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CONSIDERATIONS IN CANNABIS BASED TREATMENT

Christine Roussel, PharmD, BCOP

HOUSEKEEPING



Cell Phones



Download the Slides



Questions



No photography, audio, or video recordings



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CHRISTINE ROUSSEL, PharmD, BCOP



- Board-certified oncology pharmacist
- Director of Pharmacy, Doylestown Hospital, Pennsylvania
- Adjunct Professor, University of the Sciences, Philadelphia
- BSc Toxicology and Doctorate in Pharmacy, Philadelphia College of Pharmacy
- Previous positions including Cancer Center and Speciality Pharmacy leadership
- Expert in hazardous compounding

Disclosure: Consultant, MEDISCA Inc.



DISCLOSURES

- No disclosures relevant to the Cannabis industry
- Dr. Roussel is a pharmacy consultant, educator and content author for LP3/Medisca



LEARNING OBJECTIVES

PHARMACISTS

- 1. Discuss the endocannabinoid system, cannabinoid pharmacology, cannabinoid products, and common formulations.
- 2. Apply information from the medical literature to specific patient case scenarios for the safe therapeutic use of medical cannabis.
- 3. Design a role for the pharmacist related to medical cannabis for patient counseling in various settings.
- 4. Develop a plan for the pharmacist when patients report medical cannabis use and their desire to continue therapy across transitions of care.



LEARNING OBJECTIVES

PHARMACY TECHNICIANS

- 1. Discuss the endocannabinoid system, cannabinoid pharmacology, and cannabinoid products.
- 2. Review different formulations and dosage forms commonly applied in cannabis therapy.
- 3. Evaluate important safety considerations for medical cannabis use.
- 4. Recognize important information to communicate to the patients receiving cannabis therapy.



DISCLAIMER

- Cannabis is currently not FDA-approved for any condition
- Cannabis is currently DEA Schedule 1 (Federal)
- Investigational use only
 - IND applications must receive triple agency approvals: National Institute of Drug Abuse (NIDA) / DEA / FDA
 - Product for Federal Research is Sole Source through NIDA (Unless Import Permission is granted)



ROLE OF THE U.S. GOVERNMENT

US GOVERNMENT OWNS PATENT

"Cannabinoids are found to have particular application as neuroprotectants, for example 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 dimension."

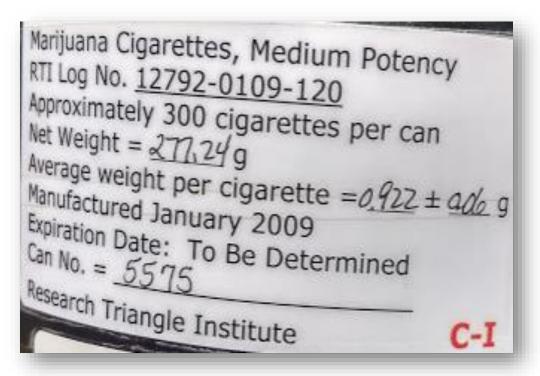
Publication number US8630507 B1 Publication type Grant Application number US 09/674.028 PCT/US1999/008769 PCT number Oct 7, 2003 Publication date Filing date Apr 21, 1999 Priority date (?) Apr 21, 1998 Fee status (?) Paid Also published as CA2329828A1, 4 More » Aidan J. Hampson, Julius Axelrod, Maurizio Inventors Grimaldi Original Assignee The United States Of America As Represented By The Department Of Health And Human Services **Export Citation** BiBTeX, EndNote, RefMan Patent Citations (22), Non-Patent Citations (29), Referenced by (41), Classifications (16), Legal Events (5) External Links: USPTO, USPTO Assignment, Espacenet



ROLE OF THE U.S. GOVERNMENT

THE US GOVERNMENT GROWS CANNABIS AND SUPPLIES IT TO PATIENTS







1977 – 1993 Federal Compassionate IND (n=13) Grown by University of Mississippi & NIDA Pictures Provided by Irvin Rosenfeld. Used with Permission.

PROGRAM OUTLINE





THE SYNAPTIC CLEFT

1. Neurotransmitters Presynaptic synthesized and stored Neuron in vesicles until ready to release 2. Neurotransmitter binding to corresponding receptor 3. Initiates Postsynaptic downstream Neuron effects

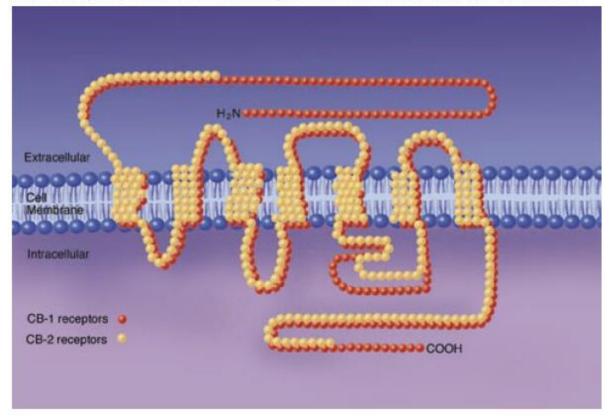
Neuro signal transmission across the synaptic cleft

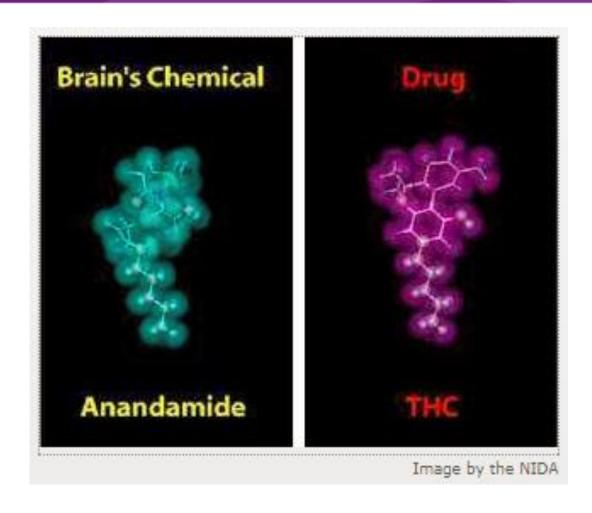
ENDOCANNABINOIDS AT THE SYNAPTIC CLEFT

Presynaptic **Neurotransmitter signaling** Neuron 3. Binding at the CB1 Endocannabinoid receptor stabilizes vesicles signaling is retrograde to decrease neurotransmitter release inhibition Glutamate **GABA** 2. Endocannabinoids Acetylcholine Norepinephrine (anandamide, 2-AG) Dopamine synthesized on demand for 5-HT3 immediate release Cholecystokinin 1. Too much activity Postsynaptic Neuron

CANNABINOID RECEPTORS & MOLECULAR COMPARISON

Figure 1. Subtypes of cannabinoid receptors. Cannabinoid-1 (CB-1) receptors primarily modulate psychoactive effects. Cannabinoid-2 (CB-2) receptors primarily modulate immune responses. Illustration by Marie Dauenheimer, CMI. Adapted, with permission, from reference 6.





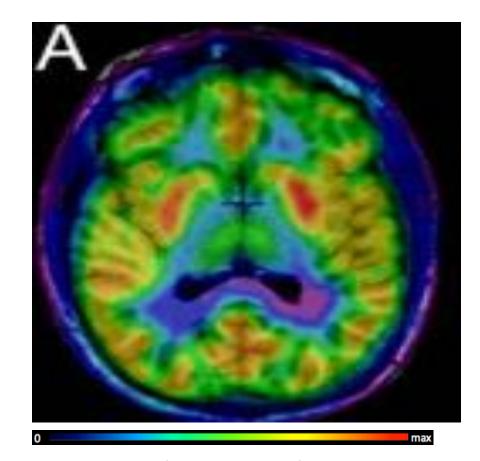
Am J Health-Syst Pharm-Vol 64 May 15, 2007



Original publication: Seamon, MJ. Medical marijuana and the developing role of the pharmacist. Am J Health-Syst Pharm—Vol 64 May 15, 2007] © [2007], American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted with permission.

