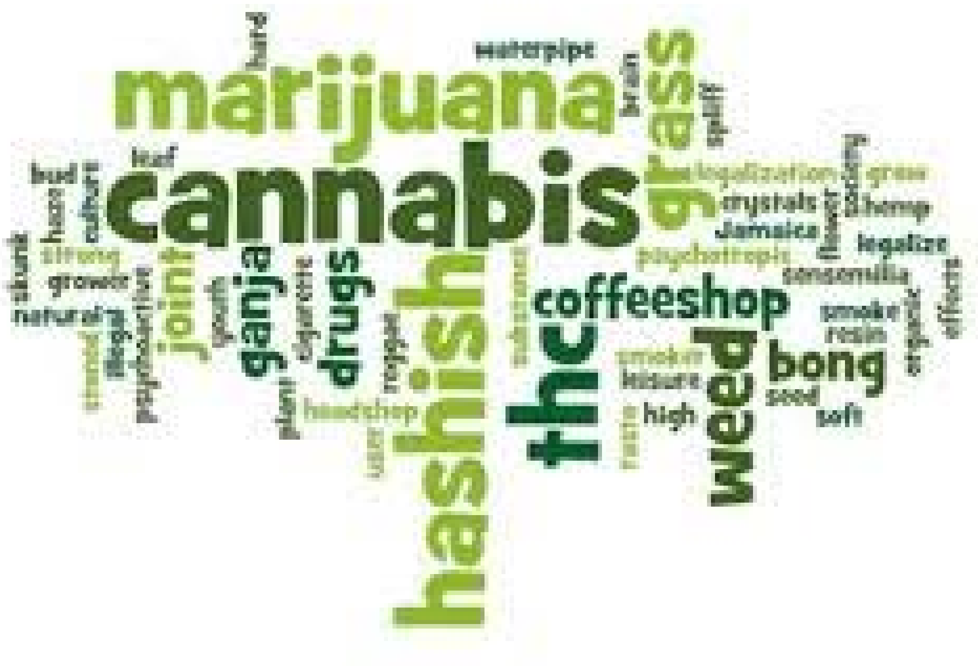
Stephen Dahmer, MD
Chief Medical Officer
Vireo Health

Assistant Clinical Professor
| Family Medicine & Community Health |
ICAHN

Many Names


marijuana
cannabis
hashish
thc
weed
grass
coffeeshop
bong
drugs
ganja
joint
waterpipe
legalization
crystals
Jamaica
hemp
legalize
psychotropic
smoke
high
soft
bud
leaf
spliff
brain
growing
natural
headshop

Stigma

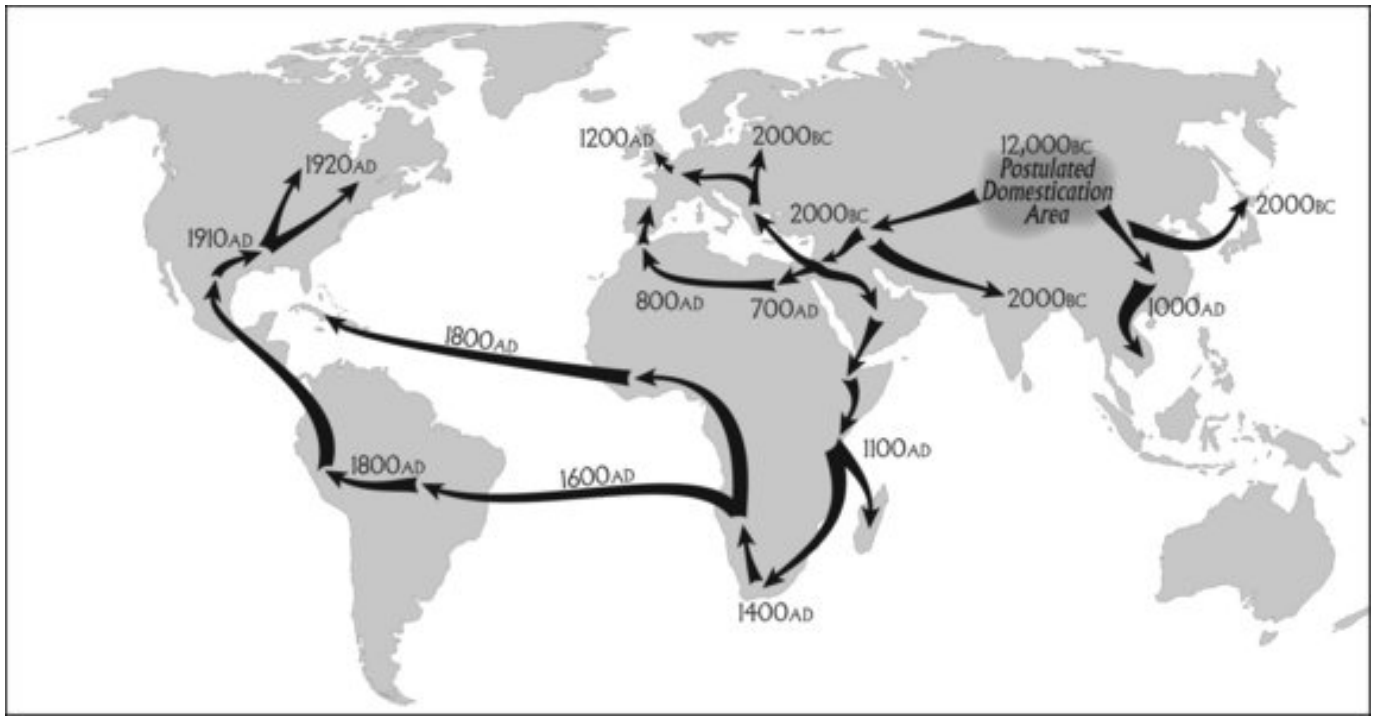
- "IF CANNABIS were unknown, and bioprospectors were suddenly to find it in some remote mountain crevice, its discovery would no doubt be hailed as a medical breakthrough. Scientists would praise its potential for treating everything from pain to cancer, and marvel at its rich pharmacopoeia—many of whose 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)
- Δ-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, THC) Review*

Marinol® (Dronabinol, THC) Review*

- Dose:
  - CINV: 5mg/m^2 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 (↑absorption, ↑ADR's), amphetamines (↑BP, ↑HR)

ENTOURAGE


entourage effect
entourage (ahn-too-rahzh) n.
a group of attendants or associates, as of a person of rank or importance:
The opera singer traveled with an ento_
terpenes
simple esters
simple acids
steroids
ketones
amino acids
non-cannabinoid phenols

Natural Antagonism

THC	CBD
euphoria	no (or less) euphoria
anxiety	anti-anxiety
psychosis	anti-psychotic
cognitive impairment	neuroprotective
tachycardia	bradycardia

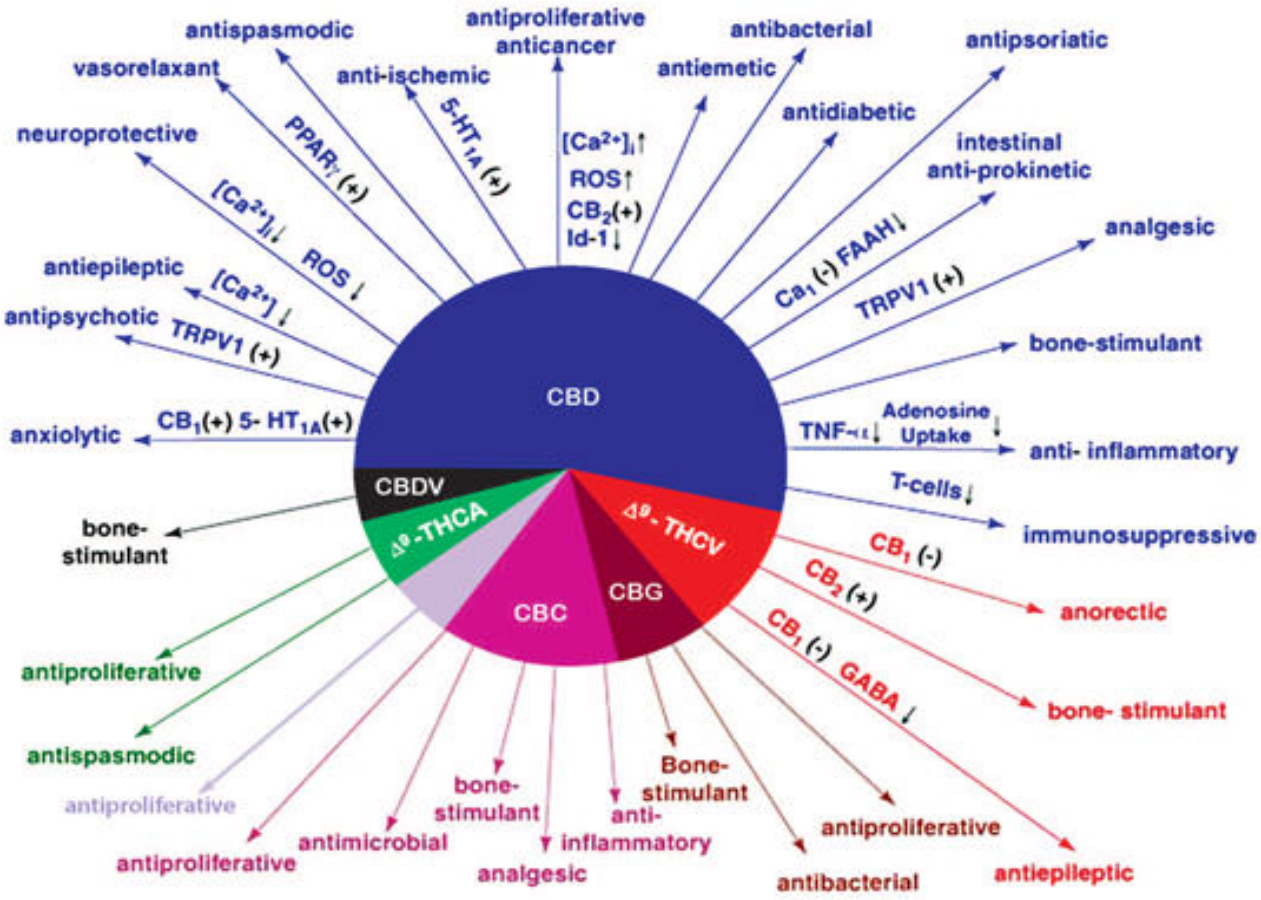
Loss of antagonism may lead to increased side effects and poor tolerability.

