

Stephen Dahmer, MD Chief Medical Officer Vireo Health



Assistant Clinical Professor

| Family Medicine & Community Health | ICAHN



Stigma

"IF CANNABIS were unknown, and bioprospectors were suddenly to find it in some remote mountain crevice, its discovery would no doubt be hailed as a medical breakthrough. Scientists would praise its potential for treating everything from pain to cancer, and marvel at its rich pharmacopoeia—many of whose chemicals mimic vital molecules in the human body."

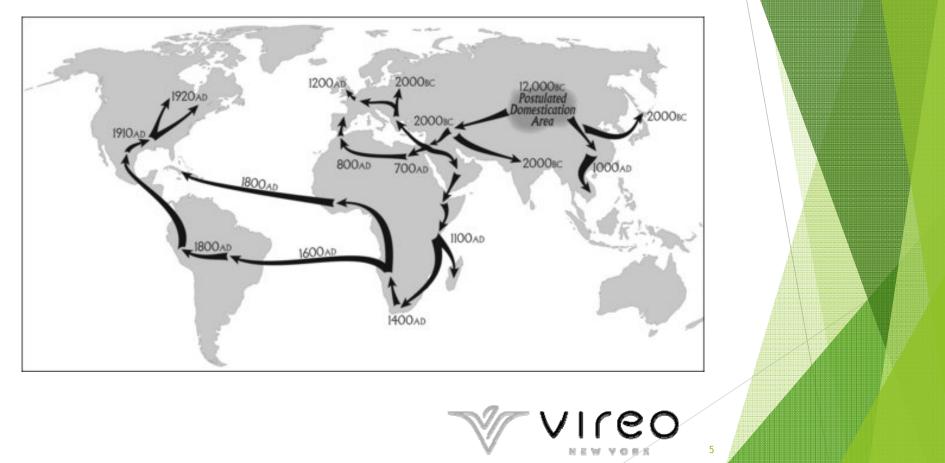
> The Economist April 27, 2006 http://www.economist.com/node/6849915



General and Historical Background

- The cannabis plant (*Cannabis sativa*, *C. indica and C. ruderalis*) is an annual flowering herb
- It has more than 60 unique compounds (>500 total)
- $\blacktriangleright \Delta$ -9-tetrahydrocannabinol (THC) is intoxicating
- Cannabidiol (CBD) is not; may ameliorate some THC effects
- Earliest recorded use of medicinal cannabis ("ma") dates back to 2900BC - Emperor Fu Hsi
- Emperor Shen Nung discovers healing property (2700BC)

Cannabis Plant SPREAD



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Marinol® (Dronabinol, <u>THC</u>) Review



Marinol® (Dronabinol, <u>THC</u>) Review*

Dose:

CINV: 5mg/m² PO 1-3h prior to chemo, then every 2-4h after.

AIDS/cancer anorexia: 2.5mg PO before lunch and dinner

Contraindications, Warnings and Precautions:

- CI: allergy to sesame oil
- History of addiction or drug abuse, mental illness*
- Adverse Drug Reactions:
 - Psychoactive effects (24% for CINV), dizziness/drowsiness, hallucinations, anxiety, altered mental state

Major DDI's:

Ethanol (\uparrow absorption, \uparrow ADR's), amphetamines (\uparrow BP, \uparrow HR)

ENTOURAGE



Natural Antagonism

<u>THC</u> euphoria anxiety psychosis cognitive impairment tachycardia

<u>CBD</u>

no (or less) euphoria anti-anxiety anti-psychotic <u>neuroprotective</u> bradycardia

Loss of antagonism may lead to increased side effects and poor tolerability.

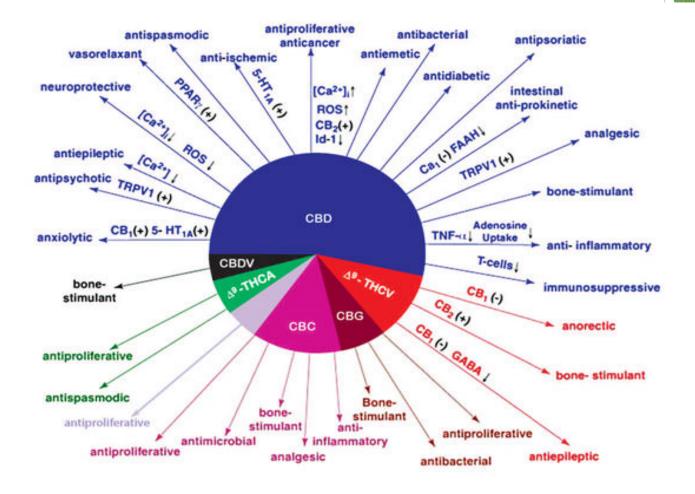
(Russo. Br J Pharmacol. 2011)

