administration.
- The ED_{50} of morphine administered in combination with THC is 3.6 times lower than the ED_{50} of morphine alone (95% CI 1.95, 6.76; n = 6).
- The ED_{50} for codeine administered in combination with THC was 9.5 times lower than the ED_{50} of codeine alone. (95% CI 1.6, 57.5, n = 2)

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Nielsen et al., 2017 58

Endocannabinoid Neurophysiology Summary

- Retrograde synaptic transmission
- Neuroprotection
- Neuroplasticity
- Autonomic regulation
- Antinociception
- Synergy with opioid system

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59

Dysregulation Of The Endocannabinoid System

EXTRA STEP integr8

60

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Cannabinoid Deficiency Syndromes?

In human studies, ECS deficiencies have been implicated in:

- Schizophrenia
- Migraine
- Multiple sclerosis
- Huntington's
- Parkinson's
- Irritable bowel syndrome
- Anorexia
- Chronic motion sickness
- Fibromyalgia
- Menstrual symptoms

(reviewed in Russo, 2016) 61

Cannabinoid Receptor Polymorphisms

Associated with:

- Schizophrenia Subtypes (Ujike, 2002)
- Alcohol Dependence (Schmidt, 2002)
- Body Mass Index (Gazzerro, 2006)
- Central Obesity (Jaeger, 2008)
- ADHD and PTSD (Lu, 2008)
- Happiness (Matsunaga, 2014)
- Serum lipid profiles (Luis et al., 2016)
- Headache w/ nausea during life stress (Juhasz et al., 2016)
- Response to a Mediterranean hypocaloric diet (de Luis et al., 2016)
- Risk of cyclic vomiting syndrome (Wasilewski et al., 2017)
- Marijuana demand (Aston et al., 2017)

62

Cannabinoid Hyperemesis Syndrome

- Characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and frequent hot bathing.
- Cyclic vomiting syndrome shares several similarities with CHS and the two conditions are often confused.
- Occurs in individuals with long-term high dose cannabis use, onset is years after initiating cannabis use.

Galli, 2011) 63

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Summary

- The ECS is widely distributed throughout the body.
- The primary function of the ECS is cellular homeostasis.
- Our understanding of the ECS is incomplete, emerging, and suggests significant complexity.
- Manipulation of the ECS may provide effective treatment for a wide variety of diseases.

64

"...modulating endocannabinoid system activity may have therapeutic potential

in almost all diseases affecting humans,

including obesity/metabolic syndrome; diabetes and diabetic complications; pain; neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal and skin diseases; psychiatric disorders; cachexia; cancer; and chemotherapy-induced nausea and vomiting, amongst many others."

Pacher, Pál, and George Kunos. "Modulating the endocannabinoid system in human health and disease–successes and failures." *FEBS Journal* 280.9 (2013): 1918-1943.

65

Phytocannabinoid Pharmacology

66

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The Plant *cannabis sativa*

- Herb (female flower): medicinal and spiritual uses
  - Sinsemilla
  - More oils, more potent
- Hemp
  - Fiber (stalk) –
  - Hurd –
  - Seed –

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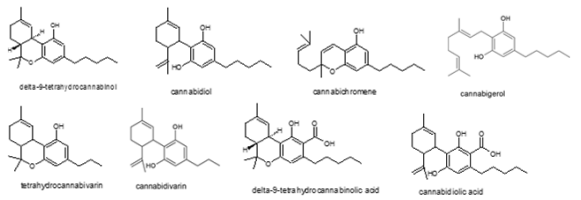
67



Russo and Marcu 2017 Cannabis pharmacology: The usual suspects and a few promising leads. *Adv Pharmacol* (in press).

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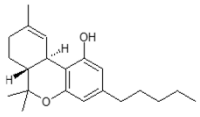
Δ^9-tetrahydrocannabinol (THC)



delta-9-tetrahydrocannabinol

Photo ©BR, courtesy of Bedrocan

- **Isolated and identified 1964** (Gaoni & Mechoulam)
- **K_i=53.3 at CB_1, 75.3 at CB_2** (Felder 1995)
- **Analgesic & antipruritic** (Neff 2002)
- **Bronchodilatory** (Williams 1976)
- **Neuroprotective antioxidant** (Hampson 1998)
- **THC has 20X A-I power of ASA, 2X A-I power of hydrocortisone** (Evans 1991)
- **Muscle relaxant**
- **Antiemetic**
- **Primary psychoactive component**
- THC not a COX-1 or COX-2 inhibitor (Stott 2005)
- ↓ β-amyloid (Eubanks 2006)

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Many Phytocannabinoids Are Non-psychotropic Yet Therapeutic

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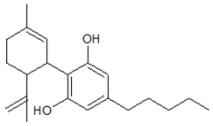
70

Cannabidiol (CBD) I



cannabidiol

GS CBD trichomes Photo: DJP

- Isolated 1940 (Adams), but identified positively in 1963 (Mechoulam & Shvo)
- Hardly binds CB_1, but shows unique ability to antagonize the receptor in low nM range (Thomas 2007)
- Works as a negative allosteric modulator on CB_1 (Laprairie 2015)
- Neuroprotective AO, strongly inhibits glutamate excitotoxicity, also anti-oxidant > Vitamins C and E (Hampson et al. 1998)
- Now known to be a TRPV1 agonist (like AEA) with EC_{50} 3.2-3.5 µM (Bisogno et al. 2001)
- Inhibits uptake of the AEA, and weakly inhibits its hydrolysis (Bisogno et al. 2001)
- Alerting vs. THC in clinic (Nicholson 2004)

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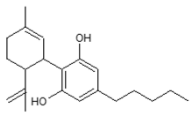
Cannabidiol (CBD) II



cannabidiol

GS CBD trichomes Photo: DJP

- Anticonvulsant (Cunha; Jones 2010)
- Anti-anxiety (Crippa 2011)
- Cytotoxic in breast cancer (IC_{50} 6-10.6 µM) and many other cancer cell lines while being cytopreservative for normal cells (Ligresti 2006)
- Antagonist at GPR55 and GPR18 (McHugh et al. 2010)