(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#, α-pinene, ß-pinene, terpinolene, myrcene, limonene, Linalool, phytol, squalene
- Carotenoids
  - ß-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

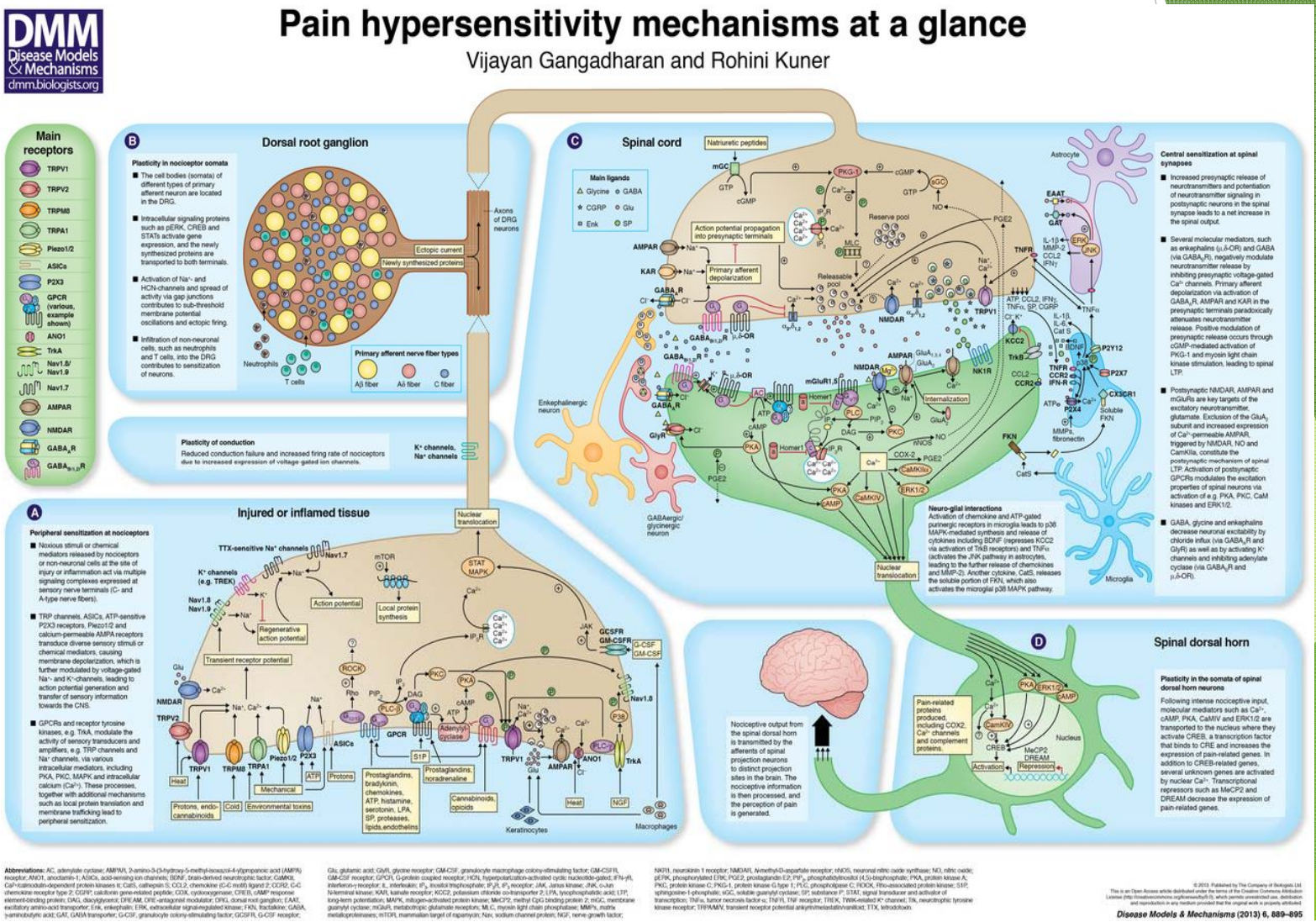
ECS (ENDOCANNABINOID SYSTEM)



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

ENDOCANNABINOIDS and pain



ENDOCANNABINOIDS and pain

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

(Roquem, Nature Reviews, 2012)

Endocannabinoid Imbalance

- Migraine
- Fibromyalgia
- Causalgia
- Post-traumatic stress disorder (PTSD)
- Bipolar disease
- Autism
- 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 some aspect*

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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)
  - Authorized cannabis brand and formulation
  - Dosing information for patient' proper use
  - Any limitations 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 must 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

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

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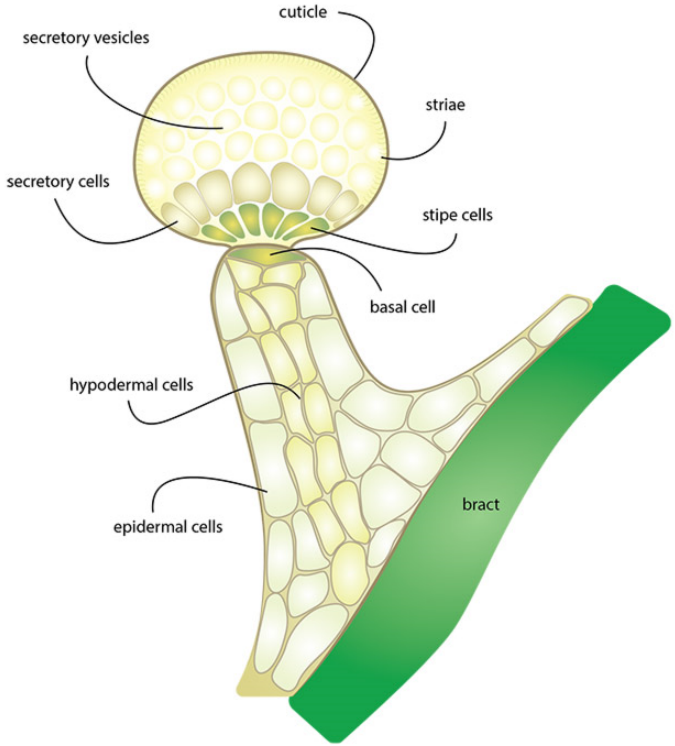
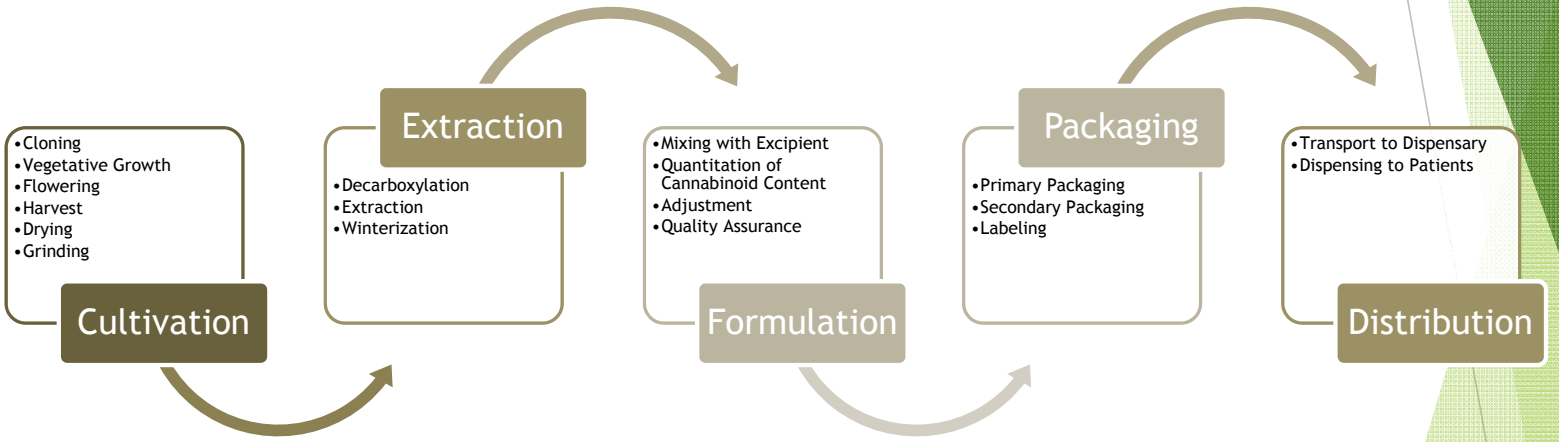

cuticle
secretory vesicles
striae
secretory cells
stipe cells
basal cell
hypodermal cells
bract
epidermal cells