CB1 RECEPTORS

- CB1 Primarily in Brain
 - NOT significant in brainstem (RR,HR)
- Other Locations
 - Adipocytes
 - **Endocrine and Exocrine Glands**
 - Hepatocytes
- Cannabinoid Pharmacology in CNS
 - Anti-Nociceptive
 - Parasympathetic (Anti-Emetic)
 - Neuroprotection
 - Neuroplasticity



Human brain after injection of radio tracer to show the regional distribution of CB1R

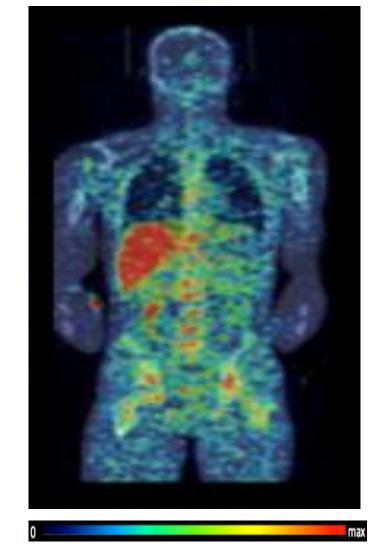


Original publication: Burns, et al. [18F]MK-9470, a positron emission tomography (PET) tracer for in vivo human PET brain imaging of the cannabinoid-1 receptor. PNAS June 5, 2007 vol. 104 no. 23. Pg. 9800–9805 © [2007] All rights reserved. Reprinted with permission.

Shohami E and Horowitz M (ed). Cannabinoids in Health and Disease. Themed special issue, Journal of Basic and Clinical Physiology and Pharmacology Copyright © 2018 LP3 Network 18 2016; 27(3).

CB2 RECEPTORS

- Signally \downarrow release of activators and sensitizers
- Immunomodulation:
 - Monocytes and Macrophages
 - B-cells and T-cells
- Liver, Spleen, Tonsils
- Central & Enteric Nervous System
- **Endocrine and Exocrine Glands**





Originally publication: Ahmad R,, et al. 2016 Whole-body bio-distribution and radiation dosimetry of the cannabinoid type 2 receptor ligand [11C]-NE40 in healthy subjects. Mol Imaging Biol. 2013 Aug;15(4):384-90© [2013]All rights reserved. Reprinted with permission.

MEDICAL CANNABIS VS MARIJUANA

CANNABIS SATIVA



- Plant reliably grown and handled
- Good Manufacturing Practices
- Assayed, labeled and dated for cannabinoids and terpene content
- Proven absence of typical contaminants:
 - Mold / Yeast
 - Pesticides
 - Heavy Metals
 - Residual Solvents

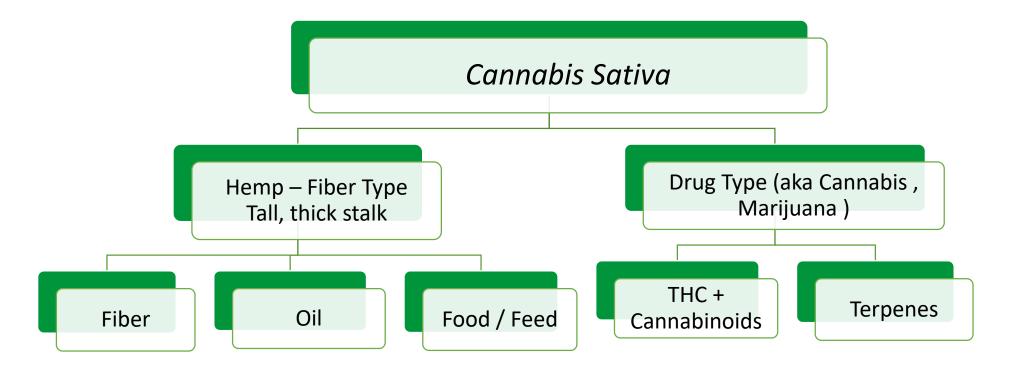


PESTICIDE USE ON MARIJUANA

- Cannabis flower with 0.03 ppm myclobutanil \rightarrow non-lethal, but clinically relevant HCN dose
- Chronic exposure to dilute hydrogen cyanide (ex. 0.008 parts per million)
 - Serious neurological, respiratory, cardiovascular, and thyroid problems
- Toxins co-extracted with cannabinoids during concentrate production
 - Accumulate at levels 250 times higher than the starting material



CANNABIS SATIVA



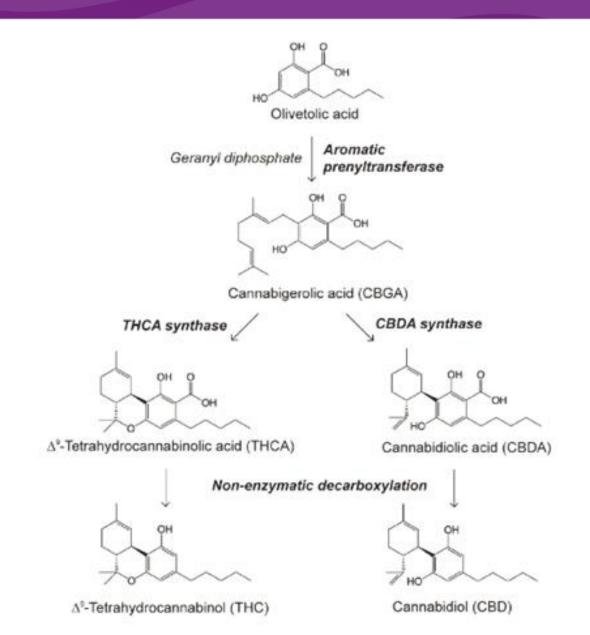
- **Industrial Hemp:** stalk and seeds are used for textiles, paper, food, detergents, building materials (excludes flower)
- THC content $\leq 0.3 \%$
- Not scheduled

- **Cannabis / Marijuana:** medicinal / recreational use of cannabinoids
- THC content 5 15+%
- DEA controlled substance



CANNABACEAE

- Unfertilized female flower
- Acidic cannabinoids
- Chemovars
- THC-predominant (Type I)
- THC:CBD mix (Type II)
- CBD-predominant (Type III)
- Indica vs Sativa vs Hybrids