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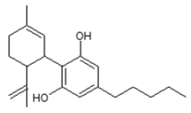
Cannabidiol (CBD) III



cannabidiol

- **Antagonizes tumor necrosis factor alpha (TNF-α) in rodent rheumatoid arthritis (Malfait 2000)**
- Not COX-1 or COX-2 inhibitor (Stott 2005)
- **Displays agonistic activity at 5-HT_{1A} receptor (Russo-Parker 2005), possible basis for observed anxiolysis (Resstel 2009; Soares 2010), CVA reduction (Mishima 2005), nausea (Limebeer 2009), & improvement of cognition in hepatic encephalopathy (Magen 2009).**
- **Enhances adenosine receptor A2A signaling via inhibition of an adenosine transporter (Carrier 2006), suggesting an important therapeutic role in various inflammatory and chronic pain states**
- Prevents prion accumulation and neuronal toxicity (Dirikoc 2007)
- **CBD stimulates bone fracture healing (Kogan 2015)**

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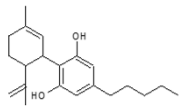
Misconceptions about Cannabidiol (CBD)



cannabidiol

- **A tiny amount is enough (actually more is better)**
- **It is not psychoactive.**
- **It is a sedative (Alerting vs. THC in clinic (Nicholson 2004), and sedation may be operative with high doses, drug-drug interactions or terpenoid effects, i.e., myrcene)**
- **It is "legal in all 50 states"**
- **It turns into THC in the body (Merrick 2016) (Russo 2017) (actually upregulates anandamide/ECS)**

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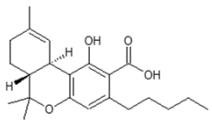
Tetrahydrocannabinolic Acid (THCA)



delta-9-tetrahydrocannabinolic acid

- THC form in fresh, unheated cannabis flowers
- Insecticidal (Sirikantaramas 2005)
- **Anti-inflammatory/anti-TNF-alpha (Verhoeckx 2006)**
- Anticonvulsant in mice only at 200 mg/kg (Karler 1978), but clinical reports in epilepsy (Russo 2016, Sulak 2017) indicate efficacy at much lower dosages
- Has high affinity for CB_1 (Rock 2013), but may be unable to cross the BBB (Moreno-Sanz 2016)
- Increased cell survival and neurite morphology in PD model (Moldzio 2012)
- Reduced N&V reactions in rodents (Rock 2013)

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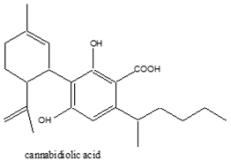
Cannabidiolic Acid (CBDA)



cannabidiolic acid

- Predominant phytocannabinoid in fresh hemp
- Natural herbicide (Shoyama 2008), as long known in retting pond usage
- Produces COX-inhibition at high doses (Takeda 2008)
- **Powerful anti-emetic via 5-HT$_{1A}$ stimulation (Bolognini 2013; Rock 2013)**
- Promising for treating tumors (historical data)

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Synthetic Cannabinoids

- Dronabinol, synthetic THC, approved as schedule II drug in 1986 and moved to schedule III in 1999.
  - 2.5mg, 5mg, 10mg caps
- Nabilone, a synthetic THC analog, approved by the FDA in 1985 as schedule II.
  - 1mg caps, ~2x potency of THC
- Both indicated for chemotherapy-induced nausea/vomiting and as an appetite stimulant for AIDS patients

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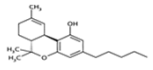
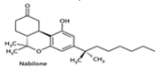
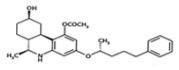
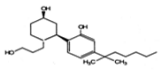
77

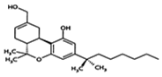
Synthetic Cannabinoids, Some With Ultrapotency

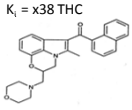

Δ^9-THC
Roxane Labs
K_i CB1 = 41 nM


Nabilone
Eli Lilly
K_i = x1.8 THC


Levonantradol
Pfizer
K_i = x38 THC


CP 55,940
Pfizer
K_i = x44 THC


HU-210
Pharmos
K_i = x600 THC


WIN 55,212-2
Sterling Winthrop
K_i = x1.7 THC

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78

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Pharmacokinetic Properties of THC

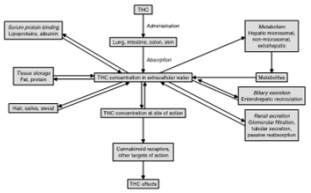

Fig. 4. Pharmacokinetic properties of Δ⁹-tetrahydrocannabinol (THC) [reproduced from Brenneisen[24] with permission].

Grotenhermen, Franjo. "Pharmacokinetics and pharmacodynamics of cannabinoids." Clinical pharmacokinetics 42.4 (2003): 327-360.

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79

Bioavailability of THC

Table III. Systemic bioavailability of Δ⁹-tetrahydrocannabinol (THC)

Subjects	Systemic bioavailability (%)		Formulation	Reference
	average	range		
Oral				
11 frequent or infrequent users	6 ± 3	4–12	THC in chocolate cookie	39
6 men, 6 women	10-20		THC in sesame oil	31
7 men, 10 women	7 ± 3	2–14	THC in sesame oil	41
Inhalational				
9 heavy users	23 ± 6	6–56	Marijuana cigarette	38
9 light users	10 ± 7	2–22	Marijuana cigarette	38
5 heavy users	27 ± 10	16–39	Marijuana cigarette	42
4 light users	14 ± 1	13–14	Marijuana cigarette	42
11 frequent or infrequent users	18 ± 6	8–24	THC in cigarette	39
Rectal				
2 patients with spasticity	190–220% of oral bioavailability		Suppository with THC-hemisuccinate	25

Grotenhermen, Franjo. "Pharmacokinetics and pharmacodynamics of cannabinoids." Clinical pharmacokinetics 42.4 (2003): 327-360.