Overall Process



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STRAINS


EXODUS
FLAMING DRAGON
GRAPE APE
HAWAIIAN
HEROJUANA
HINDU KUSH
HINDU SKUNK
JAH OG KUSH
KRYPTONITE OG
L.A. CONFIDENTIAL
LAMB'S BREAD
LEMON SKUNK X OG #18
MARTIAN CANDY
MASTER KUSH
MASTER'S MISTRESS
MATANUSKA MIST
MEMPHIS BELLE
MERCURY OG
MICHAEL PHELPS
MICHAEL PHELPS CHOICE O.G.
OBAMA
OG AFGANI
ORGANIC X J 13
PLATINUM JACK
PLATINUM OGAR KUSH
POWER TRAIN
PRESIDENTIAL BUBBA KUSH
PURPLE ERKEL
PURPLE GORILLA
PURPLE PRINCESS
PURPLICIOUS
RED HAIR MISTRESS

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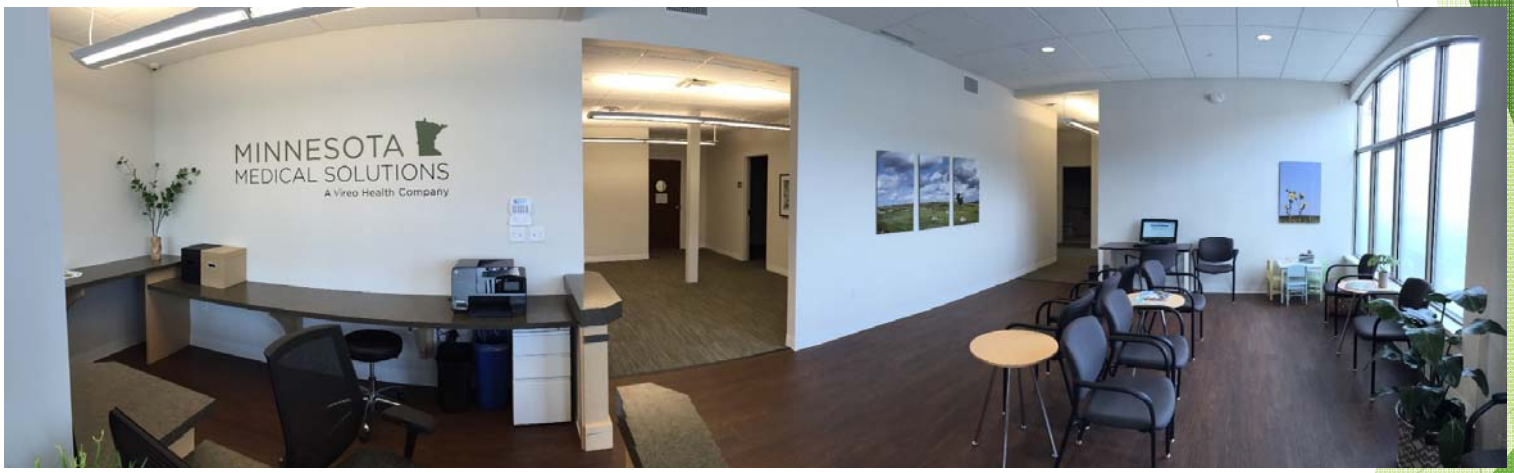
Cannabis Patient Center



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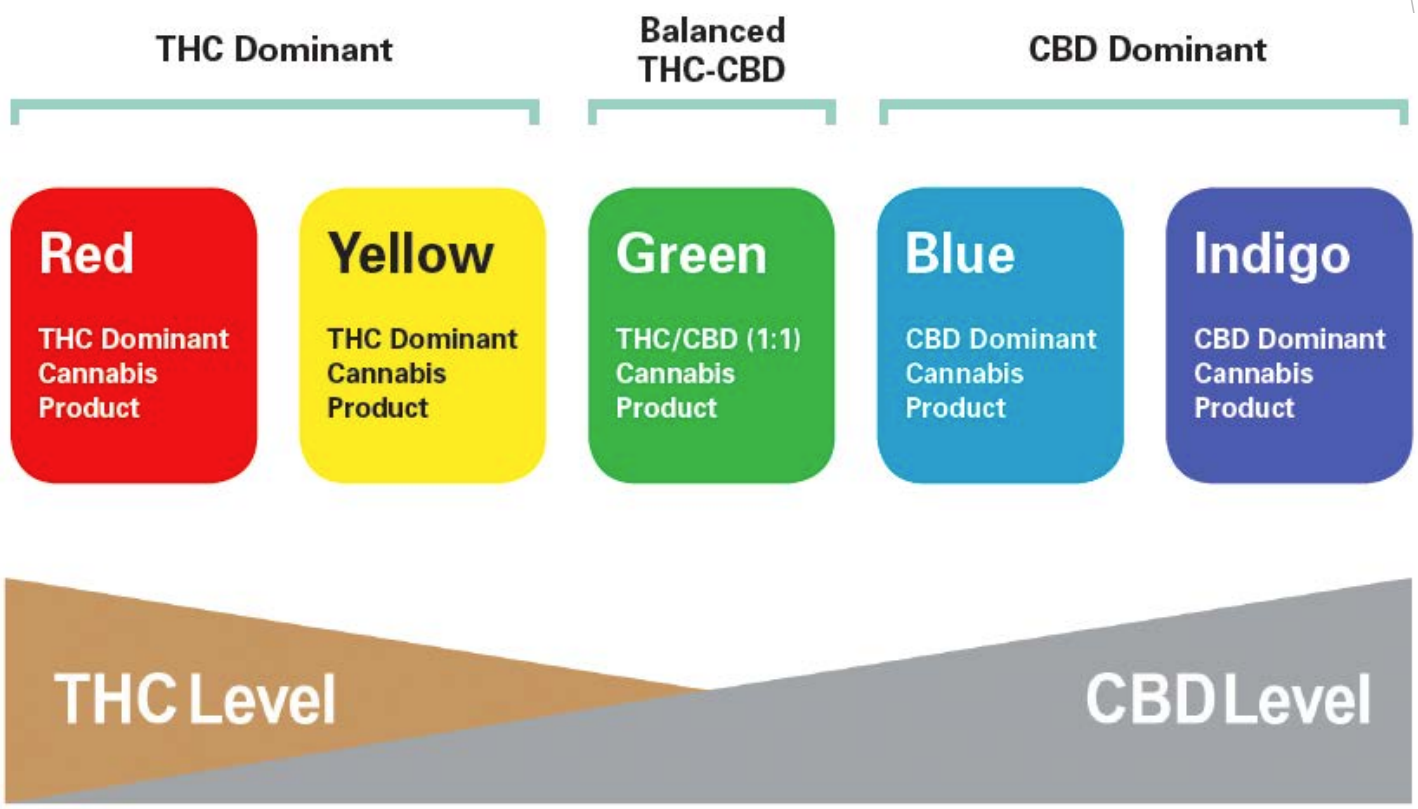
Approved Products



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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

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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)

SD1

STRENGTH OF evidence vs. Harm grading

Rating Options	Arrow	Icon
(A,1)	↑	A1
(A,2) (B,1)	↗	A2 B1
(A,3) (B,2) (C,1)	→	A3 B2 C1
(B,3) (C,2)	↘	B2 C2
(C,3)	↓	C3

Exercise in DM

Hypnosis for IBS

Zinc in Infectious Diarrhea

Opioids in Chronic Pain

Strengths of evidence vs. harm grading:

- Gives more credibility to therapies that have little potential harm. e.g. social support, reducing stress, and enhancing spiritual connection
- 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 (most harm)	This therapy has the potential to result in death or permanent disability. Example: Major surgery under general anesthesia or carcinogenic effects of the botanical Aristolochia (birthwort).
Grade 2 (moderate harm)	Grade 2 (moderate harm) This therapy has the potential to cause reversible side effects or interact in a negative way with other 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 – InCrowd 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)
  - 10% recommended medical cannabis