Biological Components of Cannabis

Cannabinoids THC* CBD* Minor Cannabinoids CBC, CBG*, CBN*, THC-V*, CBD-V*, THCA*, CBDA*, CBC-V, Terpenes trans-caryophyllene[#], α-caryophyllene[#], a-pinene, B-pinene, terpinolene, myrcene, limonene, Linalool, phytol, squalene Carotenoids B-carotene[#] **Fatty Acids** Linoleic acid, Palmitoleic acid, Linolenic acid, Palmitic acid, Oleic acid, Stearic acid, Myristic acid, **Arachidonic** Sterols B-sitosterol, campesterol, stigmasterol Vitamins Vitamin E

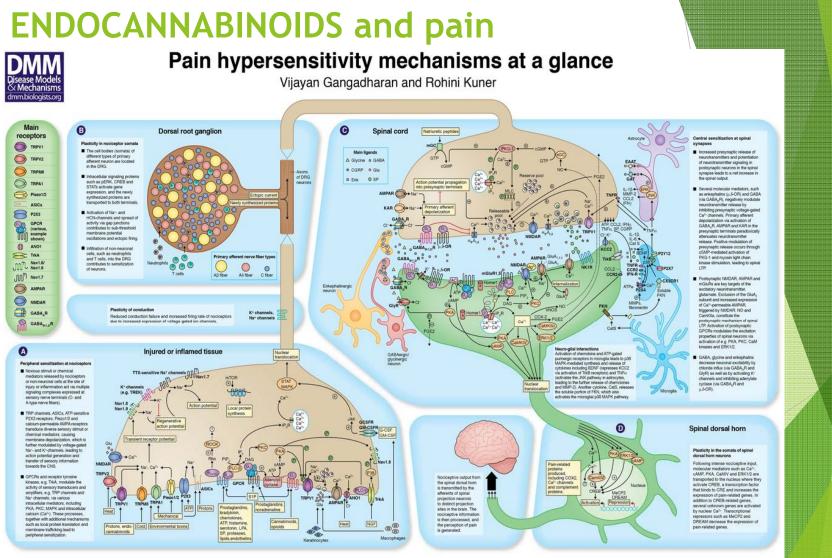
Triglycerides

ECS (ENDOCANNABINOID SYSTEM)



ENDOCANNABINOIDS

- Thermoregulatory centers
- Regulation of perceptive, cognitive, motor functions
- Suggested roles in synaptic plasticity, brain development
- Hypothalmic hormone secretion
- Release of dynorphins-analgesic
- Blood pressure and heart rate



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ENDOCANNABINOIDS and pain

- Endogenous neuromodulators
- Similar location to opioid receptors:
 - Peripheral nocioceptive nerves
 - Sensory neuron transduction pathway
 - Descending modulatory pathways
- o One key difference
 - Absence in the brainstem

(Roquem, Nature Reviews, 2012)

Endocannabinoid Imbalance

- o Migraine
- o Fibromyalgia
- o Causalgia
- Post-traumatic stress disorder (PTSD)
- o Bipolar disease
- o Autism
- o Epilepsy
- Neurodegenerative disease

(Russo, Cannabis and Cannabinoid Research. 2016)

Prevalence of Use and Legal Status

- 28 States (plus the District of Columbia and Guam) have legislature in place for medicinal cannabis
- Some States have legalized it recently, but have no programs implemented yet (MD, NH, PA)
- Estimates of over 2,600,000* medicinal cannabis patients in the USA
- * Some States have voluntary registration (CA, ME) or do not have any registration policies (WA)
- 11 States (AL, FL, IA, KY, MS, MO, NC, SC, TN, UT, WI) have passed laws legalizing <u>some</u> aspect*



Prescribing or Recommending?

- Prescribers can't prescribe medicinal cannabis on an Official New York State Prescription Blank, but they can "recommend" it on separate forms
- On the recommendation form must be written:
 - Patient-specific information (like a regular prescription)

eo

- Authorized cannabis <u>brand</u> and <u>formulation</u>
- Dosing information for patient' proper use
- Any <u>limitations</u> to the use of the approved product
- The total amount of product that can be dispensed
- Quantity can NEVER exceed a 30 day supply!
- Prescriber must retain records for 5 years

QUALIFYING CONDITIONS

- Prescribers must be qualified to treat ≥1 of the following chronic health conditions:
 - 1. Cancer
 - 2. HIV/AIDS
 - 3. Epilepsy
 - 4. Neuropathies
 - 5. Amyotrophic lateral sclerosis (ALS)
 - 6. Huntington's disease
 - 7. Parkinson's disease
 - 8. Multiple sclerosis (MS)
 - 9. Inflammatory bowel disease (IBD)
 - 10. Damage to spinal cord nervous tissue with intractable spasticity
 - 11.Chronic Pain (Recently Added)
- The Commissioner may add or remove approved conditions

Disease-Accompanying Symptoms

- One or more of the conditions <u>must</u> include:
 - 1. Severe or chronic pain causing a substantial limitation of function
 - 2. Severe nausea
 - 3. Seizures
 - 4. Cachexia or wasting syndrome
 - 5. Severe or persistent muscle spasms
 - The Commissioner may add or remove disease-accompanying symptoms



What is Different about NY?