SEED TO SALE TRACKING









Pictures by Christine Roussel

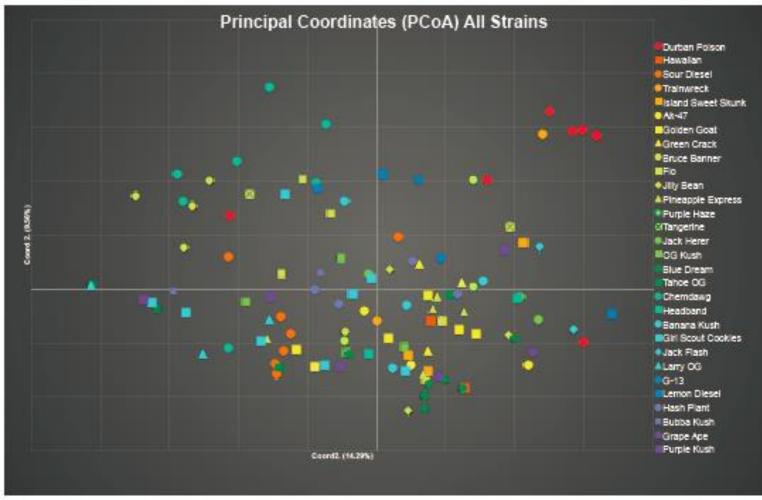
CARBON DIOXIDE EXTRACTION







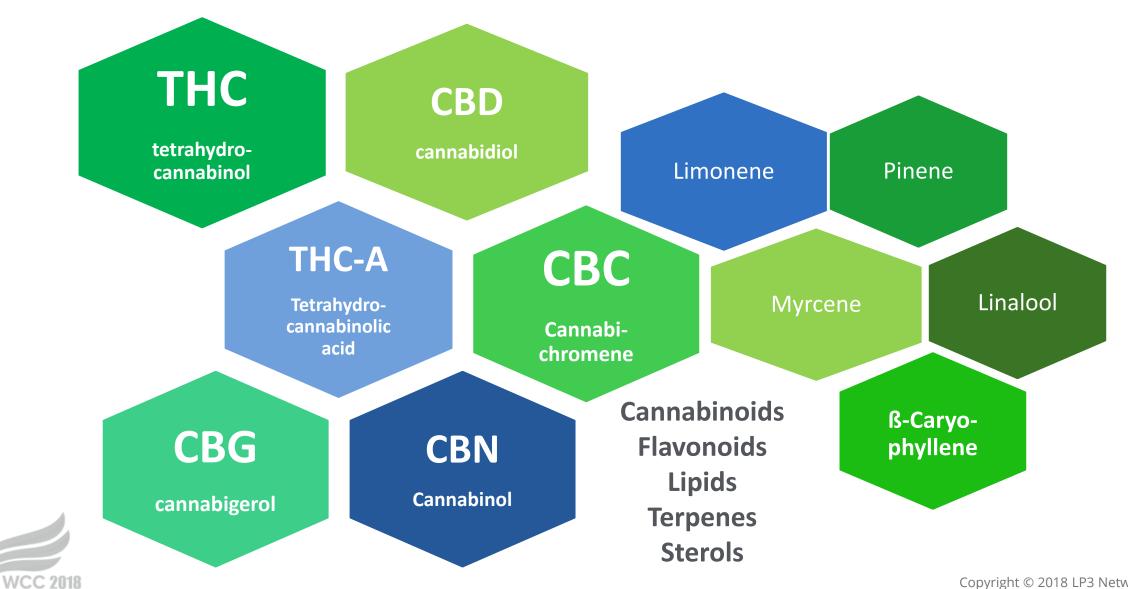
GENETIC TOOLS IN CANNABIS SATIVA



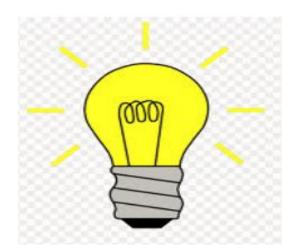
- No consistent genetic differentiation between the widely held perceptions of Sativa and Indica Cannabis types.
- Instances were found where samples within strains are not genetically similar.

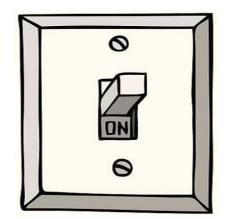


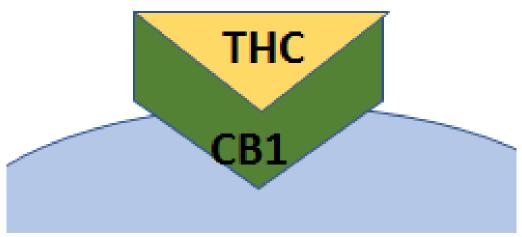
CANNABIS: ENTOURAGE EFFECT



TETRAHYDROCANNABINOL (THC)







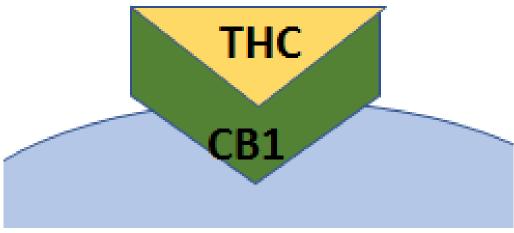
- Partial agonist of CB1 and CB2
- Euphoria
- Analgesia (primary pain relief molecule)
- Muscle relaxant
- Bronchodilator
- Anxiolytic (low dose) → Anxiogenic (higher doses)



TETRAHYDROCANNABINOL (THC)

ADVERSE EFFECTS

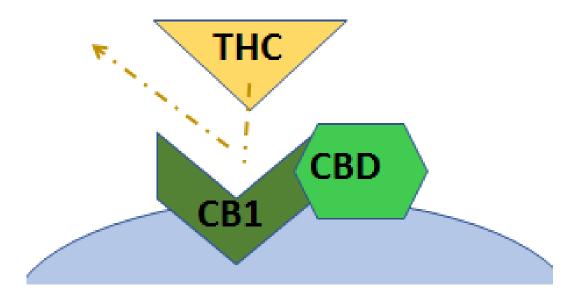
- Psychoactivity vs Psychotoxicity
 - Impaired cognition
 - Difficulty concentrating
 - Memory Impairment



- Dizziness, Weakness
- Increase risk of falls
- Tachycardia
- Vasodilation, Hypotension
- Addiction (1 in 10 chronic recreational users)
- Caution in patients with unstable mental health conditions (especially bipolar disorder and schizophrenia)

CANNABIDIOL (CBD)

- Enhances natural endocannabinoid activity
- Agonist at 5-HT (anti-nausea) and TRPV1 (pain relief)
- Potent Immune Modulator = strong antiinflammatory activity
- Anti-seizure
- Neuroprotective
- Decrease negative effects of THC (anxiety, memory impairment, psychoactivity)



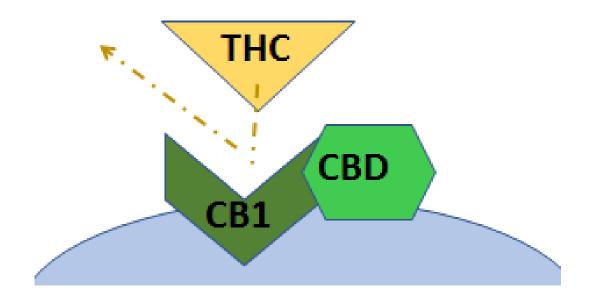
Negative Allosteric Modification



CANNABIDIOL (CBD)

ADVERSE EFFECTS

- Diarrhea
- Headache
- **Suppress Appetite**
- Stimulating (trouble sleeping)
 -Somnolence
- **Drug Interactions**



** NOT ASSOICATED with Psychoactivity. ** **Considered NOT to have Addictive Properties. **

Information for Health Care Professionals Cannabis (marihuana, marijuana) and the cannabinoids Prepared by Health Canada. 2018

WHO. Cannabidiol (CBD) Critical Review Report. World Health Organization, Expert Committee on Drug Network 31 Dependence, Fortieth Meeting, Geneva, 4-7 June 2018

SELECT PHYTOCANNABINOIDS and PHARMACOLOGY

| | Cannabinoid | Areas of Investigation |
|-------|-----------------------------|---|
| CBD-A | Cannabidiolic acid | Anti-emetic, anti-anxiety |
| THC-A | Tetrahydrocannabinolic acid | Anti-inflammatory effects via antagonism of tissue necrosis factor alpha (TNF- α); anti-emetic, anti-convulsant, clinical trial on-going for diabetes |
| CBN | Cannabinol | 1/10 th the psychoactive potency, sedative, antibacterial, inhibition of keratinocytes in psoriasis |
| СВС | Cannabichromene | anti-inflammatory, anti-fungal, anandamide reuptake inhibitor |
| CBG | Cannabigerol | DGABA uptake inhibitor, antibacterial, inhibition of keratinocytes in psoriasis |



TERPENES



LINALOOL

Sedative Anxiolytic Analgesic

Modulate GABA

and Glutamate

WCC 2018



MYRCENE

Analgesic
Anti-Inflammatory via
PGE-2

Anti-Convulsant

Skeletal Muscle



B CARYOPHYLLENE

Select CB2 Agonist

Analgesic

Gastric Protective

Anti-Inflammatory via

PGE-1





TERPENES



PINENE

Anti-Inflammatory
Bronchodilator
Acetylcholinesterase
Inhibitor (Aids memory)



LEMONENE

Antidepressant Anti-oxidant Anticonvulsant Antimicrobial



NEROLIDOL

Enhances Skin
Penetration
Antiprotozoal
Antifungal



RESPIRATORY EFFECTS OF CANNABIS

Short-term (Acute) cannabis smoking

Bronchodilation and consistent

- improve specific airway conductance
- ↑ peak flow measurements
- ↑ forced expiratory volume (FEV1)
- reverse bronchospasm in methacholine challenges

Dries mucus membranes of mouth and nasal passages



Cardio-pulmonary exchange transfers cannabinoids to blood then brain Smoke may irritate large air passages of lungs, throat, windpipe

Heavy habitual smokers of cannabis alone

- symptoms of chronic bronchitis (cough and sputum)
- Histopathological bronchial mucosa abnormalities (destruction of ciliated epithelial cells, increase mucus secreting surface epithelial cells)
- Not associated with increase lung cancer



- National Academy of Science, 2017; Taskin 2015
- Handbook of Cannabis and Related Pathologies.