Detailed list of more than 150 peer-reviewed studies

Link	Pain	Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in	K F Boehnke; E Litinas; D J Clauw	2016	Cannabis	Retrospective Cross-Section	Cannabis use was associated with 64% lower opioid use, better quality of life, and fewer medication side effects a
Link	Pain	Cannabis in Pain Treatment: Clinical and Research Considerations	Savage S.R.; Fanciullo G.; Savage S.R.; Romero-S	2016	Cannabis	Review	Counsel patients on individualized clinical risks and potential benefits of cannabis on the basis of their symptoms
Link	Pain	An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabi	Barth Wilsey; Thomas D Marcotte; Reena Deutsch	2016	Cannabis	A crossover, randomized, pla	ignificant analgesic response for vaporized cannabis
Link	Pain	β-caryophyllene, A Dietary Cannabinoid, Complexed With With β-cyclodextri	Quintans-Júnior LJ1, Araújo AA2, Brito RG3, Sant	2016	Cannabis	Animal	βCP-βCD attenuates the non-inflammatory chronic muscle pain in mice
Link	Pain	The Effect Of Medicinal Cannabis On Pain And Quality Of Life Outcomes In Chr	Haroutounian S1, Ratz Y, Ginosar Y, Furmanov K, S	2016	Cannabis	Survey	Improved pain and functional outcomes, and significant reduction in opioid use.
Link	Pain	Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy	Wallace MS, Marcotte TD, Umlauf A, Gouaux B, At	2015	Cannabis	Controlled study	Inhaled cannabis demonstrated a dose dependent reduction in peripheral treatment-refractory neuropathic pa
Link	Chronic Pain	Profiles of medicinal cannabis patients attending compassion centers in rhode	Zaller N, Topletz A, Frater S, Yates G, Lally M.	2015	Cannabis	Survey	Most participants report that medicinal cannabis improves their pain symptomology.
Link	Pain	Experience of adjunctive cannabis use for chronic non-cancer pain: Findings f	Degenhardt L, Lintzeris N, Campbell G, Bruno R, C	2015	Cannabis	Survey	Pain patients, who receive opioids, experience better pain relief if they also take cannabis.
Link	Pain	Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual p	Andreae M.H., Carter G.M., Shaparin N., Suslov K.	2015	Cannabis	Review	Inhaled cannabis appears to provide short-term relief from chronic neuropathic pain for 1 in 5 to 6 patients treat
Link	Cancer	Patterns of Use of Medical Cannabis Among Israeli Cancer Patients: A Single I	Waissengrin B, Urban D, Leshem Y, Garty M, Wolf I.	2015	Cannabis	Open study	Cannabis use "is perceived as highly effective" by some patients with advanced cancer.
Link	Appetite loss/weight loss;C	Improving Quality of Life With Nabilone During Radiotherapy Treatments for I	Côté M, Trudel M, Wang C, Fortin A.	2015	Nabilone	Controlled study	Nabilone did not reduce pain and nausea in patients treated for head and neck cancer.
Link	Pain	Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: a	de Vries M, van Rijckevorsel DC, Vissers KC, Wilder	2015	Delta-9-TH	Controlled study	No effect of a single low dose of THC on abdominal pain resulting from chronic pancreatitis in clinical study.
Link	Dependency/withdrawal;P	The prescription of medical cannabis by a transitional pain service to wean a p	Meng H, Hanlon JG, Katznelson R, Ghanekar A, Mc	2015	Cannabis	Uncontrolled case report	The use of cannabis reduced opioid consumption
Link	Pain	The Pharmacokinetics, Efficacy, Safety, and Ease of Use of a Novel Portable I	Eisenberg E, Ogintz M, Almog S	2014	Cannabis	Open study	A significant reduction in pain intensity was achieved after cannabis inhalation with a vaporizer.
Link	Pain	A double-blind, randomized, placebo-controlled, parallel group study of THC/	Serpell M, Ratcliffe S, Hovorka J, Schofield M, Ta	2014	Cannabis	Controlled study	Significant improvements in pain, sleep quality and subjective evaluations of patients.
Link	Pain;Posttraumatic stress	Use of a Synthetic Cannabinoid in a Correctional Population for Posttraumat	Cameron C, Watson D, Robinson J.	2014	Nabilone	Open study	Nabilone caused significant improvements in insomnia, nightmares, chronic pain and other symptoms in patients
Link	Parkinson's disease	Cannabis (medical marijuana) treatment for motor and non-motor symptoms	Lotan I, Treves TA, Roditi Y, Djaldetti R.	2014	Cannabis	Open study	Analysis of specific motor symptoms revealed significant, also sleep and pain improvement after treatment with
Link	Multiple sclerosis;Spasticit	Clinical experiences with cannabinoids in spasticity management in multiple s	Lorente Fernández L, Monte Boquet E, Pérez-Mir	2014	Cannabis	Open study	The cannabis extract was effective in 80% of patients.
Link	Pain	A double-blind, placebo-controlled, crossover pilot trial with extension using	Lynch ME, Cesar-Rittenberg P, Hohmann AG.	2014	Cannabis	Controlled study	Reduction in pain intensity
Link	Pain	The subjective psychoactive effects of oral dronabinol studied in a randomize	Issa MA, Narang S, Jamison RN, Michna E, Edwards	2014	Cannabis;D	Controlled study	Oral THC had similar psychoactive effects to smoked marijuana
Link	Cancer chemotherapy;Pai	A Double-Blind, Placebo-Controlled, Crossover Pilot Trial With Extension Usin	Lynch ME, Cesar-Rittenberg P, Hohmann AG.	2013	Cannabis	Controlled study	Five patients tended to respond to a treatment with cannabis
Link	Pain	The Subjective Psychoactive Effects of Oral Dronabinol Studied in a Random	Issa MA, Narang S, Jamison RN, Michna E, Edwards	2013	Cannabis;D	Controlled study	In pain patients, oral dronabinol has similar psychoactive effects to smoking cannabis.
Link	Cancer;Pain	An open-label extension study to investigate the long-term safety and tolerab	Johnson JR, Lossignol D, Burnell-Nugent M, Fallon	2013	Cannabis	Open study	The cannabis extract Sativex was generally well tolerated, with no evidence of a loss of effect for pain relief.
Link	Multiple sclerosis;Pain	A double-blind, randomized, placebo-controlled, parallel-group study of THC	Langford RM, Mares J, Novotna A, Vachova M, No	2013	Cannabis	Controlled study	No significant difference between placebo and Sativex in Phase A; Phase B demonstrated an analgesic effect.
Link	Pain	Low-dose vaporized cannabis significantly improves neuropathic pain	Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai	2013	Cannabis	Controlled study	Cannabis reduced pain. No difference in efficacy between the two doses.
Link	Gastrointestinal disorder;I	Marijuana Use Patterns Among Patients with Inflammatory Bowel Disease.	Ravikoff Allegretti J, Courtwright A, Lucci M, Kor	2013	Cannabis	Survey	Patients find cannabis very helpful for symptom control.
Link	Pain	Comparison of the analgesic effects of dronabinol and smoked marijuana in da	Cooper ZD, Comer SD, Haney M.	2013	Cannabis;D	Controlled study	THC (dronabinol) and smoked cannabis (marijuana) caused similar effects on pain sensitivity and pain tolerance
Link	Multiple sclerosis;Spasticit	A new multiple sclerosis spasticity treatment option: effect in everyday clinic	Flachenecker P.	2013	Cannabis	Open study	The cannabis extract sativex is effective in a large number of patients and well-tolerated in the long-term.
Link	Multiple sclerosis;Spasticit	Endocannabinoid system modulator use in everyday clinical practice in the UK	García-Merino A.	2013	Cannabis	Open study	Sativex appears to be a well-tolerated and useful add-on therapy in patients with spasticity due to multiple sclero
Link	Multiple sclerosis;Pain;Spa	Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-c	Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcot	2012	Cannabis	Controlled study	Smoked cannabis was superior to placebo in reducing spasticity and pain.
Link	Pain	Palmitoylethanolamide in the Treatment of Chronic Pain Caused by Different	Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabat	2012	Other cann	Open study	Significant pain relief with palmitoylethanolamide (PEA)
Link	Pain	An efficient randomized, placebo-controlled clinical trial with the irreversibl	Huggins JP, Smart TS, Langman S, Taylor L, Youn	2012	Other cann	Controlled study	A FAAH inhibitor was not more effective than a placebo.
Link	Pain	Herbal cannabis use in patients labeled as fibromyalgia is associated with neg	Ste-Marie PA, Fitzcharles MA, Gamsa A, Ware MA	2012	Cannabis	Survey	Many patients with fibromyalgia use cannabis products.
Link	Pain;Spasticity	Cannabis derivatives therapy for a seronegative stiff-person syndrome: a cas	Vicente-Valor MI, Garcia-Llopis P, Mejia Andujar L	2012	Cannabis	Uncontrolled case report	The cannabis extract was effective in a patient with stiff person syndrome.
Link	Cancer;Pain	Nabiximols for opioid-treated cancer patients with poorly-controlled chronic	Portenoy RK, Ganae-Motan ED, Allende S, Yanagi	2012	Cannabis	Controlled study	Additional pain reduction following the two lower doses.
Link	Posttraumatic stress disor	Mitigation of post-traumatic stress symptoms by Cannabis resin: A review of t	Passie T, Emrich HM, Karst M, Brandt SD, Halpern	2012	Cannabis	Uncontrolled case report	Cannabis reduced course and intensity of symptoms.
Link	Multiple sclerosis;Pain;Spa	A questionnaire survey of patients and carers of patients prescribed Sativex a	Notcutt WG.	2012	Cannabis	Survey	Most respondents experienced improvements across a range of symptoms.
Link	Multiple sclerosis;Pain;Spa	Multiple Sclerosis and Extract of Cannabis: results of the MUSEC trial.	Zajicek JP, Hobart JC, Slade A, Barnes D, Mattiso	2012	Cannabis	Controlled study	Significant improvement by the cannabis extract Cannador of spasticity and pain.
Link	Pain	Intractable neuropathic pain due to ulnar nerve entrapment treated with cann	Hesselink JM, Kopsky DJ.	2012	Cannabis	Uncontrolled case report	Significant pain improvement with cannabis and ketamine.
Link	Pain	Lack of effect of central nervous system-active doses of nabilone on capsaici	Kalliomäki J, Philipp A, Baxendale J, Annas P, Kar	2012	Nabilone	Controlled study	The cannabinoid had no significant effect on acute experimental pain.
Link	Gastrointestinal disorder;I	Impact of cannabis treatment on the quality of life, weight and clinical disease	Lahat A, Lang A, Ben-Horin S	2012	Cannabis	Open study	Improvement in general health perception, social functioning, ability to work, physical pain and depression; weig
Link	Appetite loss/weight loss;H	A pilot study of the effects of cannabis on appetite hormones in HIV-infected a	Riggs PK, Vaida F, Rossi SS, Sorkin LS, Gouaux B,	2012	Cannabis	Controlled study	Cannabis administration was associated with significant increases in plasma levels of ghrelin and leptin, and dec
Link	Pain	A Randomized, Controlled Study to Investigate the Analgesic Efficacy of Sin	Ostenfeld T, Price J, Albanese M, Bullman J, Guill	2011	Other cann	Controlled study	No superior analgetic effect of the synthetic cannabinoid GW842166 over placebo.
Link	Appetite loss/weight loss;C	[Cannabinoids in children] [Article in German] Cannabinoide bei Kindern.	Gottschling S.	2011	Delta-9-TH	Uncontrolled case report	Reduced pain, spasticity and improved appetite and nausea
Link	Pain	Cannabis use in patients with fibromyalgia: effect on symptoms relief and hea	Fiz J, Durán M, Capellà D, Carbonell J, Farré M.	2011	Cannabis	Open study	The use of cannabis was associated with reduction of some fibromyalgia symptoms.
Link	Gastrointestinal disorder;I	Cannabis use amongst patients with inflammatory bowel disease.	Lal S, Prasad N, Ryan M, Tangri S, Silverberg MS,	2011	Cannabis	Survey	Cannabis use is frequent in patients with chronic intestinal inflammation
Link	Posttraumatic stress disor	Medical cannabis use in post-traumatic stress disorder: a naturalistic observa	Reznik I.	2011	Cannabis	Open study	In most cases a significant improvement in quality of life and pain, with some positive changes in severity of post
Link		The medicinal use of cannabis and cannabinoids: an international survey on m	Hazekamp A, Grotenhermen F, Abrams D, Russo E	2011	Cannabis;D	Survey	Preferred modes of use were smoking of cannabis (62.9 per cent), inhalation of cannabis with a vaporizer (23.6 p