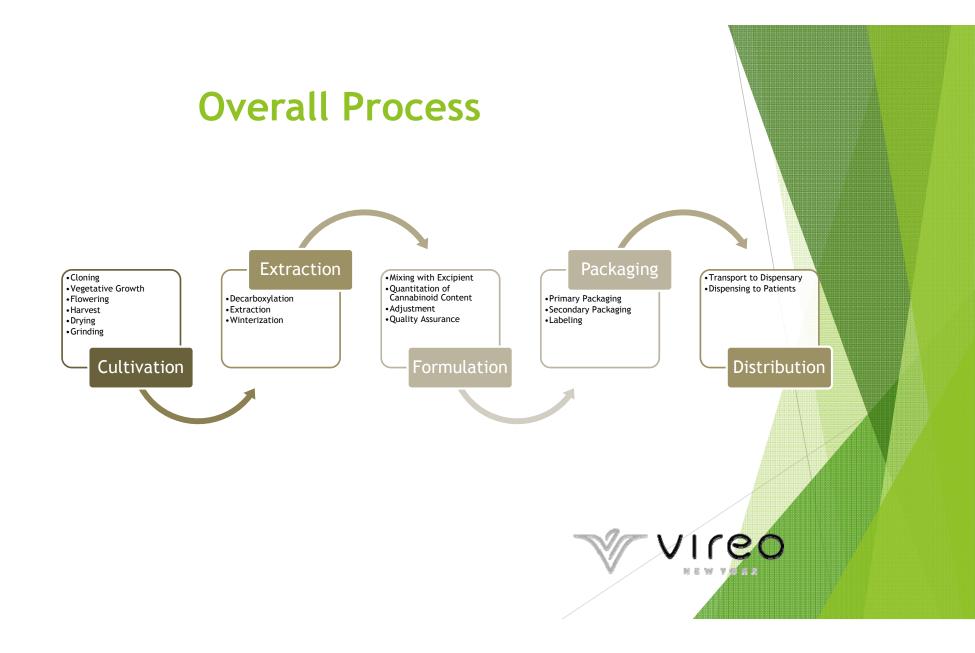
- Licensed Pharmacists/Medical Model
- CO2 Extraction
- Formulation/"Real Dose"
- Physician/Provider recommendation
- Precision of final product
- 3rd Party testing (Heavy metals, bacteria, etc)

Ireo

- Only active ingredients matter (major cannabinioids)
- No popularized names/strains
- No advertising
- 11 Qualifying Conditions







STRAINS





EXODUS



KRYPTONITE OG



PLATINUM OGAR KLISH



MEMPHIS BELLE MERCURY OG



L.A. CONFIDENTIAL

POWER TRAIN



GRAPE APE



LAMB'S BREAD

MICHAEL PHELPS



LEMON SKUNK X OG #18

MICHAEL PHELPS CHOICE O.G.



PURPLE ERKEL

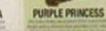


OBAMA



PURPLE GORILLA







HINDU KUSH

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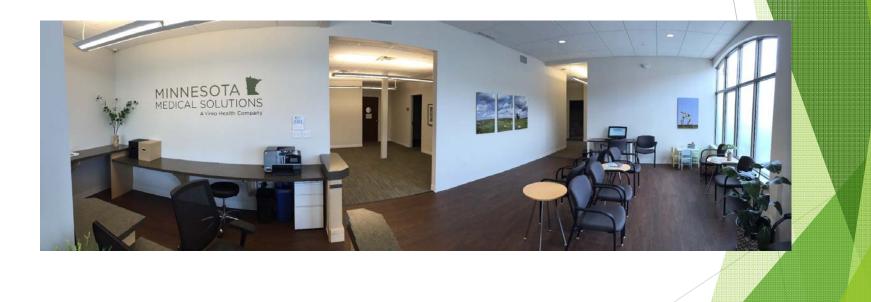


MARTIAN CANDY

HEROJUANA



Cannabis Patient Center



vireo





Delivery Forms



Green Capsules, 30 Capsules \$86.00

CAPSULES



Green Prefilled Vaporizer Cartridge, 0.5mL Cartridge **\$94.00**

VAPORIZERS



Green Oral Solution, 12.5mL Bottle

\$165.00

ORAL SOLUTION

vireo

Capsules	Onset: 1 to 3 hr	Duration: 4 to 24 hr
Oral solutions	Onset: 30 to 60 min	Duration: 4 to 12 hr
Tinctures	Onset: 15 to 60 min	Duration: 2 to 8 hr
Vapes and Oil	Onset: 1 to 15 min	Duration: 2 to 6 hr