ECS AND THE GASTROINTESTINAL TRACT

- ECS regulates energy balance & food intake, acting both in brain & GI tract
 - Anandamide (AEA) is mediator of hunger in intestines
 - Starvation increases AEA levels & CB1 expression
 - THC increases food uptake via CB1 activation
- Anandamide on CB receptors in adipose tissue stimulates lipogenesis.
 - Increased adiposity, insulin resistance
- Inhibit nausea and vomiting



Handbook of Cannabis and Related Pathologies. Chapter 45 Cannabis, Cannabinoids, and Visceral Pain by R. Abalo, M. Isabel Martin-Fontelles and National Academy of Science, 2017; K Gyires and Z. Zádori. Role of Cannabinoids in Gastrointestinal Mucosal Defense and Inflammation. Current Neuropharmacology, 2016, 14, 935-951

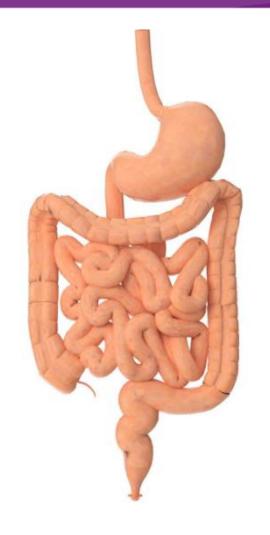
ECS IN THE GITRACT AND CANNABINOIDS

THC = Direct activation of CB 1 receptors

- Analgesia
- ↓ gastric acid secretion
- ↓ contractility
- ↓ motility
- ↓ formation of gastric mucosal lesions through enhanced intestinal epithelial barrier functions
- Stimulates hunger sensation

CBD = targets upregulated **CB2** receptors

- Anti-inflammatory
- Control fluid accumulation
- ** controls hunger **





Handbook of Cannabis and Related Pathologies. Chapter 45 Cannabis, Cannabinoids, and Visceral Pain by R. Abalo, M. Isabel Martin-Fontelles and National Academy of Science, 2017; K Gyires and Z. Zádori. Role of Cannabinoids in Gastrointestinal Mucosal Defense and Inflammation. Current Neuropharmacology, 2016, 14, 935-951

ENDOCANNABINOID ROLE IN SKIN INTEGRITY

Human Skin Contains:

- endogenous lipid ligands
- enzymes for their synthesis and degradation

CB1 receptors:

- Hair follicle cells (differentiated)
- Keratinocytes in epidermis
- CB2 receptors
- undifferentiated keratinocytes in stratum basale
- hair follicles

Structure of the Epidermis

Stratum corneum

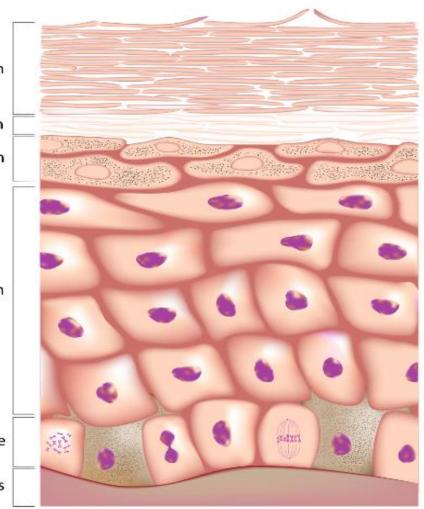
Stratum lucidum

Stratum granulosum

Stratum spinosum

Stratum basale

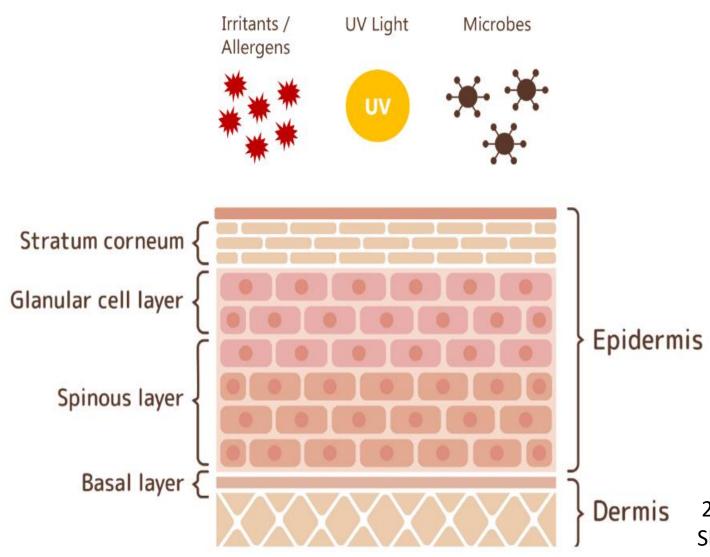
Handbook of Cannabis and Related Pathologies. 2015 Chapter 57. Regulatory Dermi Role of Cannabinoids for Skin Barrier Functions and Cutaneous Inflammation. By Tuting and Gaffal.



YOUNG

OLD

CB1 RECEPTOR MODULATION OF INFLAMMATION



CB receptor agonist (endogenous, THC)

- ↓ contact hypersensitivity
- ↓ allergic swelling
- Inhibition of chemokine production
- \$\square\$ infiltration of myeloid cells in inflamed tissue

Handbook of Cannabis and Related Pathologies.
2015 Chapter 57. Regulatory Role of Cannabinoids for Skin Barrier Functions and Cutaneous Inflammation. By Tuting and Gaffal.

MEDICAL GOALS OF THERAPY

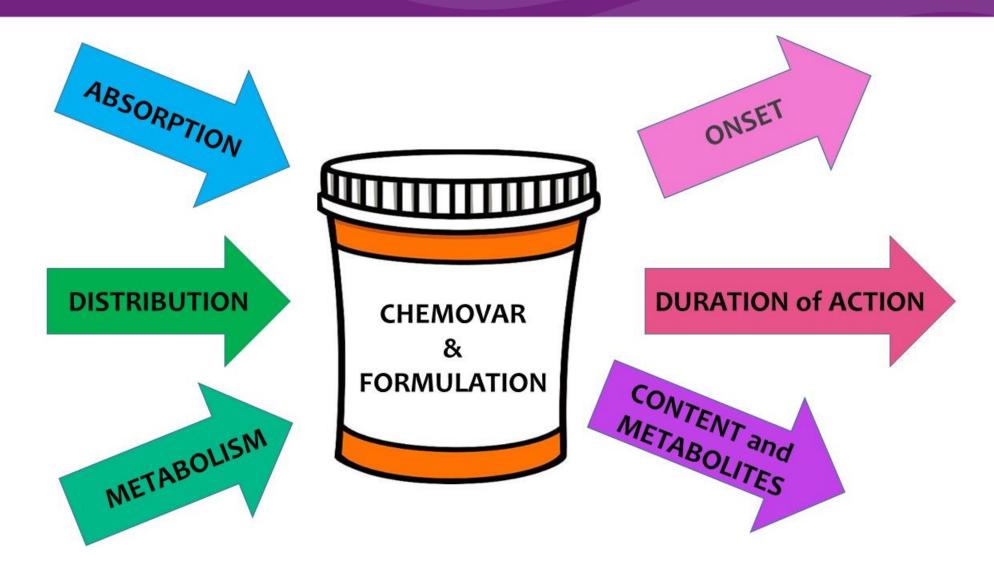
SYMPTOM MANAGEMENT VS DISEASE MODIFICATION