AT LEAST five high-quality randomized controlled clinical trials establishing the pain 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
n	10	11
Women	4	6
Caucasian	8	9
Mean age (range)	42.9 (33–55)	47.1 (28–61)
Mean opioid dose (mg) (range)	62 Twice daily (10–200)	53 Twice daily (10–120)
Mean pain score day 1 (95% CI)	34.8 (29.4, 40.1)	43.8 (38.6, 49.1)

CI, confidence interval.

Table 2 Pain by study day

		Day 1	Day 5	Difference	Percentage change
	n	Mean (95% CI)	Mean (95% CI)	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 nabiximols (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.

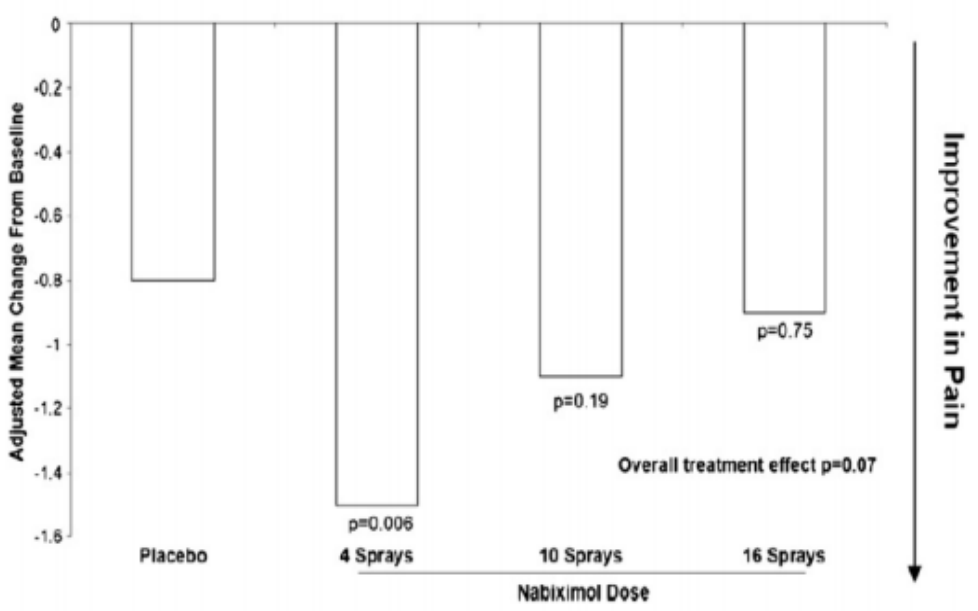


Figure 4. Analysis of change from baseline in NRS average pain score.

(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%)

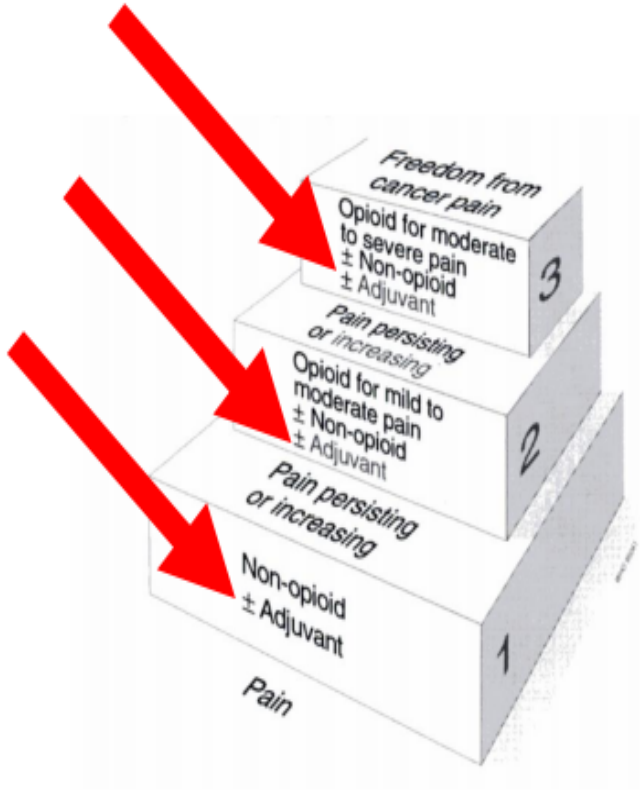
NOTE. Study participants reported using fewer medication classes of all categories after initiation of cannabis.