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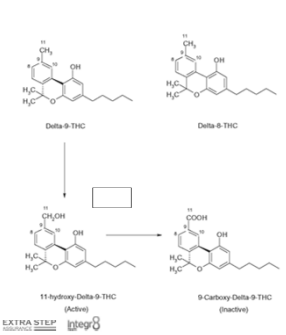
80



Metabolism of THC

- Occurs mainly in the liver by microsomal hydroxylation and oxidation cata-lysed by enzymes of the cytochrome P450 (CYP) complex
- Nearly 100 metabolites have been identified for THC.
- Besides the liver, other tissues are also able to metabolize cannabinoids but to a much lesser degree.

Grotenhermen, Franjo. "Pharmacokinetics and pharmacodynamics of cannabinoids." Clinical pharmacokinetics 42.4 (2003): 327-360.

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81

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Drug Interactions

- CYP450 inhibition (Stout & Cimino, 2013)
  - THC & CBN: 2C9, 3A4
  - CBD: 2C19, 3A4
  - Warfarin, most statins, erythromycin, azole antifungals, clobazam & other AEDs
- Alcohol and benzodiazepines: potentiation of sedation (Grotenhermen, 2003)
- NSAIDs, particularly indomethacin, can partially antagonize some of the effects of THC. (Perez-Reyes et al., 1991; Chen et al., 2013)
- Cholinergic drugs can modulate the effects of cannabis. Anticholinergic drugs may increase psychoactive side effects. (McPartland et al., 2008)

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82

Pharmacokinetic Properties of THC

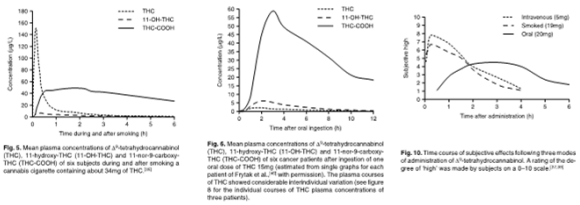

Fig. 5. Mean plasma concentrations of Δ⁹-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) of six subjects during and after smoking a cannabis cigarette containing about 34mg of THC.[30]

Fig. 6. Mean plasma concentrations of Δ⁹-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) of six cancer patients after ingestion of one oral dose of THC 15mg (estimated from single graphs for each patient of Frytak et al.,[34] with permission). The plasma courses of THC showed considerable interindividual variation (see figure 8 for the individual courses of THC plasma concentrations of three patients).

Fig. 10. Time course of subjective effects following three modes of administration of Δ⁹-tetrahydrocannabinol. A rating of the degree of 'high' was made by subjects on a 0–10 scale.[51,84]

Grotenhermen, Franjo. "Pharmacokinetics and pharmacodynamics of cannabinoids." Clinical pharmacokinetics 42.4 (2003): 327-360.

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83

What Are Terpenoids?

- These are aromatic molecules in plants produced in flowers, fruit, leaf and sap.
- They are formed of isoprene (5 carbon) units.
- Terpenes contain only C and H.
- Terpenoids also contain O.
- Monoterpenoids = 10 C (e.g., limonene, pinene)
- Sesquiterpenoids = 15 C (e.g., caryophyllene)
- Diterpenoids = 20 C (e.g., phytol)
- Triterpenoids = 30 C (e.g., friedelin, found in cannabis roots)

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84

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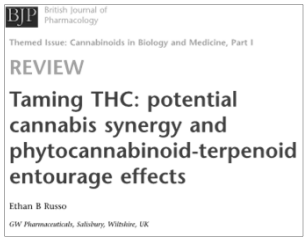
Cannabis Terpenes



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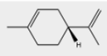
Cannabis Terpenes

Limonene



Lemon

Potent AD/immunostimulant via inhalation (Komori *et al.*, 1995)
Anxiolytic (Carvalho-Freitas and Costa, 2002; Pultrini Ade *et al.*, 2006) via 5-HT$_{1A}$ (Komiya *et al.*, 2006)
Apoptosis of breast cancer cells (Vigushin *et al.*, 1998)
Active against acne bacteria (Kim *et al.*, 2008)
Dermatophytes (Sanguinetti *et al.*, 2007; Singh *et al.*, 2010)
Gastro-oesophageal reflux (Harris, 2010)

α-Pinene

Pine

Anti-inflammatory via PGE-1 (Gil *et al.*, 1989)
Bronchodilatory in humans (Falk *et al.*, 1990)
Acetylcholinesterase inhibitor, aiding memory (Perry *et al.*, 2000)

EXTRA STEP integr8 Russo, 2011 86

β-Myrcene

Hops

Blocks inflammation via PGE-2 (Lorenzetti *et al.*, 1991)
Analgesic, antagonized by naloxone (Rao *et al.*, 1990)
Sedating, muscle relaxant, hypnotic (do Vale *et al.*, 2002)
Blocks hepatic carcinogenesis by aflatoxin (de Oliveira *et al.*, 1997)

Linalool

Lavender

Anti-anxiety (Russo, 2001)
Sedative on inhalation in mice (Buchbauer *et al.*, 1993)
Local anesthetic (Re *et al.*, 2000)
Analgesic via adenosine A$_{1A}$ (Peana *et al.*, 2006)
Anticonvulsant/anti-glutamate (Elisabetsky *et al.*, 1995)
Potent anti-leishmanial (do Socorro *et al.*, 2003)

β-Caryophyllene

Pepper

AI via PGE-1 comparable phenylbutazone (Basile *et al.*, 1988)
Gastric cytoprotective (Tambe *et al.*, 1996)
Anti-malarial (Campbell *et al.*, 1997)
Selective CB$_2$ agonist (100 nM) (Gertsch *et al.*, 2008)
Treatment of pruritus? (Karsak *et al.*, 2007)
Treatment of addiction? (Xi *et al.*, 2010)

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CANNABIS EXPERTISE

We will now take a short break, please submit questions now for the first half of this presentation.