- Pain
- Spasticity
- Inflammation
- Sleep Disorders

- Nausea / Vomiting
- Appetite
- Anxiety / Depression



DRUG INTERACTIONS





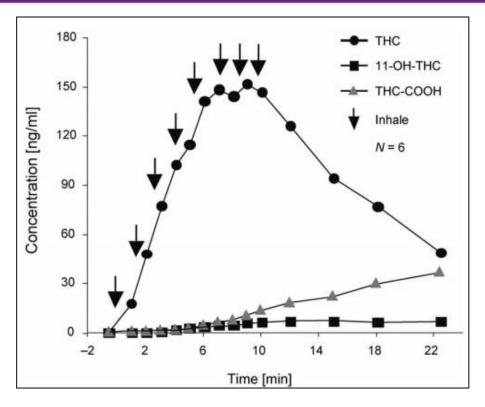
FORMULATIONS

- Oils for vaporization
- Dry Flower (mainly for inhalation, but could be oral)
- Oral liquids (tinctures, solutions, suspensions, sublingual sprays)
- Capsules
- Patches (transdermal, buccal)
- Suppositories (vaginal, rectal)
- Topicals: lotion, balm, cream, etc

Goal of medical forms should be controlled and consistent dose administered each time



INHALATION



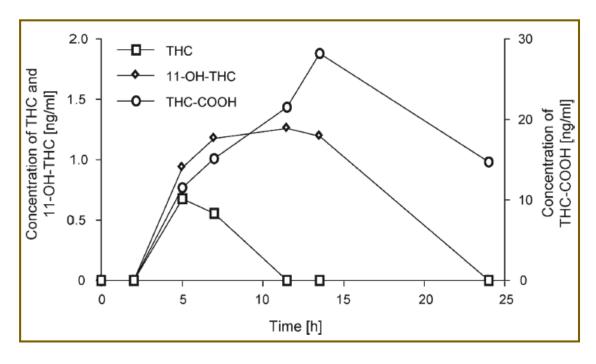
- Typical onset 0 10 min
- Duration 2- 4 hours
- Intra- and inter patient variability due to smoking dynamics

- Bioavailability 10 60%
 - Depth of inhalation
 - Duration of breath holding
 - Temp of vaporizer
- Good for titration and breakthrough because of rapid effects
- Important to teach:
 - Proper patient technique
 - To wait 5 -10 minutes between inhalations during titration



- Huestis M. Human Cannabinoid Pharmacokinetics. Chem Biodivers. 2007 August; 4(8): 1770–1804.
- MacCullum C and Russo E. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine*. 49 (2018) 12-19.

ORAL ADMINISTRATION



After administration of 2.5 mg Dronabinol

- Onset 30 120 min
- ↑ Inter/Intra patient variable absorption
- Absorption ↑ w/ high fat meal
 - Contribution of Matrix
- Duration 4-8 hours
- *Up to 24 hours dose dependent
- Lower Peak [THC]
- 个 [11-Hydroxy-THC]
 - Longer t_{1/2}
 - More potent analgesic activity
 - More lipophilic



Huestis M. Human Cannabinoid Pharmacokinetics. Chem Biodivers. 2007 August; 4(8): 1770–1804.

MacCullum C and Russo E. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine. 49 (2018) 12-19.

ORAL ADMINISTRATION

IMPORTANT TO TEACH PATIENTS

- Ensure you are ingesting products with a known amount of cannabinoids
- Wait at least 90 minutes between doses
- THC is best before meals for appetite. Before or after meals, depending on food-related symptoms
- Avoid edible products
- Dosing may not be precise, difficult to dose food
- Help patients with the math
- Recommend providing written visual instructions







Huestis M. Human Cannabinoid Pharmacokinetics. Chem Biodivers. 2007 August; 4(8): 1770–1804.

MacCullum C and Russo E. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine. 49 (2018) 12-19.

SUBLINGUAL / OROMUCOSAL

- Typical onset 10 60 min
- Duration 2 to 12 hours
- Avoids first-pass metabolism
- More consistent absorption
- Must teach patients:
 - One drop can be a realistic starting dose
 - Wait an hour before repeat dosing
 - May not feel any benefit with first administration







OTHER ROUTES OF ADMINISTRATION

RECTAL

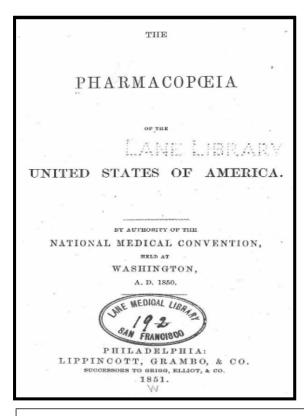
- Suppository matrix effect
- Rectal or vaginal
- Bioavailability of the rectal route was approximately twice that of the oral route due to higher absorption and lower firstpass metabolism.

TRANSDERMAL

- Onset: 15 120 minutes
- 1-8 hours
- Matrix effect (absorption enhanced by alcohol and terpenes)
- Avoids first pass
- Patches for sustained effects

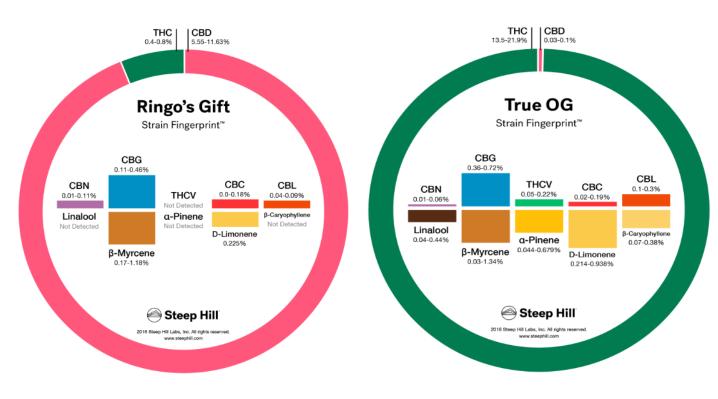


DEFINING PRODUCTS



USP Expert Panel on Cannabis

- Botanical Identification
- Chemical Analysis & Contaminants
- Monograph Development



Cannabis Strain Analysis. Steep Hill Labs. All rights reserved.

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THC:CBD CHEMOTYPES OR RATIOS

THC-predominant

Ex. 50:1, 19:1, 16:1

Psychoactivity **Balanced = Intermediate**

Ex. 1:1, 4:1

CBD-dominant Ex. CBD Only, 1:>20 Psychoactivity is dosedependent and can be affected by tolerance and setting.

DOSING

THC – 1-2 mg SAFE STARTING DOSES

- Start with products with known potency
- Elderly / Sensitive Patients start 1 mg or lower
- Initial doses ideally SHOULD NOT elicit a psychoactive effect
- Waiting appropriate time between doses during titration
- Tincture may start with as little as one drop wait 90 minutes
- Inhalation start with a single puff wait 5 10 minutes



MacCullum C and Russo E. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine. 49 (2018) 12-19.