Average Ranges (subject to variability)

STRENGTH OF evidence vs. Harm grading

Rating Options	Arrow	Icon		
(A,1)	↑		Exercise in DM	
(A,2) (B,1)	7		Hypnosis for IBS	
(A,3) (B,2) (C,1)	→		Zinc in Infectious Diarrhea	
(B,3) (C,2)	Ы	B⊖2 °00 ⁵	Opioids in Chronic Dain	
(C,3)	$\mathbf{\Psi}_{-}$	ୢୖ୕ୖୣ	Opioids in Chronic Pain	4

Strengths of evidence vs. harm grading:

o Gives more credibility to therapies that have little potential harm. e.g. social support, reducing stress, and enhancing spiritual connection

o Helps us honor our primary goal, which is to "first, do no harm."

Slide 32

SD1 Stephen Dahmer, 4/1/2017

Levels of Evidence

Grade A	Based on consistent, good-quality, patient-oriented evidence (e.g., systematic review or meta-analysis showing benefit, Cochrane Review with clear recommendation, high-quality patient-oriented randomized controlled trial). Example: Acupuncture for nausea and vomiting.
Grade B	Based on inconsistent or limited-quality patient-oriented evidence. Example: Ginger for osteoarthritis.
Grade C	Based on consensus, usual practice, opinion, disease-oriented evidence (e.g., study showing a reduction in blood sugar but no studies in humans to show a benefit to those with diabetes).

GRADING POTENTIAL HARM

Grade 3	This therapy has the potential to result in death or permanent
(most	disability. Example: Major surgery under general anesthesia or
harm)	carcinogenic effects of the botanical Aristolochia (birthwort).
Grade 2	Grade 2 (moderate harm) This therapy has the potential to cause
(moderate	reversible side effects or interact in a negative way with other
harm)	therapies. Example: Pharmaceutical or nutraceutical side effects.
Grade 1 (least hearm)	This therapy poses little, if any, risk of harm. Examples: Eating more vegetables, increasing exercise, elimination diets, encouraging social connection.

We're caught in the middle - InCrow survey

- InCrowd survey of 225 U.S. primary care, emergency department, and pain medicine physicians
 - 73% survey respondents said they want opioid alternatives (tired to trying to treat pain with NSAIDs, PT and exercise)
 - 50% recommended behavioral health interventions
 - 20% recommended vitamin and herbal supplements (InCrowd, 2016)
 - o10% recommended medical cannabis

Detailed list of more than 150 peerreviewed studies

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AT LEAST five high-quality randomized controlled clinical trials establishing the relieving efficacy of cannabis

- Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S: A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 9:506-521, 2008.
- Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH: Smoked me- dicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. Neuropsychopharmacology 34: 672-680, 2009.
- Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH: Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain 16:616-627, 2015.
- Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett GJ, Collet JP: Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. CMAJ 182:E694-E701, 2010.
- Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL: Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo- controlled trial. Neurology 68:515-521, 2007

Synergy with opioids

Individuals with chronic pain requiring opioids (musculoskeletal, post-traumatic, arthritic, peripheral neuropathy, cancer, fibromyalgia, migraine, MS, sickle cell disease, TOS).

Table 1 Participant characteristics

Morphine group	Oxycodone group	
10	11	
4	6	
8	9	
42.9 (33-55)	47.1 (28-61)	
62 Twice daily (10-200)	53 Twice daily (10–120)	
34.8 (29.4, 40.1)	43.8 (38.6, 49.1)	
	10 4 8 42.9 (33–55) 62 Twice daily (10–200)	

CI, confidence interval.

Table 2 Pain by study day						
		Day 1	Day 5	Difference	Percentage change	
	n	Mean (95% CI)	Mean (95% Cl)	Mean (95% CI)	Mean (95% CI)	
Overall	21	39.6 (35.8, 43.3)	29.1 (25.4, 32.8)	-10.7 (-14.4, -7.3)	-27.2 (-45.5, -8.9)	
Morphine	11	34.8 (29.4, 40.1)	24.1 (18.8, 29.4)	-11.2 (-16.5, -6.0)	-33.7 (-63.8, -3.5)	
Oxycodone	10	43.8 (38.6, 49.1)	33.6 (28.5, 38.6)	-10.3 (-14.8, -5.8)	-21.3 (-47.0, 5.3)	

CI, confidence interval.

Synergistic effects with opioids, providing pain relief with lower opioid doses and with less side effects. Did not change opioid blood levels.