EXTRA STEP integr8 88

Recommending Cannabis as a Medicine: Dosing & Delivery

EXTRA STEP integr8 89

Recommending Cannabis as a Medicine: Dosing and Delivery

- Cannabis dosing
  - Wide range
  - Multiphasic dose-response
  - Widening of therapeutic window
  - Bidirectional effects
  - THC & CBD
  - Acidic Cannabinoids
- Basic dosing strategies
  - cannabis naïve
  - non-psychoactive
  - experienced users
- Drug interactions
- Chemovars

EXTRA STEP integr8 90

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Qualifying Conditions In Ohio

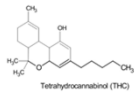
1. AIDS
2. Alzheimer's disease
3. Amyotrophic lateral sclerosis
4. Cancer
5. Chronic traumatic encephalopathy
6. Crohn's disease
7. Epilepsy or another seizure disorder
8. Fibromyalgia
9. Glaucoma
10. Hepatitis C
11. Inflammatory bowel disease
12. Multiple sclerosis
13. Pain (chronic & severe or intractable)
14. Parkinson's disease
15. Positive status for HIV
16. Post-traumatic stress disorder (PTSD)
17. Sickle cell anemia
18. Spinal cord disease or injury
19. Tourette's syndrome
20. Traumatic brain injury (TBI)
21. Ulcerative colitis

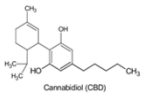
EXTRA STEP integr8 91

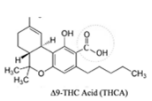
Clinical Dosing Terminology











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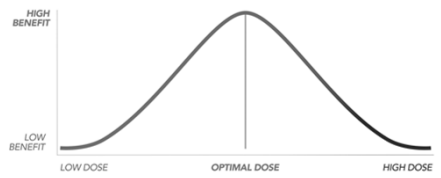
Dosing By The Milligram

Oral dosing range effective in my 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
(Thompson et al., 1974)

EXTRA STEP integr8 93

Biphasic Dose-Response



EXTRA STEP Integr8 94

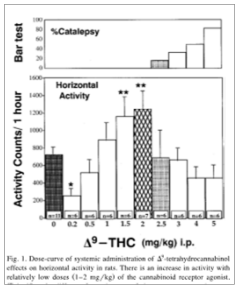


Fig. 1. Dose-curve of systemic administration of Δ9-tetrahydrocannabinol effects on horizontal activity in rats. There is an increase in activity with relatively low doses (1–2 mg/kg) of the cannabinoid receptor agonist.

Multiphasic Dose-Response

Example: THC & Locomotor activity in rats

EXTRA STEP Integr8 (Sañudo-Peña et al, 2000) 95

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)

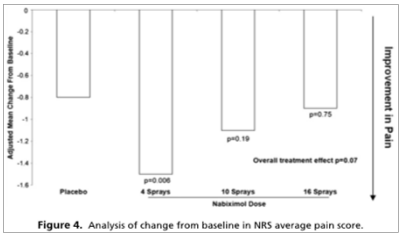


Figure 4. Analysis of change from baseline in NRS average pain score.

EXTRA STEP Integr8 20.8mg 52mg 83.2mg 96

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Widening of Therapeutic Window

- Cannabis-naïve patients demonstrate more frequent adverse effects (Hall et al. 1994)
- Regular users demonstrate less psychotomimetic, perceptual altering, amnestic, and endocrine effects. (D'Souza et al., 2008)
- THC can widen its own therapeutic window
  - Heterogeneous tolerance (reviewed in Pertwee, 2004)
  - Therapeutic effects (De Vry et al., 2004)

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Bidirectional Effects

The same medicine can cause opposite responses in different individuals.

- Anxious subjects tended to become less anxious. More euphoric, non-anxious individuals tended to become somewhat more anxious. (Abel, 1971)
- Sedation vs stimulation
- Appetite stimulant vs suppressant

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Bidirectional Effects

- The same medicine can cause opposite responses in the same individual:
  - Different doses (Hollister, 1986)
  - Different settings (Gregg et al, 1976)
- Different cannabis cultivars or cannabinoid ratios can cause opposite responses in the same individual

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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.

EXTRA STEP integr8 Russo and Guy, 2006 100

THC vs THC/CBD

- 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing
- Patients were randomized to THC:CBD extract (n=60), THC extract (n=58), or placebo (n=59).

Each Spray:
2.5mg CBD + 2.7mg THC
vs
2.7mg THC

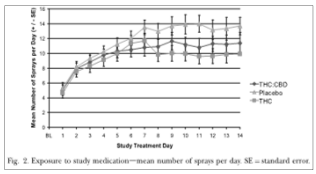

Fig. 2. Exposure to study medication—mean number of sprays per day. SE = standard error.

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CBD Dosing Adjustments

Total Milligrams:
THC < THC+CBD < CBD

low doses stimulating ⟷ CBD ⟷ high doses sedating?

Some conditions respond to 100-500 mg per dose

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New User Dosing Tips

- Starting dose:
  - Tincture or oil 1-2mg up to 3x daily
  - Vapor 1-2 puffs up to 3x daily
- Choose initial CBD:THC ratio based on symptoms and goals, adjust later.
  - 1:1 is broadly effective and well-tolerated.
- Track and document response

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Nabiximols Titration Schedule

Day	Number of sprays in the morning	Number of sprays in the evening	(Total number of sprays per day)
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5
8	2	4	6
9	2	5	7
10	3	5	8
11	3	6	9
12	4	6	10
13	4	7	11
14	5	7	12

Each spray = 2.5mg CBD + 2.7mg THC

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Non-Psychoactive Strategies

- Low dose THC after widening therapeutic window
- CBD:THC ratio > 3:1
- Acidic (raw) cannabinoids
- Topical delivery

EXTRA STEP integr8 105

Dosing: Experienced User

1. Sensitization Protocol: 6 days
2. Try switching from inhalation to oromucosal delivery
3. Mitigate side effects and enhance benefits – adjust strain or CBD:THC ratio

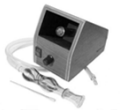
106

Delivery Methods

- Inhalation: Vaporizing, smoking
  - Strength:
  - Weakness:
  - Clinical Utility:
  - Bioavailability varies widely: 10-35% (reviewed in Grotenhermen, 2003)

107

Delivery Methods: Inhalation


108

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Delivery Methods

- Oromucosal (tincture, oil)
  - Strength: intermediate onset, easy dose titration
  - Weakness: variable onset and effects if swallowed vs held in mouth, not fast enough onset for some conditions, palatability
  - Clinical Utility: broadly applicable, good for cannabis-naïve patients
- Enteral (capsules, edible, tincture if swallowed)
  - Strength: convenient, long duration
  - Weakness: erratic bioavailability, slow onset, first-pass metabolism, most common to be used inappropriately and to cause adverse effects, may be more psychoactive, non-homogenous products
  - Clinical Utility: baseline dosage, insomnia