DOSING

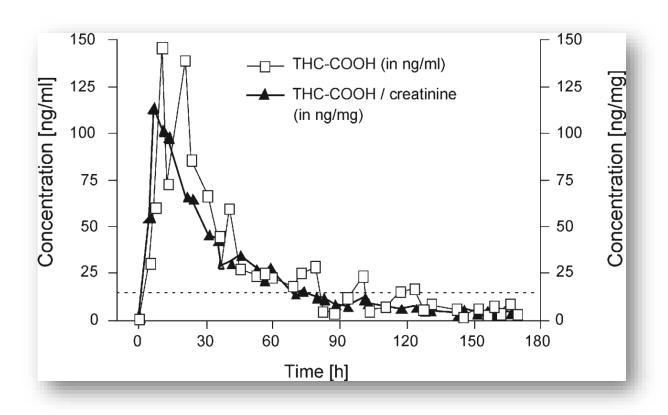
CBD – 5-10 mg SAFE STARTING DOSES

- Start with products with known potency
- Start once a day, then move to twice a day
- Once at twice a day can titrate up dose
- Waiting Appropriate time (1-2 weeks) between dose increases
- Taking with food increases bioavailablity (and saves \$)
- Use alone and as "CBD Cushion"



CANNABIS ELIMINATION

- 95-99% protein bound
- Lipophilic Crosses BBB and placenta; breast milk
- Rapid liver metabolism
- Eliminated in urine and feces
- Inactive metabolites THC-COOH detectable days to weeks after administration in oral fluid, plasma and urine





- Aggarwal SK. Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. Clin J Pain. 2013 Feb;29(2):162-71.
- Huestis M. Human Cannabinoid Pharmacokinetics. Chem Biodivers. 2007 August; 4(8): 1770–1804.
- Goodwin, et al.. Urinary Elimination of 11-Nor-9-carboxy- 9-tetrahydrocannnabinol in Cannabis Users During Continuously Monitored Abstinence LAnal Toxicol 2008 Oct. 32(8): 562-569

WILL TAKING CBD MAKE ME TEST POSITIVE FOR MARIJUANA?

- Limited studies converted CBD to THC in a laboratory Environment
- Studies of human oral consumption of CBD have been summarized:
- Concluded that high doses of oral CBD "consistently fail to demonstrate": clinically relevant THC-like subjective or physiological effects
- appreciable plasma concentrations of THC or its metabolites



PATIENT SELF-TITRATION - > PATIENT EDUCATION

Dose

Higher Doses associated with increased ADRs and possible decrease in efficacy for certain symptoms

decrease in efficacy for ce symptoms timal Dose

Finding the Optimal Dose
"The Sweet Spot"
Minimal Side Effects

Start Low and Go Slow Cannabis Sensitization Protocols Sub-Psychoactive Dosing Want Upregulation of Endocannabinoid Receptors, Not Down Regulation

Rooted in the Concept: Less is Really More

NATIONAL ACADEMY OF SCIENCE 2017

BENEFICIAL ASSOCIATIONS

- Effective for chronic pain in adults
- Effective for Chemo Induced Nausea and Vomiting (CINV)
- Effective for MS spasticity and improved sleep
- Effective for short-term sleep outcomes associated with obstructive sleep apnea syndrome, fibromyalgia and chronic pain

HARMFUL ASSOCIATIONS

- Worsening of respiratory symptoms and chronic bronchitis
- Increased risk of motor vehicle crashes
- Chronic Cannabis use in pregnancy = Low Birth Weight
- Frequent user and development of schizophrenia



ADVERSE EVENTS

Systematic Review: 23 RCT + 8 observational

Wang et al. CMAJ 2008; 178 (13): 1669-78

Non-Serious Events (n = 4615)

Rates of Non-Serious Events more common with Cannabis [RR] 1.86 95% CI 1.57-2.21)

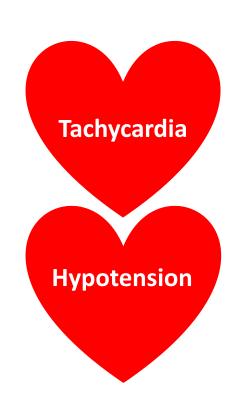
Dizziness

Serious Events (n=164)

Rates of Serious Events did NOT differ compared to controls [RR] 1.04. 95% CI 0.78-1.39)

> Respiratory Gastrointestinal Nervous system

RELATIVE CONTRAINDICATIONS: CV DISEASE



- **Population Analysis**
 - 4.8-fold higher risk of MI
 - 124 / 3882 patient cohort
 - 2.5-fold increased risk of death (weekly use)
 - 54/1913 adults follow-up for h/o MI
- Increased CVD in cannabis users
 - 316,397 of > 20 million
- Marijuana not associated with increased CVD
 - 4286 with h/o marijuana use





- Pacher P, et al. Cardiovascular effects of and synthetic cannabinoids: The good, the bad and the ugly, Nature Reviews Cardiology, Online 2017
- Kattoor A, et al Marijuana and Coronary Heart Disease. ACC Expert Analysis Online, 2016 Sept 22

COMPARATIVE SIDE EFFECTS

| | Benzodiazepines | Cannabis |
|-------------------------|-----------------|----------|
| Memory Impairment | X | X |
| Delayed Reflexes | X | X |
| Decreased Alertness | X | X |
| Driving Hazard | X | X |
| Slurred Speech | X | X |
| Falls / Gait Issues | X | X |
| Dependence | X | X |
| Confusion | X | X |
| Hypotension | X | X |
| Respiratory Suppression | X | |



- Ativan (Lorazepam) prescribing information. Pfizer. Revised October 2014.
- Xanax (Alprazolam) prescribing information. Pfizer. Revised September 2016
- Nabiximols Summary of Medicinal Product Characteristics European Medicines Agency 3/15
- Information for Health Care Professionals Cannabis (marijuana) and the cannabinoids Prepared by Health Canada. February 2013

CANNABIS USE DISORDER (CUDIT-SF)

- How often in the past 6 months:
 - Did you find you were unable to stop using cannabis once you had started?
 - Have you devoted a great deal of your time to getting, using or recovering from cannabis?
 - Have you had a problem with memory or conversation after using cannabis?
- Never(0) Less than monthly (1) Monthly (2) Weekly (3) Daily (4)

CUD PRESENTS WITH ≥ 2



DRUG INTERACTIONS

CANNABIS EFFECTS ON OTHER DRUGS

- Potentiate the Effects of Other CNS Depressants
 - Alcohol, Opioids, Benzos, Muscle Relaxers
- Cardiac Effects
 - Amphetamines
- CYP Interactions 2C19, 2C9, 3A4
 - Cancer
 - HIV
 - Anti-Seizure



CANABIDIOL AND WARFARIN INTERACTION



[•] Grayson, L, et al. An interaction between warfarin and cannabidiol, a case report. Epilepsy & Behavior Case Reports 9 (2018) 10–1. Reprinted with Permission. All rights reserved.

CANNABIDIOL AND CLOBAZAM INTERACTION

Cannabidiol



Clobazam

CYP3A4

60% Increased Concentration

N-desmethylclobazam (Active Metabolite)

CYP 2C19

500% Increased Concentration



• Geffrey et al. Drug-Drug Interaction Between Clobazam and Cannabidiol in Children with Refractory Epilepsy. Epilepsia 2015; 56:1246-1251.

SUBSTITUTION OF MEDICAL CANNABIS FOR PHARMACEUTICAL AGENTS

FOR PAIN, ANXIETY AND SLEEP

- 1,513 patients in Mass. (online questionnaire)
 - 76.7% of patients decreased opioid use
 - 71.8% decreased anti-anxiety use
 - 66.7% migraine medication
 - 65.2% decreased sleeping medications
 - 42.0% decreased alcohol use
 - 37.6% decreased antidepressants use



Piper BJ Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. J Psychopharmacol. 2017 May;31(5):569-575.