(Abrams, 2011)

GW pharmaceuticals phase 3 trials of nabiximol (Sativex) show benefit for cancer pain

- · Randomized 360 subjects to placebo or one of three experimental groups
- Best results with 4 sprays per day (10mg THC / 10 mg CBD)
- Higher doses were not well-tolerated
 - · more adverse events
 - higher drop-out rates.

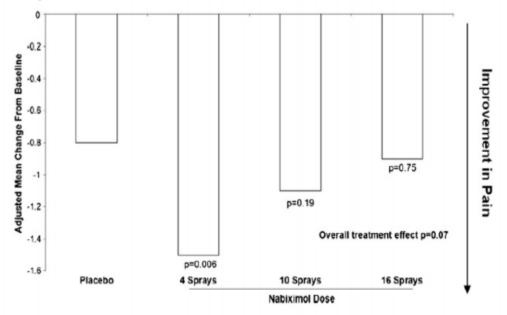


Figure 4. Analysis of change from baseline in NRS average pain score.

(Portenoy 2012)

Patients with chronic pain successfully substitute medical cannabis for opioids

- Online survey of 244 medical cannabis patients with chronic pain to examine whether medical cannabis changed individual patterns of opioid use
- N=184 analyzed
- · Found that cannabis was associated with
 - Decrease in opioid use (64%)
 - Improved quality of life (45%)

Medication type	Use before initiation of cannabis (n/N)	Use after initiation of cannabis (n/N)
Opioids	119/184 (65%)	33/184 (18%)
NSAIDs	115/184 (62%)	38/184 (21%)
Disease-modifying antirheumatic drugs (DMARDs)	15/184 (8%)	3/184 (2%)
Anti-depressants	72/184 (39%)	25/184 (14%)
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	13/184 (7%)	3/184 (2%)
Selective serotonin reuptake inhibitors (SSRIs)	34/184 (18%)	8/184 (4%)
Other	69/184 (38%)	40/184 (22%)

NOTE. Study participants reported using fewer medication classes of all categories after initiation of cannabis.

(Boehnke, Journal of Pain, 2016)

40

Cannabis is A beneficial adjuvant on all steps of analgesic ladder

- Synergistic actions between cannabinoids and opioids can lower dose of opioids needed to control pain
- Cannabis-based medicine containing both THC and CBD appears to be more effective and better tolerated than synthetic THC (dronabinol)
- Modified WHO analgesic ladder includes cannabinoids as adjuvant medications that may be considered at all steps of treatment of cancer or other chronic pain [1]

(Vargas-Schaffer, Can Fam Phys, 2010)

Freedom from cancer pain Opioid for moderate to severe pain

3

Von-opioid

increasing Sistin

Opioid for mild to

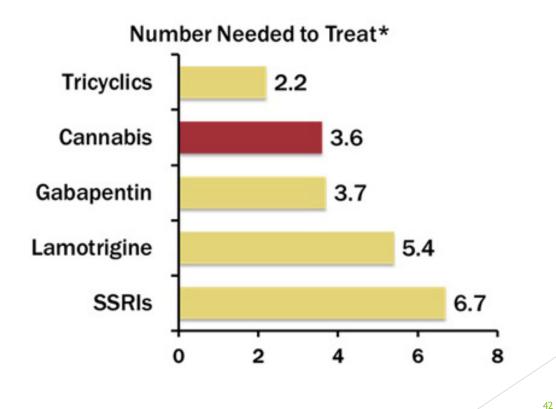
moderate pain Non-opioid Adjuvan

Pain persisting increasing

Non-opioid ± Adjuvant

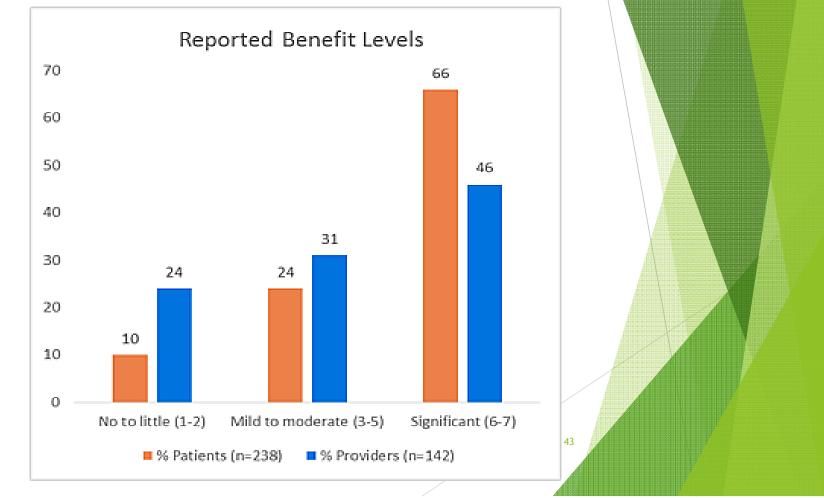
Pain

NNT - Painful sensory neuropathY



(AMA EthicsVirtual Mentor. May 2013)