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109

Delivery Methods: Oromucosal and Enteral






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Dronabinol

- Synthetic THC: approved for marketing by the FDA in the U.S.
- 1985: nausea/vomiting associated with cancer chemotherapy
- 1992: appetite loss associated with weight loss in HIV/AIDS
- Available by prescription in 2.5, 5 and 10 mg

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Delivery Methods

- Topical (salves, liniments)
  - Strengths: non-psychoactive at most doses, anti-pruritic and analgesic, anti-inflammatory, muscle-relaxant
  - Weakness: little research
  - Clinical Utility: eczema, psoriasis, arthritis, trigger points
- Transdermal (patch)
  - Strengths: convenient, likely high bioavailability, low abuse potential
  - Weakness: slow onset, may be difficult to achieve correct dosage
  - Clinical Utility: personal preference, need for consistent dosing, avoid first-pass metabolism
- Rectal
  - Strengths: potentially higher bioavailability and faster onset than oral with less psychoactive effects, avoid first-pass metabolism
  - Weakness: inconvenient, formulation can affect absorbability
  - Clinical Utility: end-of-life, pelvic and low back symptoms

EXTRA STEP integr8 112 112

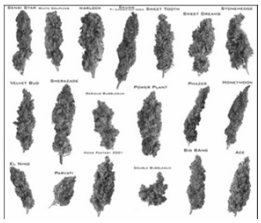
Delivery Methods: Topical, Transdermal, Rectal

EXTRA STEP integr8 113

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

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Treatment Plans

- Goal of treatment: _____
- Route of administration: _____
- Starting dose: CBD __mg + THC __mg
- Frequency: _____
- Titration: Increase dose by __% every __days

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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

EXTRA STEP integr8 116

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 ≥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)

EXTRA STEP integr8 (Hashibe et al. 2006) 117

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.

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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

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Cannabis Dependence in Illicit Users

- Lifetime risk of dependence
  - Cannabis
  - Stimulants (other than cocaine)
  - Alcohol
  - Cocaine
  - Heroin
  - Nicotine
- Highest risk of cannabis dependence:
  - Poor academic achievement, deviant behavior in childhood and adolescence, rebelliousness, poor parental relationships, parental history of drug and alcohol problems.

Anthony, 2006
Anthony et al. 1994

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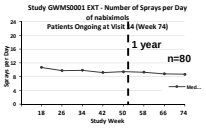
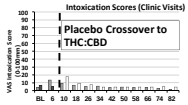
Tolerance and Intoxication



No evidence of tolerance

Wade DT, Makela PM, House H, Bateman C, Robson PJ. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in Multiple sclerosis. *Multiple Sclerosis.* 2006;12:639-645.

Examples: Intoxication Scores

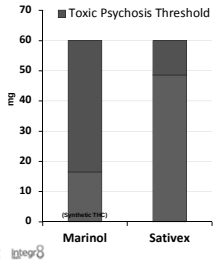


Nabiximols vs THC vs Placebo

	nabiximols	THC	Placebo
Pre-Dose	6.45	8.22	6.59
2 hours	9.75	11.21	8.41
4 hours	9.63	12.17	7.44

121

Sellers, E. M., et al. 2013. A Multiple-Dose, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group QT/QTc Study to Evaluate the Electrophysiologic Effects of THC/CBD Spray. *Clinical Pharmacology in Drug Development* 2 (3):285-294.

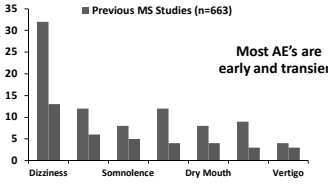


Results imply a markedly better therapeutic index and safety margin for nabiximols/Sativex over pure THC

Marinol info from: Favrat B, et al. Two cases of "cannabis acute psychosis" following the administration of oral cannabis. *BMC Psychiatry.* 2005;5:17.

122

Nabiximols Safety Profile: Adverse Events, Incidence >3%



Improved safety profile as result of modified dose titration regimen

123

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IV THC Can Induce Acute Psychosis

- Twenty-two healthy adult males mean age 28 +/-6 years
- THC (2.5 mg) administered IV in double-blind, placebo-controlled conditions.
- Self-rated and investigator-rated measurements of mood and psychosis were made at baseline and at 30, 80 and 120 min post-injection.
- Conclusion: THC can induce a transient, acute psychotic reaction in psychiatrically well individuals.

Morrison et al., 2009 124

Cannabis & Schizophrenia: No Proven Causation

- Cannabis use is a risk factor for psychosis
- No prospective study has shown that cannabis directly causes psychosis or psychotic disorders, including in adolescents.
- Having an increased familial morbid risk for schizophrenia may be the underlying basis for schizophrenia in cannabis users and not cannabis use by itself.

Reviewed in Proal et al., 2014 125

The use of cannabis in schizophrenic patients is associated with less negative symptomatology.

Peralta and Cuesta, 1992
Bersani et al., 2002
Compton et al., 2004

126

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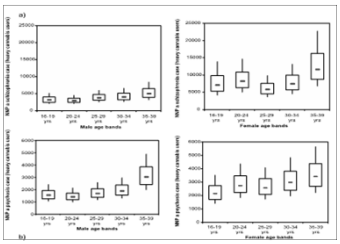
Number Needed to Prevent Psychosis and Schizophrenia



- Data from a recent meta-analysis: adjusted risk ratio (RR) of 2.1 between 'heavy cannabis use' and psychosis outcome, compared to non-users
- Combined with epidemiologic data.