DRUG INTERACTIONS

THC

- Dronabinol
- Nabilone

Nabiximols

CBD

Cannabidiol

| | US Approval | DEA Schedule |
|-------------------------------------|--------------|---------------------------|
| Dronabinol (Marinol) | 1985 | Solid = III; Liquid = II |
| Nabilone (Cesamet) | 2006 | II |
| Cannabidiol (Epidiolex) | 2018 | Pending Scheduling |
| Nabiximols (Sativex) (1:1 THC: CBD) | NOT APPROVED | I (listed as such in NDA) |

SLOW TITRATION DECREASES ADVERSE EFFECTS

- The focus is on maintaining / establishing favorable endocannabinoid tone
- Most adverse effects are early and transient
- Goal is avoid patients ever feeling uncomfortable
- Safety profile is improved by going slow and low

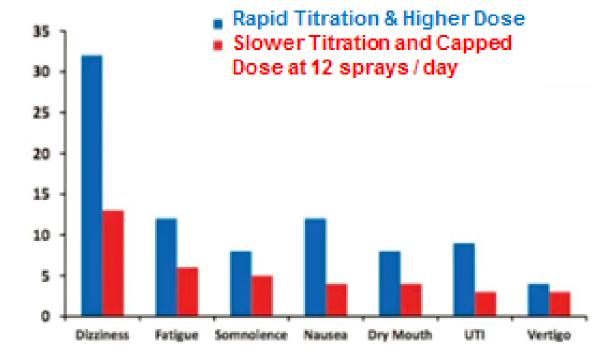


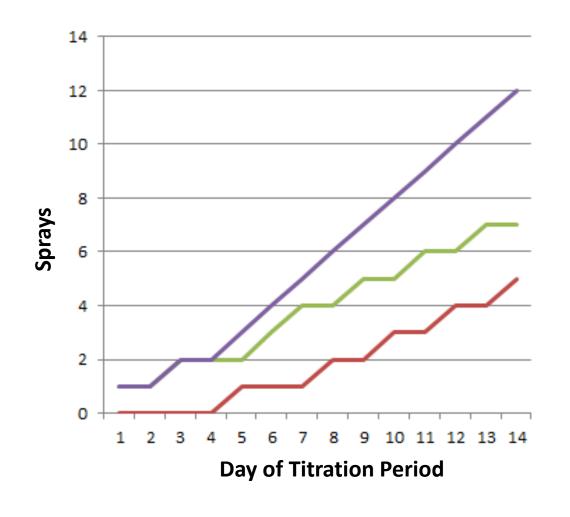
Fig. 1. Graphic comparison of nabiximols adverse events encountered in > 3% of multiple sclerosis RCT patients with rapid titration and higher dosing (blue) vs. slower titration and capping dosing at 12 sprays per day (red) (32.4 mg THC, 30 mg CBD). (For



MacCullum C and Russo E. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine. 49 (2018) 12-19.

NABIXIMOL (SATIVEX®) TITRATION

- According to the package insert
- A titration period is required to reach optimal dose
- Timing and number of sprays
- To obtain optimum symptom control
- Can increase by 1 spray/day
- Max = 12 sprays / day
- At least a 15-minute gap between sprays
- Max consecutive sprays must not exceed 7 within a 3 hour period.





Product information for AusPAR Nabiximols Sativex Novartis Pharmaceuticals Australia Pty Limited PM-2011-00150-3-1 Final 27 September 2013.

CANNABIDIOL (EPIDIOLEX) >98% CBD

US Indication for the treatment of seizures in patients 2 years & older with:

Lennox-Gastaut syndrome (LGS)
Dravet syndrome (DS)

Oral solution: 100 mg/mL Each bottle contains 100 mL of a clear, colorless to yellow solution (strawberry flavored)



FDA Approved in June 2018
DEA Rescheduled Sept 2018:
Controlled Substance Schedule V

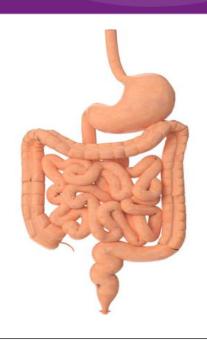


CCB! AGONISM MODULATES INFLAMMATION

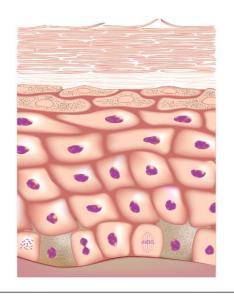


reverse bronchospasm in methacholine challenges





↓ Formation of gastric mucosal lesions through enhanced intestinal barrier functions



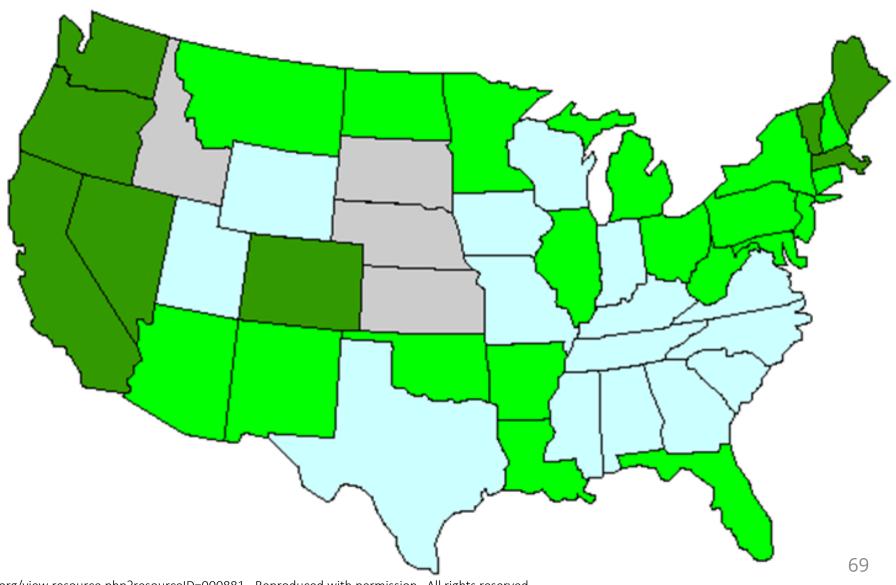
Inhibition of chemokine production
And subsequent decreased infiltration of myeloid cells in inflamed tissue

STATE CANNABIS LAWS

- Recreational
- Medical
- High CBD, Low THC
- No Laws







• https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881. Reproduced with permission. All rights reserved.

ROLE OF PHYSICIANS

PHYSICIANS CANNOT PRESCRIBE MEDICAL MARIJUANA

- Physicians may NOT:
 - Order a patient to consume/obtain or order the dispense of a CS I
- Physicians can:
 - Discuss treatment options, Pros/Cons (including cannabis products)
 - Recommend that a patient consider the use of cannabis for symptoms
- The court held that what it regarded as physicians' "legitimate need to discuss with and to recommend to their patients all medically acceptable forms of treatment" outweighs the government's "legitimate interest in suppressing and controlling the flow of dangerous drugs and controlled substances within the United States."



HETEROGENEITY OF STATE PROGRAMS

Regulation = Patient Safety

Licensed HCP + State Regulated Products

Budtenders + State Regulated Production

State Allowed Home Grown

Illegally Obtained



STATE JURISDICTION

APPROVED FOR RECREATIONAL AND MEDICAL USE

- Alaska
- California
- Colorado
- Maine
- Massachusetts

- Nevada
- Oregon
- Vermont
- Washington

Is there a difference between medical and recreational products and process?

- Medical users need cards to access
- Separate counters
- Higher potency products for medical users
- Tax



PERMIT SELF-CULTIVATION OF MARIJUANA

- Arizona
- California
- Colorado
- Hawaii
- Maine
- Massachusetts
- Michigan

- Montana
- Nevada
- New Mexico
- North Dakota
- Oregon
- Rhode Island
- Vermont

- Potency?
- Home Extraction?
- Contamination?
- Labelling?



APPROVED FOR MEDICAL USE ONLY LICENSED HCP NOT REQUIRED FOR DISPENSING

- **Arkansas**
- Delaware
- District of Columbia
- Florida
- Hawaii
- Illinois
- Louisiana
- Maryland

- Michigan
- Montana
- New Jersey
- **New Mexico**
- North Dakota
- Oklahoma
- Ohio
- Rhode Island

"Budtender Model"





https://www.leafly.com/news/strains-products/budtender-product-spotlight-austintucker-dockside-cannabis-sodo-seattle Austin Tucker, budtender at Dockside SODO in Seattle. Reproduced with Permission. All rights reserved.