RIPT

(Boehnke, Journal of Pain, 2016)

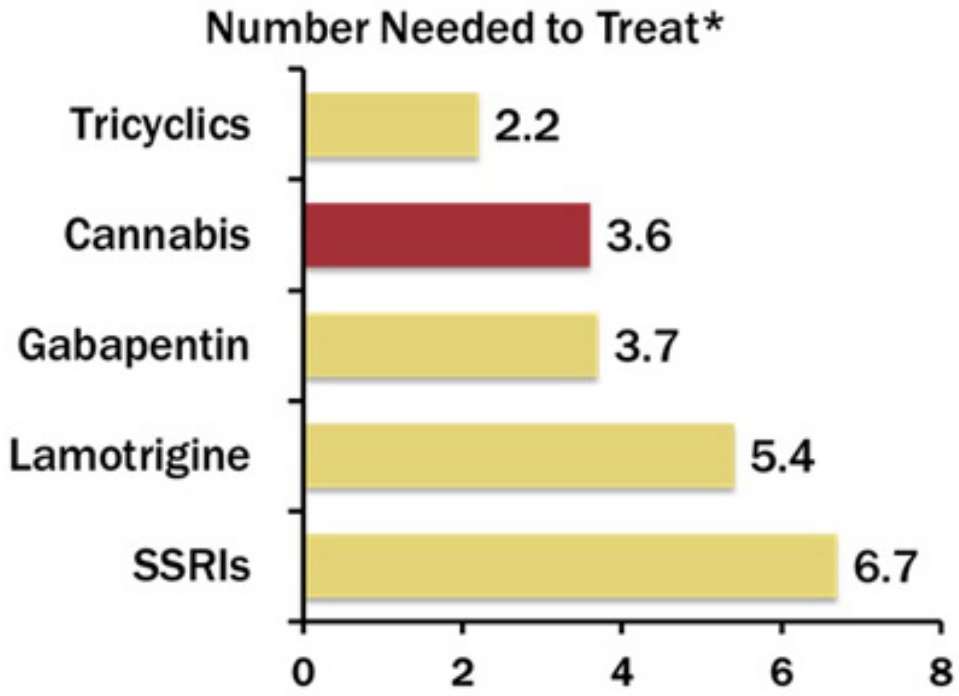
Cannabis is A beneficial adjuvant on all steps of analgesic ladder

- 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]



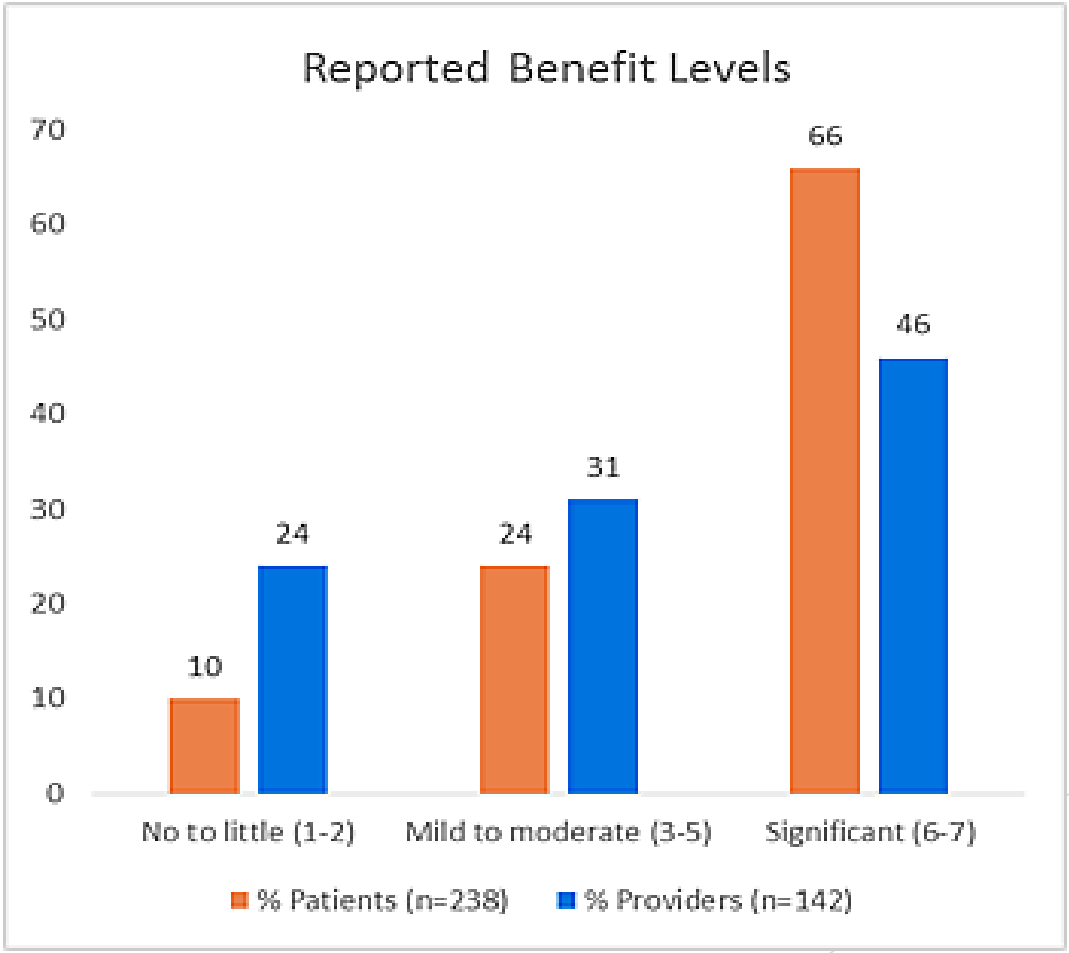
(Vargas-Schaffer, Can Fam Phys, 2010)

NNT – Painful sensory neuropathY



(AMA EthicsVirtual Mentor. May 2013)

Efficacy Data: MINNESOTA DEPARTMENT OF HEALTH - ONE YEAR



MEDICAL CANNABIS CONTRAINDICATIONS

- **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

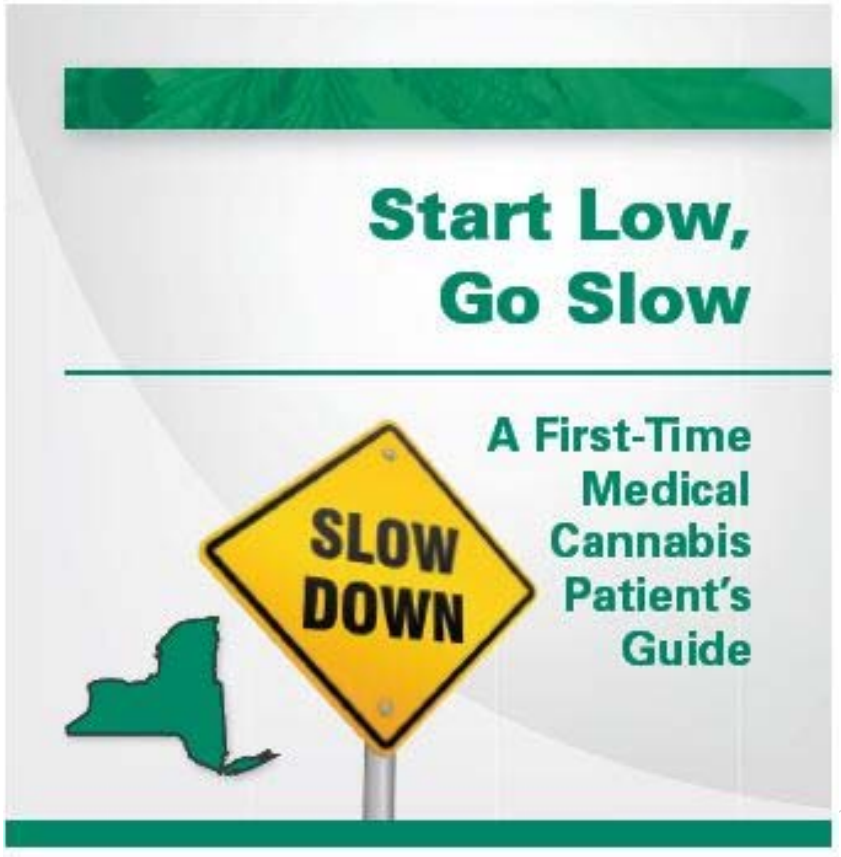
"Medical cannabis used for chronic pain over one year appears to have a reasonable safety profile (199 Patients; no difference in risk of serious adverse events)."

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.