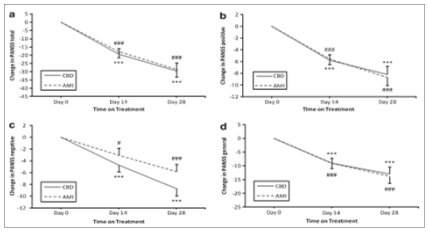
Hickman et al., 2009 127

Oral THC Improves Schizophrenia Symptoms

- 6 treatment-refractory patients with severe chronic schizophrenia
- Self-reported history of improving with marijuana abuse
- 4 improved with dronabinol.
  - ↓ core psychotic symptoms in 3/4 responders, not just nonspecific calming.
- No clinically significant adverse effects

Schwarcz et al., 2009 128

CBD vs. Amisulpride RCT



n=39 acutely exacerbated schizophrenic patients
Leweke et al., 2012

129

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Cannabis As An Exit Drug

- n=350, survey at medical cannabis dispensary
- 40% substitute for alcohol
- 26% substitute for illicit drugs
- 66% substitute for prescription drugs.
- The most common reasons given for substituting were:
  - (65%)
  - (57%)
  - (34%)

Reiman, 2009 130

Cannabis & Driving

- Avoid when possible
- Studies show:
  - More cautious, slower driving
  - Longer decision time
  - Increased variability in lane position and headway
  - Awareness of impairment and compensation

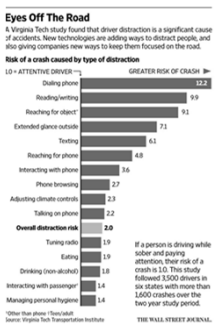
Ward, N. J., and L. Dye. "Cannabis and driving: A review of the literature and commentary." *ROAD SAFETY RESEARCH REPORT 12* (1999).

131

Driving

- THC-positive drivers associated with an OR ~1.3 following adjustments.

Reviewed in Rogeberg & Elvik, 2016



132

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Cannabis in Pregnancy & Lactation

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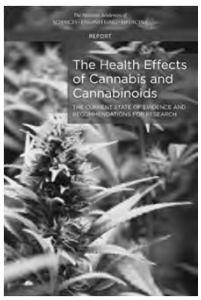
NASEM Report Conclusions



- 10-1 There is limited evidence of a statistical association between maternal cannabis smoking and pregnancy complications for the mother.
- 10-2 There is substantial evidence of a statistical association between maternal cannabis smoking and lower birth weight of the offspring.
  - Findings for birth weight are consistent with the effects of non-cannabinoid substances in smoked cannabis and cigarette smoking.
  - Leemaqz et al. (2016) similarly did not find an association between cannabis exposure and SGA (defined as a birth weight less than the 10th percentile) when adjusted for any smoking (aOR, 1.13; 95% CI = 0.80–1.60)
- 10-4 There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and later outcomes in the offspring (e.g., SIDS, cognition/academic achievement, and later substance use).

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Cannabis and Lactation

- Cannabinoids are present in breast milk of recent users.
  - Bound to protein
- Calculated exposure to the neonate: 0.8% of mother's exposure (per kg).

EXTRA STEP integr8 Reviewed in Hill & Reed, 2013 135

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Cautions

- Teenage patients
- Pregnancy
- Immunosuppression – mold
- Substance Abuse
- Hepatitis C
- Mental Illness

- High-CBD, low-THC strains and non-inhaled delivery method changes risk/benefit ratio in many patients.

136

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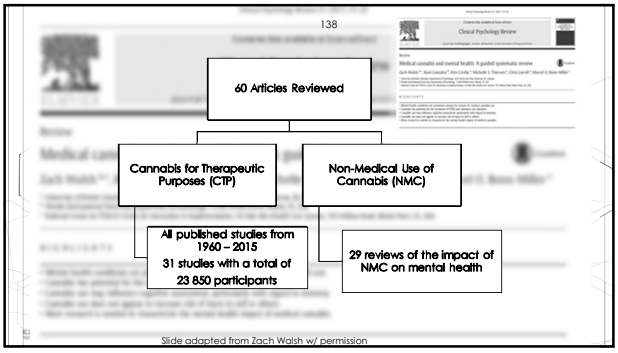

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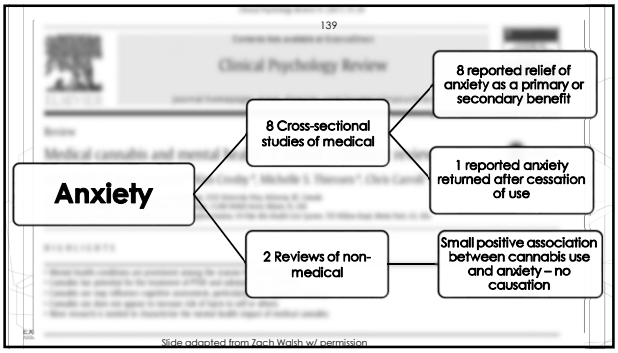

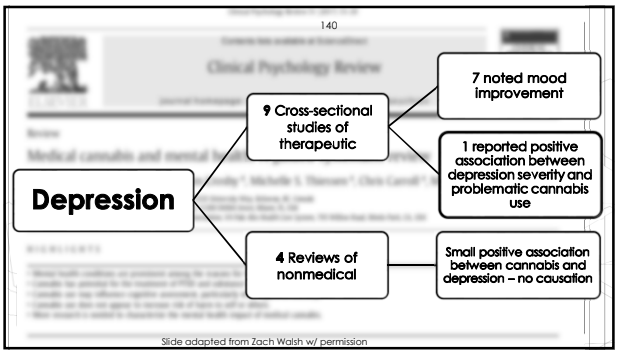

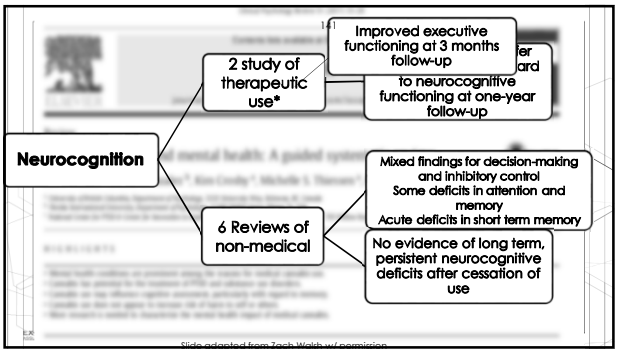

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Clinical Indications

National Academies of Sciences, Engineering, and Medicine: Health and Medicine Division