APPROVED FOR MEDICAL USE ONLY LICENSED HCP MUST BE INVOLVED

Arizona

'Dispensaries must employ or contact with a medical director (physician)'

New Hampshire

 'Board of directors must include at least one physician, advance practice RN, or pharmacist licensed to practice in NH and at least one qualifying patient'



APPROVED FOR MEDICAL USE <u>ONLY</u> LICENSED HCP <u>REQUIRED</u> IN DISPENSARY

- Connecticut
- Minnesota
- New York
- Pennsylvania
- West Virginia

- 'Permits only pharmacists to give final approval to the distribution of medical marijuana to the patient'
- 'Requires physicians or pharmacist be on site at all times during the hours when a registered dispensary is open'



ATTORNEY GENERAL POLICY STATEMENTS

2009 – Ogden Memo

 "It will not be a priority to use federal resources to prosecute patients with serious illnesses or their caregivers who are complying with state laws on medical marijuana, but we will not tolerate drug traffickers who hide behind claims of compliance with state law to mask activities that are clearly illegal."

2013 – Cole Memo

 "Based on assurance that those states will impose an appropriately strict regulatory system, the Department has informed the governors of both states that it is deferring its right to challenge their legalization at this time"



SESSIONS MEMO JANUARY 2018

SUBJECT: MARIJUANA ENFORCEMENT

- Return to 1980 Attorney General's principles
- Federal Prosecutors Decide
- Priorities set by Attorney General based on
 - Seriousness of crime
 - Deterrent effect
 - Cumulative impact on community
- Previous guidance "is unnecessary & is rescinded, effective immediately"



CONGRESS-CONTROLLED DEPARTMENT OF JUSTICE SPENDING

- Amendments to annual appropriations bill
- Prohibits DOJ from using federal funds to interfere with state medical marijuana laws.
 - Must be passed annually, not permanent
- Rohrabacher-Blumenauer Amendment (1st in 2014)
 - aka Rohrabacher-Farr Amendment
- McClintock and Polis Amendment
 - Removed the word "medical" and tried to extend protection to all state marijuana industry – but did not pass



WHERE DOES CANNABIDIOL FIT?



Permission not requested from this company that fills my email full of cannabis spam and false information that has not been requested!!



LABELING ACCURACY OF CANNABIDIOL ON THE INTERNET

- Using +/- 10% for label accuracy of CBD content (n=84)
 - 43% over label
 - 26% under label
 - 31% on label
- 18 / 84 samples (22%) contained detectable THC
- THC contamination detected as high as 6.43 mg/mL

Certificate of Analysis Please



DEA CONSIDERED CANNABIDIOL CS 1

- New drug code established for marijuana extracts An extract containing 1 or more cannabinoids that has been derived from any plant of the genus Cannabis, other then the separated resin (whether crude or purified) obtained from the plant.
- Extracts of marijuana will continue to be treated as Schedule 1 controlled substances. For practical purposes, all extracts that contain CBD will also contain at least small amounts of other cannabinoids.





Drug Enforcement Agency, Establishment of a New Drug Code for Marihuana Extract. Final rule. Federal Register 2016 Dec.14;81(240):90194-6.

http://www.ncsl.org/research/agriculture-and-rural-development/state-industrial-hemp-statutes.aspx

WHAT'S GOING ON IN THE WORLD?

| | Population | MMJ Patients | Authorized Prescribers |
|---------------|---------------|--------------|-------------------------------|
| United States | 326.7 million | 2,132,780 | ? |
| Canada | 37 million | 330,758 | 16,599 |
| Australia | 24.8 million | 1442 | 42 |



https://www.tga.gov.au/access-medicinal-cannabis-products-1

https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/licensed-producers/market-data.html

https://www.statista.com/statistics/585154/us-legal-medical-marijuana-patients-state/

AUSTRALIA

- Therapeutic Goods Administration's (TGA)
- "will have considered all clinically appropriate treatment options that are included in the ARTG before applying to access an unapproved medicinal cannabis product under the SAS"
- TGA does not vouch for the quality, safety and effectiveness of unapproved products accessed
- prescriber and patient (via informed consent) accept responsibility for any adverse consequences of treatment.

"INDICATIONS"

- chemotherapy-induced nausea and vomiting
- refractory pediatric epilepsy
- palliative care indications
- cancer pain
- neuropathic pain
- spasticity from neurological conditions
- anorexia and wasting associated with chronic illness (such as cancer).



CANADA

- Recreational October 17, 2018
- Growers are licensed through the federal government
- Provinces regulate sales and distribution
- National website contains extensive data
- Educational Document: Cannabis Monograph for Health Care Workers: 2013 and 2018
 - https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids.html

https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/licensed-producers/market-data.html https://www.pharmacists.ca/advocacy/medical-cannabis/

INTERNATIONAL RECREATIONAL CANNABIS LAW

Recreational is Legal in Certain **Forms / Situations**

- Argentina
- Canada
- Netherlands
- Spain
- Uruguay

Decriminalized

- Belize
- Belgium
- Colombia
- Croatia
- Czech Republic
- Ecuador

- Jamaica
- Mexico
- Portugal
- Russia
- Switzerland
- Ukraine



INTERNATIONAL MEDICAL CANNABIS LAW

Medical Marijuana Laws

- Argentina
- Canada
- Colombia
- Croatia
- Cyprus
- Demark
- Finland
- Greece

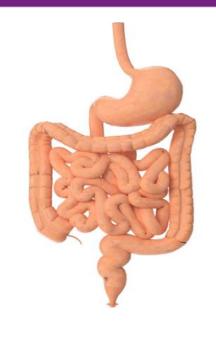
- Israel
- Jamaica
- Lesotho
- Luxembourg
- Macedonia
- Malta
- Mexico
- Netherland

- Norway
- Peru
- Poland
- Romania
- Switzerland
- Turkey
- Uruguay

+ Sold in Pharmacies

- Chile
- Czech Republic
- Germany
- Italy
- Uruguay

CONSIDERATIONS FOR COMPOUNDERS

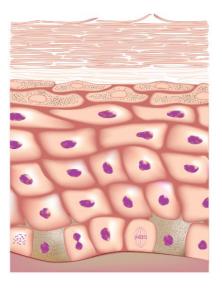


GI Discomfort

Weight Loss



PAIN!



Acne

Dermatitis

Arthritis

So Many Formulations

Mix with legend drugs

Personalized Medicine

Consistent Product

Patient Education & Safety

Cannabis has been employed medicinally throughout history, but its recent legal prohibition, biochemical complexity and variability, quality control issues, previous dearth of appropriately powered randomized controlled trials, and lack of pertinent education have conspired to leave clinicians in the dark as to how to advise patients pursuing such treatment.

—Drs. MacCallum and Russo, 2018



REFERENCES

- Information for Health Care Professionals Cannabis (marihuana, marijuana) and the cannabinoids Prepared by Health Canada. 2018
- Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy. 2013 Feb;33(2):195-209.
- Russo, E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br.J.Pharmacol. 163: 1344-1364.
- Shohami E and Horowitz M (ed). Cannabinoids in Health and Disease. Themed special issue, Journal of Basic and Clinical *Physiology and Pharmacology* 2016; 27(3).
- Cannabis Inflorescence . American Herbal Pharmacopoia. 2013:1-61.
- Herer J. The Emperor Wears No Clothes. Austin, TX: AH HA Publishing; 2010.
- Lambert DM. Cannabinoids in Nature and Medicine. Switzerland: Wiley-VCH; 2009.
- Mikuriya TH. Marijuana: Medical Papers 1839-1972. Vol One. Nevada City, CA: Symposium Publishing; 2007.
- Morillo Rodriguez E. Endocannabinoids: Molecular, Pharmacological, Behavioral and Clinical Features. Betham e Books
- Pertwee RG. Handbook of Cannabis. New York, NY: Oxford University Press; 10016.
- WHO. Cannabidiol (CBD) Critical Review Report. World Health Organization, Expert Committee on Drug Dependence, Fortieth Meeting, Geneva, 4-7 June 2018

TRACKING CODE

WCC2018CBD