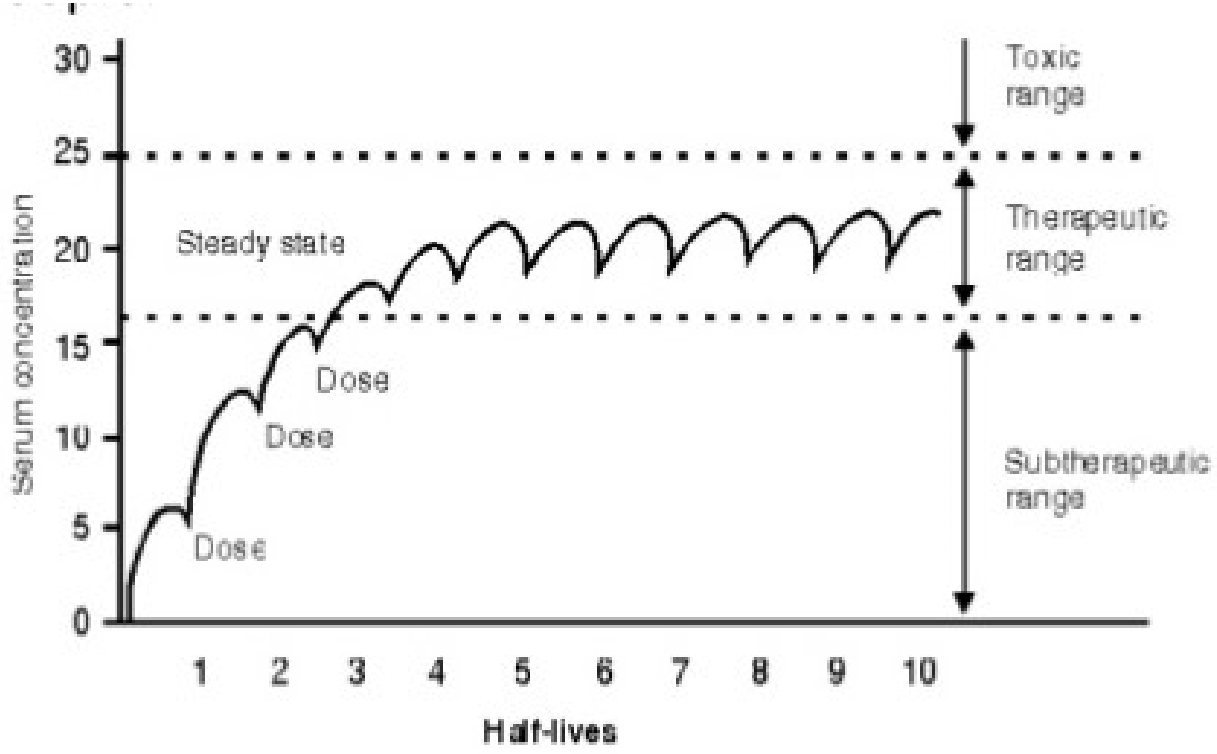
"0% of patients surveyed after one year reported a 'Great deal of Negative Physical Side Effects. 0% reported a 'Great Deal of Negative Mental Side Effects0 (241 Patients, 12 months)'"

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

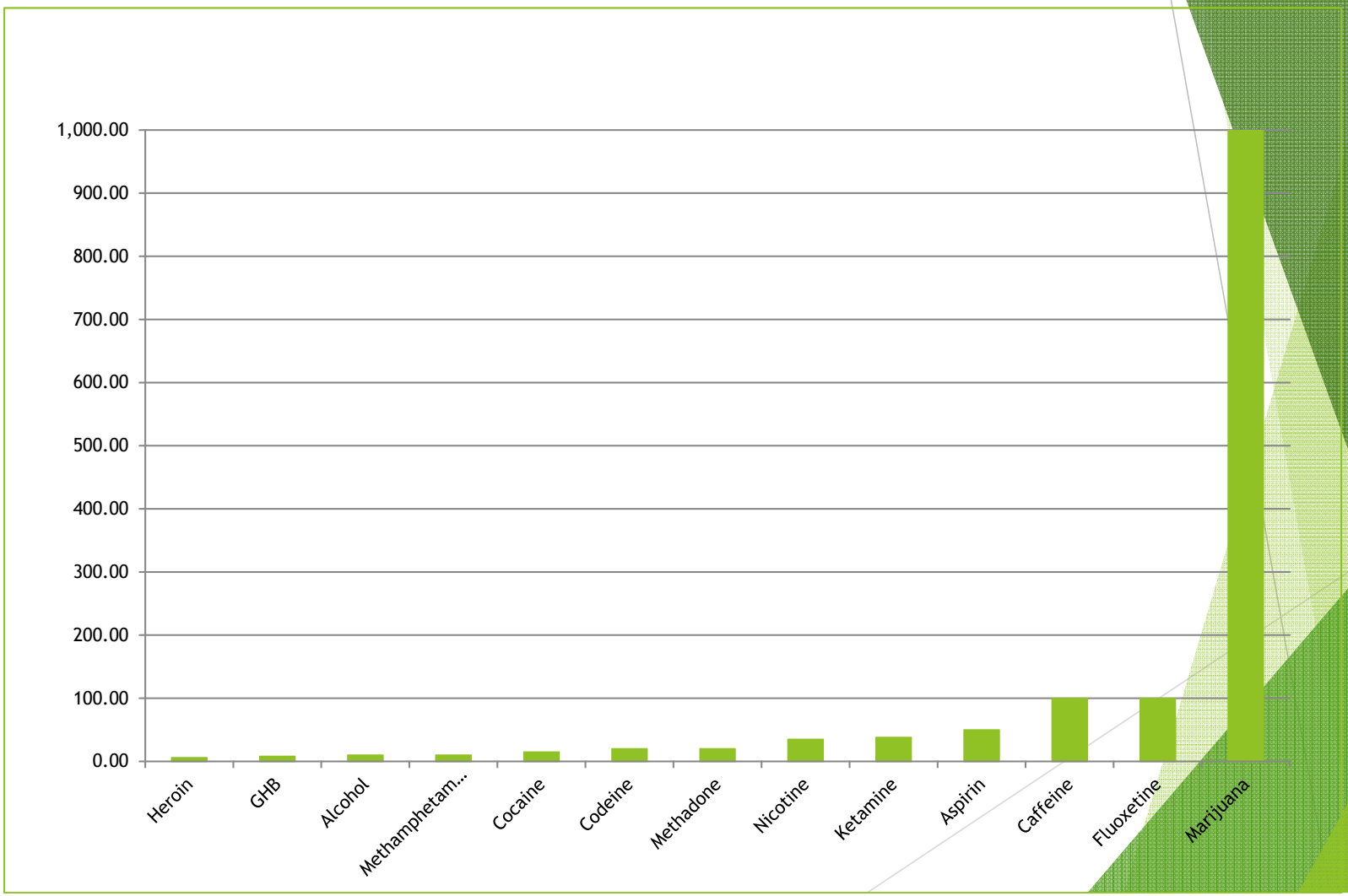
START LOW, GO SLOW



THERAPEUTIC WINDOW



LD50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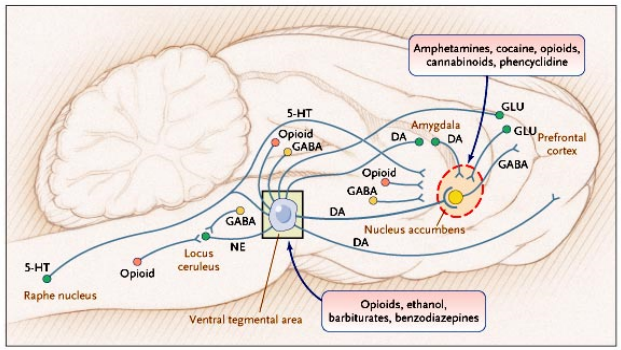
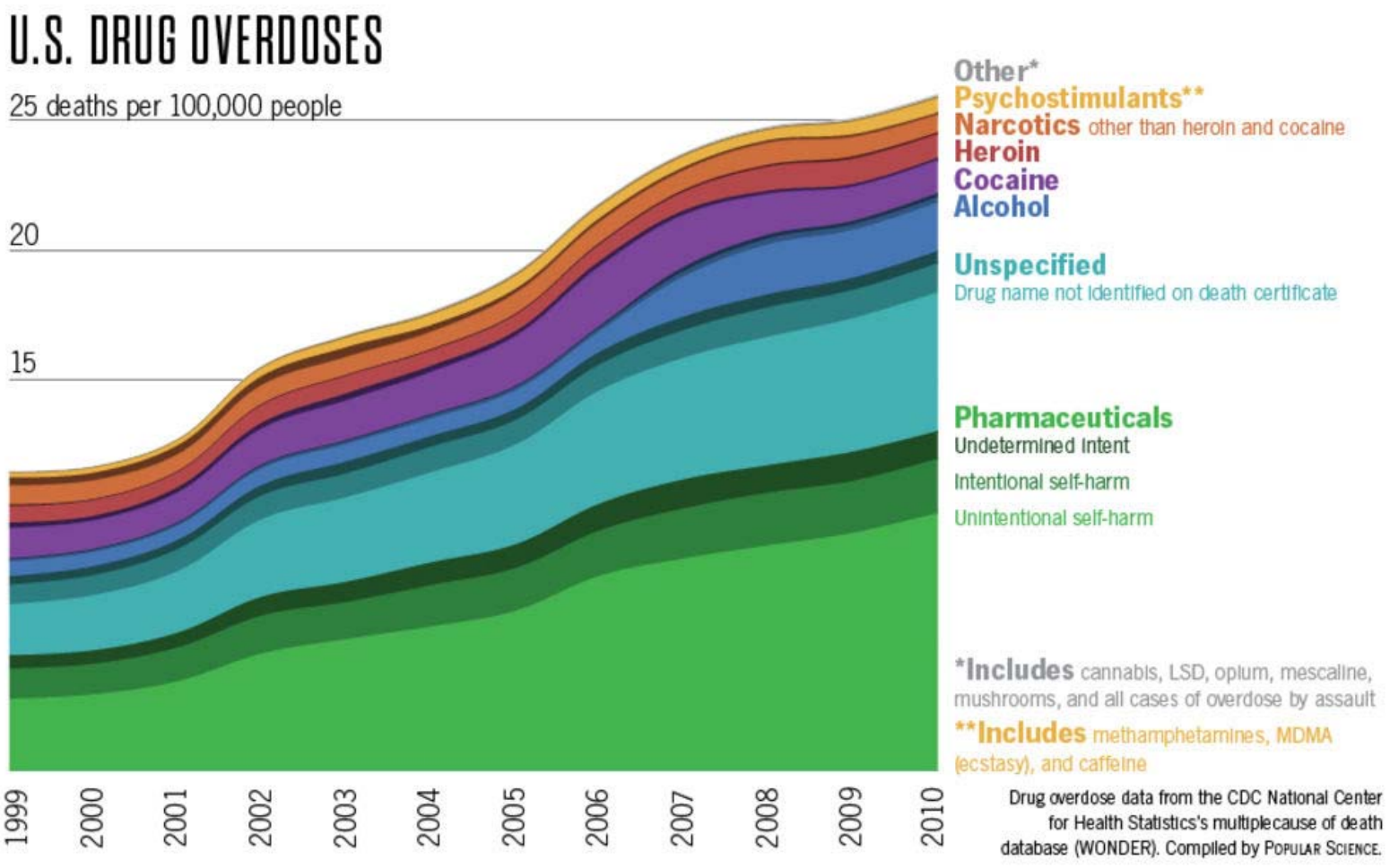
Alcohol
Methamphetam...
Cocaine
Codeine
Methadone
Nicotine
Ketamine
Aspirin
Caffeine
Fluoxetine
Marijuana