Efficacy Data: MINNESOTA DEPARTMENT OF HEALTH - ONE YEAR



MEDICAL CANNABIS CONTRAINDICAT

Absolute contraindications

Acute psychosis and other unstable psychiatric conditions

Relative contraindications

- Severe cardiovascular, immunological, liver, or kidney disease, especially in acute illness
- Cannabis may exacerbate arrhythmia or a history of arrhythmias

(Handbook on Cannabis 2015)

MEDICAL CANNABIS CAUTIONS

- Cannabis is generally well-tolerated, and serious adverse effects, including increased risk
 of cardiovascular events, are rare.
- Adverse changes in cognitive function, especially executive function, may occur, especially with fetal or adolescent exposure.
- Cannabis should be avoided by adolescents, pregnant women, and nursing mothers.
- Cannabis should be avoided in those at risk of psychosis.
- Many studies show driving impairment, but on a much lower scale than alcohol.
- Drug interactions are a concern.
 - Cannabis enhances CNS depressant effects when combined with alcohol, barbiturates and benzodiazepines, but probably not opioids
 - THC induces CYP1A2, and can reduce levels of drugs metabolized by CYP1A2.
 - CBD inhibits CYP3A4 and CYP2D6, and can increase levels of drugs metabolized by these isoenzymes. CPY3A4 metabolizes about a quarter of all drugs.

MEDICAL CANNABIS DRUG INTERACTION STUDIES

Warfarin

- THC and CBD increase warfarin levels (Yamaori et al 2012).
- Frequent cannabis use has been associated with increased INR.

Alcohol

 Alcohol may increase THC levels (Hartman 2015).

Theophylline

 Smoked cannabis can decrease theophylline levels (Stout and Cimino 2014).

Indinavir or nelfinavir

 Smoked cannabis had no effect (Abrams et al 2003).

Docetaxel or irinotecan

 Cannabis infusion (tea) had no effect (Engels et al 2007).

Clobazam

 In children treated with CBD for epilepsy, CBD increased clobazam levels (Geffrey et al 2015).

MEDICAL CANNABIS CARDIOVASCULAR

- THC can cause tachycardia; chronic users may develop bradycardia.
- Cannabis can cause changes in blood pressure.
 - High doses can cause orthostatic hypotension and syncope (Handbook on Cannabis 2015).
 - Cannabis can cause an acute increase in blood pressure (Frost et al 2013).
- Cannabis can increase the risk of angina (Frost et al 2013).
- Rarely marijuana can trigger an acute myocardial infarction (Mittleman et al 2001).
- In patients who have had a myocardial infarction, an 18-year follow up study showed no conclusive evidence that smoking marijuana increased mortality (Frost et al 2013).
- Case reports have associated cannabis use with acute coronary syndrome, arrhythmias, sudden cardiac death, cardiomyopathy, transient ischemic attack, stroke (Thomas et al 2014, Jouanjus 2014).

MEDICAL CANNABIS SAFETY

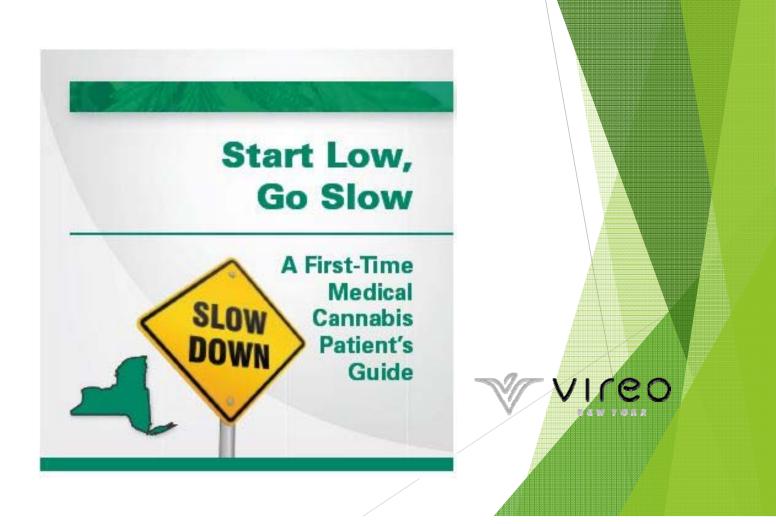
"Medical cannabis used for chronic pain over one year appears to have a reasonable safety profile (199 Patients; no difference in risk of serious adverse events)."