2017 Report, 440 pages

Full text available free:
https://www.nap.edu/download/24625

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- Chronic pain in adults (cannabis) (4-1)
- Chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- Multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

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There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss
- Improving clinician-measured multiple sclerosis spasticity symptoms
- Improving symptoms of Tourette syndrome
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders
- Improving symptoms of posttraumatic stress disorder

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

145

Medical Cannabis in the Treatment of Chronic Pain

146

Human Trial: Cancer Pain

- Δ9-THC 10 mg
- Codeine 60mg (equivalent to ~9mg morphine)
- Similar to each other and significantly superior to placebo
  - pain intensity differences
  - total pain relief
  - n=34

(Noyes, 1975) 147

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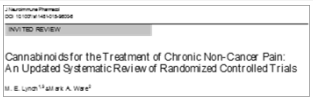

- 11 RCTs published 2010-14, n=1185 met inclusion criteria.
- Excellent quality of trials (mean 7 on Modified Oxford Scale, range 5–7)
- 7 studies demonstrated cannabinoid exhibited an analgesic effect that was significantly better than the control.
- Drug related adverse effects primarily fatigue, dizziness, dry mouth, nausea and disturbances in cognition
  - mild to moderate, transient and generally well tolerated
- Findings consistent with those from the previous review (Lynch and Campbell 2011)
- Total of 22 of 29 RCTs demonstrating that cannabinoids demonstrate a modest analgesic effect and are safe in the management of chronic pain.

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Do Opioids Help Chronic Pain?

"Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function."

- 34 studies analyzed, ≥ 18yo, ≥ 3months chronic pain and opioid Rx
- No studies evaluated long-term (>1 year) outcomes related to pain, function, or quality of life:
  - opioid vs. placebo, opioid vs. no opioid therapy, opioid vs. nonopioid therapy
- Increased risk for serious harms associated with long-term opioid therapy: overdose, opioid abuse, fractures, myocardial infarction, and markers of sexual dysfunction

EXTRA STEP integr8 Chou et al., Ann Intern Med. 2015 149

Cannabis and Pain

Helps globally:

EXTRA STEP integr8 150

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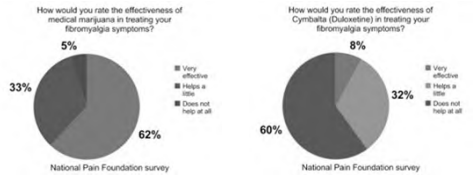
Fibromyalgia Survey

Online survey of over 1,300 fibromyalgia patients conducted by the National Pain Foundation and National Pain Report. 96% female.



151

Medical Cannabis Law and Opioid Abuse

States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws. (Bachhuber et al., 2014)

Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

	Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law		
	Primary Analysis	Secondary Analyses	
Independent Variable[a]	Estimate (95% CI)[b]	Estimate (95% CI)[c]	Estimate (95% CI)[d]
Medical cannabis law	−24.8 (−37.5 to −9.5)[e]	−31.0 (−42.2 to −17.6)[f]	−23.1 (−37.1 to −5.9)[e]
Prescription drug monitoring program	3.7 (−12.7 to 23.3)	3.5 (−13.4 to 23.7)	7.7 (−11.0 to 30.3)
Law requiring or allowing pharmacists to request patient identification	5.0 (−10.4 to 23.1)	4.1 (−11.4 to 22.5)	2.3 (−15.4 to 23.7)
Increased state oversight of pain management clinics	−7.6 (−19.1 to 5.6)	−11.7 (−20.7 to −1.7)[e]	−3.9 (−21.7 to 18.0)
Annual state unemployment rate[g]	4.4 (−0.3 to 9.3)	5.2 (0.1 to 10.6)[e]	2.5 (−2.3 to 7.5)

152

Medical Cannabis Law and Opioid Abuse

Medical cannabis laws had a 23% less hospitalizations related to opioid abuse and 13% less hospitalizations related to opioid pain reliever overdose. (Shi, 2017)

Table 1
Associations between Medical Marijuana Policies and State-Level Hospitalizations Rates Related to Marijuana and Opioid Pain Reliever, State Inpatient Databases 1997–2014.

State-level Explanatory Variable	State-level Outcome Variable: Natural Log of Hospitalization Rates per 1000 Discharges Point Estimate (95% CI)					
	Marijuana Dependence or Abuse		Opioid Dependence or Abuse		Opioid Pain Reliever Overdose	
Medical Marijuana Policy	0.16	(−0.076, 0.41)	**−0.23**	**(−0.41, −0.068)***	**−0.13**	**(−0.25, −0.018)***
Marijuana Decriminalization Policy	0.13	(−0.10, 0.36)	0.094	(−0.15, 0.33)	0.049	(−0.22, 0.32)
Prescription Drug Monitoring Program	−0.088	(−0.21, 0.042)	0.020	(−0.088, 0.12)	0.027	(−0.080, 0.13)
Pain Clinic Regulation	−0.046	(−0.17, 0.078)	0.052	(−0.12, 0.23)	−0.070	(−0.16, 0.025)
Number of State-Year Observations	382		382		382	
Number of Discharges	2,237,916		2,176,326		376,680	
R^2	0.90		0.96		0.97	

Note: The linear regressions also controlled for state and year fixed effects and state-level time-varying covariates including natural log of population size, unemployment rate, natural log of median household income in constant 2014 dollars, natural log of beer tax per gallon in constant 2014 dollars, and health uninsured rate.
Bold value highlighted statistics with p value smaller than .05.
* $p<0.05$.
** $p<0.01$.

153

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Substitution for Prescriptions

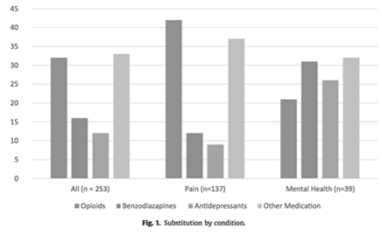


Fig. 1. Substitution by condition.