OPIOIDS and the brain

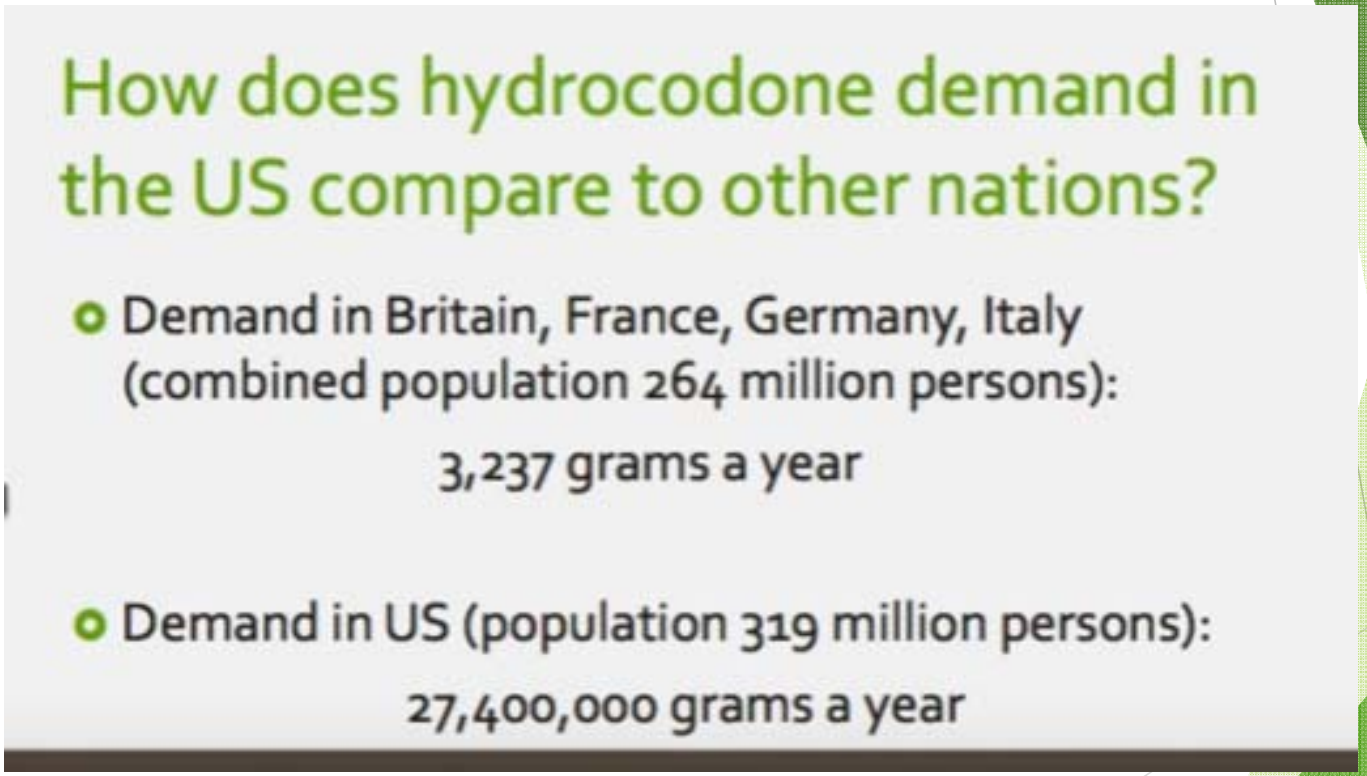
- Opiate μ receptors affect medullary and pons respiratory drive centers
- What other receptors also affect brainstem drive?
  - Benzodiazepines (GABA)
  - Alcohol (GABA)
- Apnea may result
  - High opiate dose alone
  - Synergistic combination of opiates with alcohol or benzodiazepines



U.S. DRUG OVERDOSE RISK



HOW do we compare to other countries



(Manchikati, Pain Physician, 2012)

Nsaids

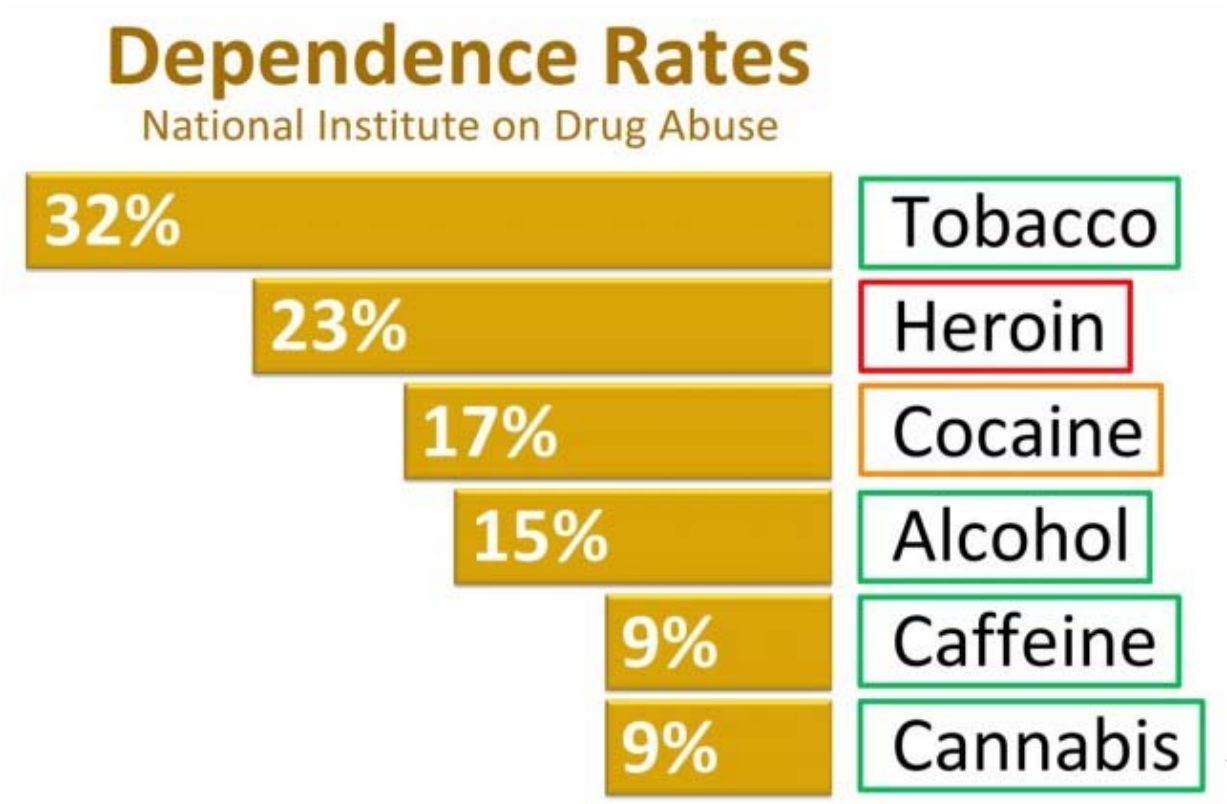
- "At least 16,500 NSAID-related deaths occur each year among arthritis patients alone..."

  Source: Am J Med, Jul 1998

- 16,651 deaths occurred in 2010 from opiate prescription overdoses

  Source: CDC MMWR, Mar 2013

CANNABIS USE DISORDER



SOURCE: Bostwick, 2012 (reference list).

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)

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