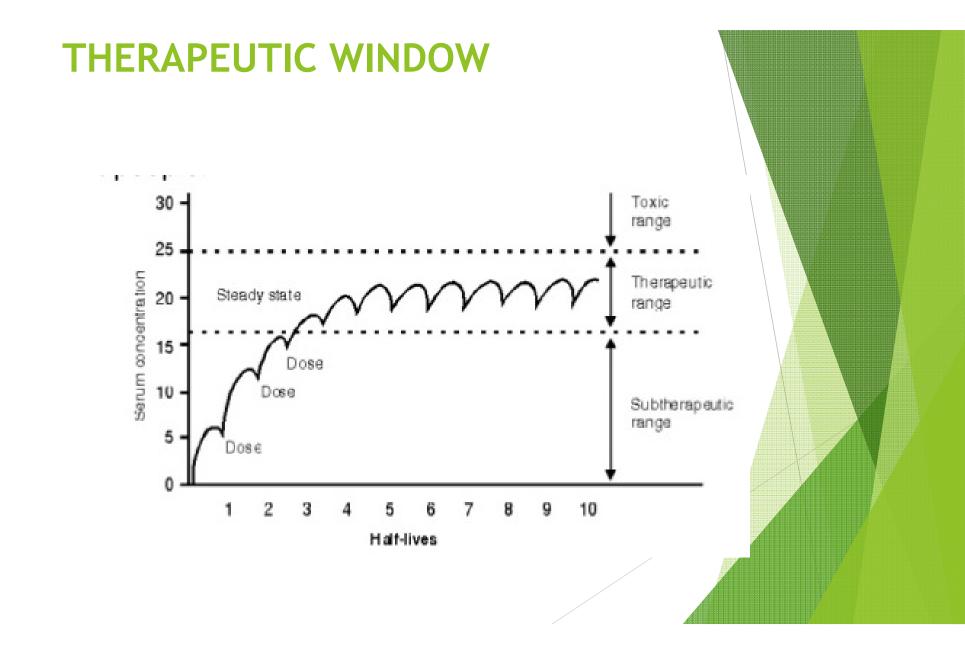
Ware MA1, Wang T2, Shapiro S3, Collet JP4; COMPASS study team. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015 Dec;16(12):1233-42. doi: 10.1016/j.jpain.2015.07.014. Epub 2015 Sep 16.

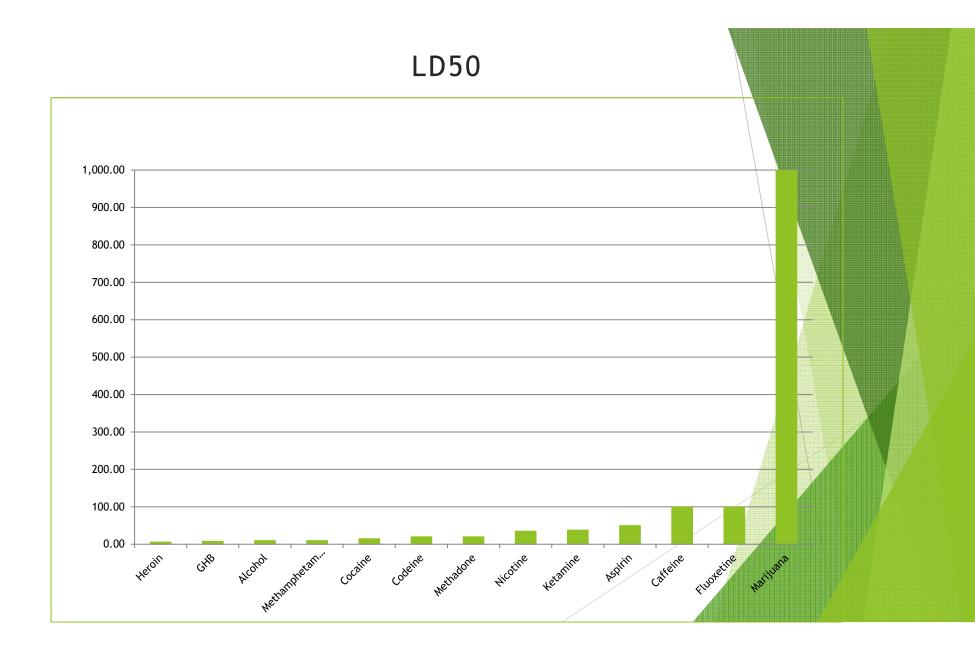
"0% of patients surveyed after one year reported a 'Great deal of Negative Physical Side Effects. 0% reported a 'Great Deal of Negative Mental Side Effects0 (241 Patients, 12 months)'"

McGriff D, Anderson S, Arneson T. Early Survey Results from the Minnesota Medical Cannabis Program. Minn Med. 2016 Jun;99(4):18-22.