Lucas & Walsh, 2017 154

National Institute on Drug Abuse

Advancing Addiction Science

Drugs of Abuse | Related Topics | Publications | Funding

Marijuana

Marijuana

Research Report Series

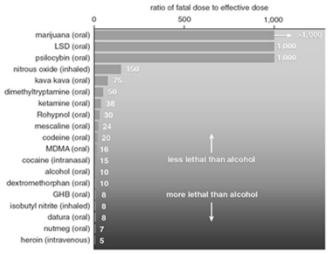
Is marijuana safe and effective as medicine?

Though none of these studies are definitive, they cumulatively suggest that medical marijuana products may have a role in reducing the use of opioids needed to control pain. More research is needed to investigate this possibility.

https://www.drugabuse.gov/publications/marijuana/marijuana-safe-effective-medicine

155

Is It Safe To Use Cannabis and Opioids Together?



156

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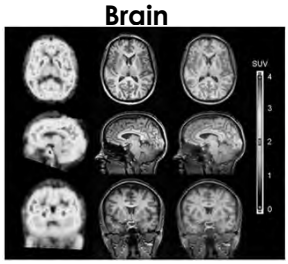
CB1 Receptor Distribution in Human Brain

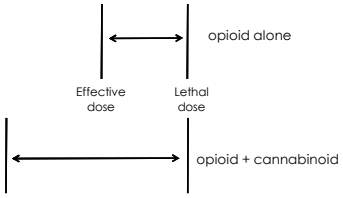


Terry et al. 2010 157

Combination Treatment Widens Therapeutic Index

- Opioid and cannabinoid receptors are co-distributed in pain centers.
- Cannabinoid receptors have low density in brainstem cardiorespiratory centers.
- Combination increases therapeutic index of opiates!

(reviewed in Cichewicz, 2004)



158

Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 65 / No. 1 March 18, 2016

CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

previously (*30*). Clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. For example, experts noted that there might be uncertainty about the clinical implications of a positive urine drug test for tetrahyrdocannabinol (THC). In addition, restricting

159

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SPECIAL ARTICLE

Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis

Report of the Guideline Development Subcommittee of the American Academy of Neurology

Cannabinoid practice recommendations:

- Clinicians might offer oral cannabis extract (OCE) to patients with MS to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain) (Level A)
- Clinicians might counsel patients that this symptomatic benefit is possibly maintained for 1 year (Level C)
- OCE is probably ineffective for improving objective spasticity measures (short-term) or tremor (Level B).

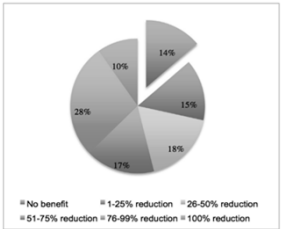
(Yadav et al. 2014) 160

Gottschling, S. 2001. Cannabinoide bei Kindern Gute Erahrungen bei Schmerzen, Spastik und in der Onkologie. *Angewandte Schmerztherapei und Palliativmedizin*, 55-57.

Dronabinol (average dose 0.2 mg/kg/d) was similarly administered to 13 severely neurologically impaired children, aged 7 months-17 years with uniform benefit on spasticity and pain, improved sleep in 10. The longest treatment duration was five years, and no tolerance or dose escalation was apparent. Similarly, more than 50 patients from the age of three months were treated for nausea and inanition from chemotherapy. Marked benefit was noted with no serious side effects aside from one self-limited case of 10-fold accidental overdose, and no withdrawal effects were seen even after abrupt withdrawal after months of therapy.

161

Sulak, D., Saneto, R., & Goldstein, B. (2017). The current status of artisanal cannabis for the treatment of epilepsy in the United States. *Epilepsy & Behavior.*



- n=272 patients w/ refractory epilepsy
- Effective total cannabinoid doses: 0.05 - 9 mg/kg/day, primarily CBD
- Effective serum levels of CBD: 1.8 - 80 ng/mL
- Case reports:
  - THCA preventing seizures
  - THC aborting GTC

162

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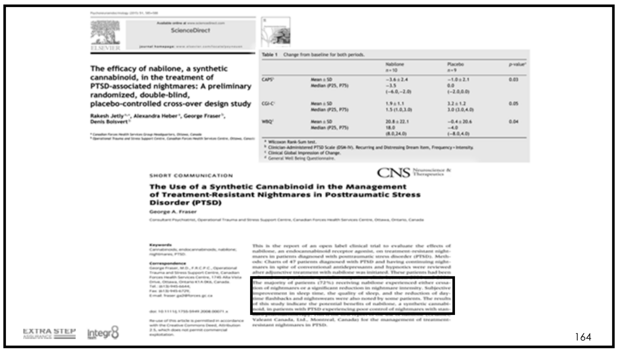

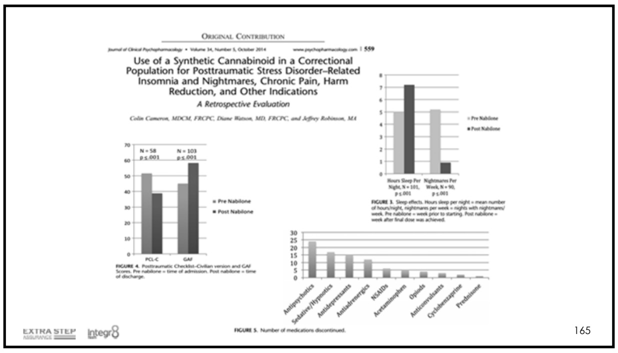

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CANNABIS EXPERTISE

Thank you for Participating in the 2-Hour Medical Cannabis Certification Course ESA102 Hosted by Cannabis Expertise

Instructions will be sent to you by email (Info@ESACertified.com) immediately following this session with full details of how to submit your request for your CME credits.

This course is a nationally accredited CME event for Healthcare Professionals. For Ohio Healthcare Providers, to be certified to recommend medical marijuana to patients, all applicants must hold an active, unrestricted MD or DO license from the State Medical Board of Ohio. Additionally, applicants will need to complete at least two hours of continuing medical education that will assist in diagnosing qualifying conditions, treating those conditions with medical marijuana and possible drug interactions. The content of this course is designed to assist Physicians per Ohio Revised Code Section 4731.301 Certificate to Recommend Medical Use of Marijuana

EXTRA STEP integr8

166