START LOW, GO SLOW

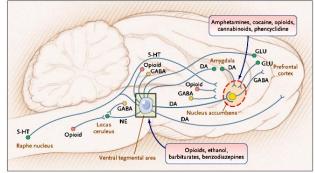






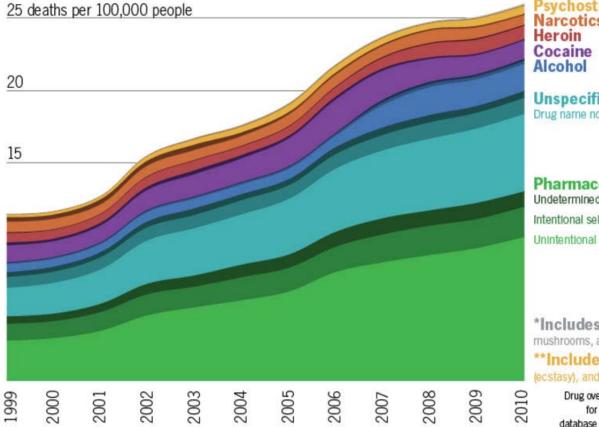
OPIOIDS and the brain

- Opiate µ receptors affect medullary and pons respiratory drive centers
- What other receptors also affect brainstem drive?
 - Benzodiazepines (GABA)
 - Alcohol (GABA)
- Apnea may result
 - High opiate dose alone
 - Synergistic combination of opiates with alcohol or benzodiazepines



U.S. DRUG OVERDOSE RISK

U.S. DRUG OVERDOSES



Other* Psychostimulants** Narcotics other than heroin and cocaine

Unspecified Drug name not identified on death certificate

Pharmaceuticals Undetermined Intent Intentional self-harm Unintentional self-harm

*Includes cannabis, LSD, oplum, mescaline, mushrooms, and all cases of overdose by assault

**Includes methamphetamines, MDMA (ecstasy), and caffeine

Drug overdose data from the CDC National Center for Health Statistics's multiplecause of death database (WONDER). Complied by POPULAR SCIENCE.

HOW do we compare to other count

How does hydrocodone demand in the US compare to other nations?

 Demand in Britain, France, Germany, Italy (combined population 264 million persons):

3,237 grams a year

 Demand in US (population 319 million persons): 27,400,000 grams a year

(Manchikati, Pain Physician, 2012)

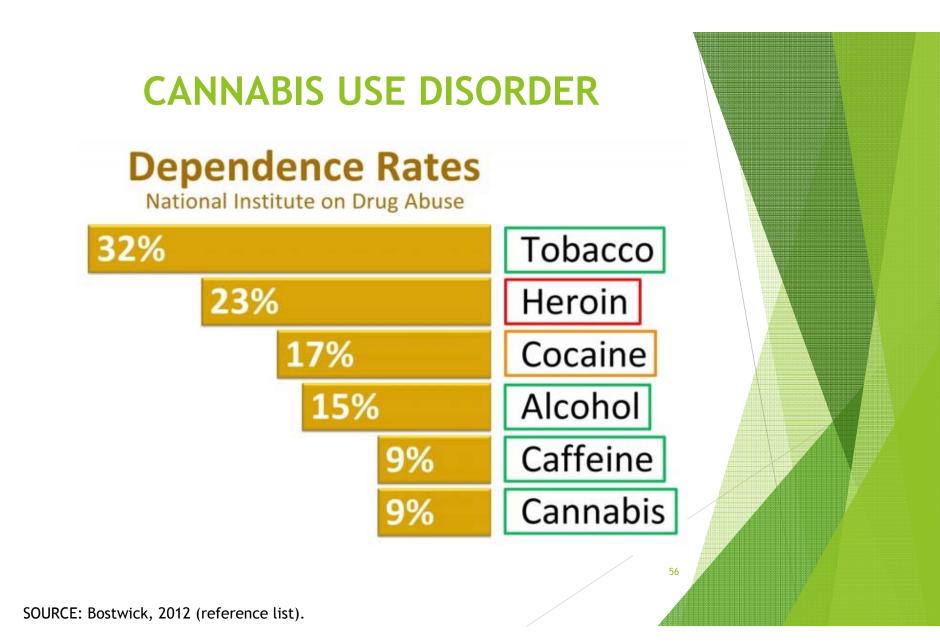
Nsaids

 "At least 16,500 NSAID-related deaths occur each year among arthritis patients alone..."

Source: Am J Med, Jul 1998

 16,651 deaths occurred in 2010 from opiate prescription overdoses

Source: CDC MMWR, Mar 2013



Summary

 Cannabis does not kill patients (no case of death from marijuana overdose has ever been reported) • Medical cannabis is has been shown to be effective for the treatment of chronic pain Neuropathy has the highest quality evidence • Medical cannabis has a very well-tolerated side effect profile • Medical cannabis works synergistically with opioids • The medical community should be a pillar of education and support surrounding medical cannabis/ECS

Thank you.(Questions) stephendahmer@vireohealth.com

