Cannabis for pain: from pills to pot?

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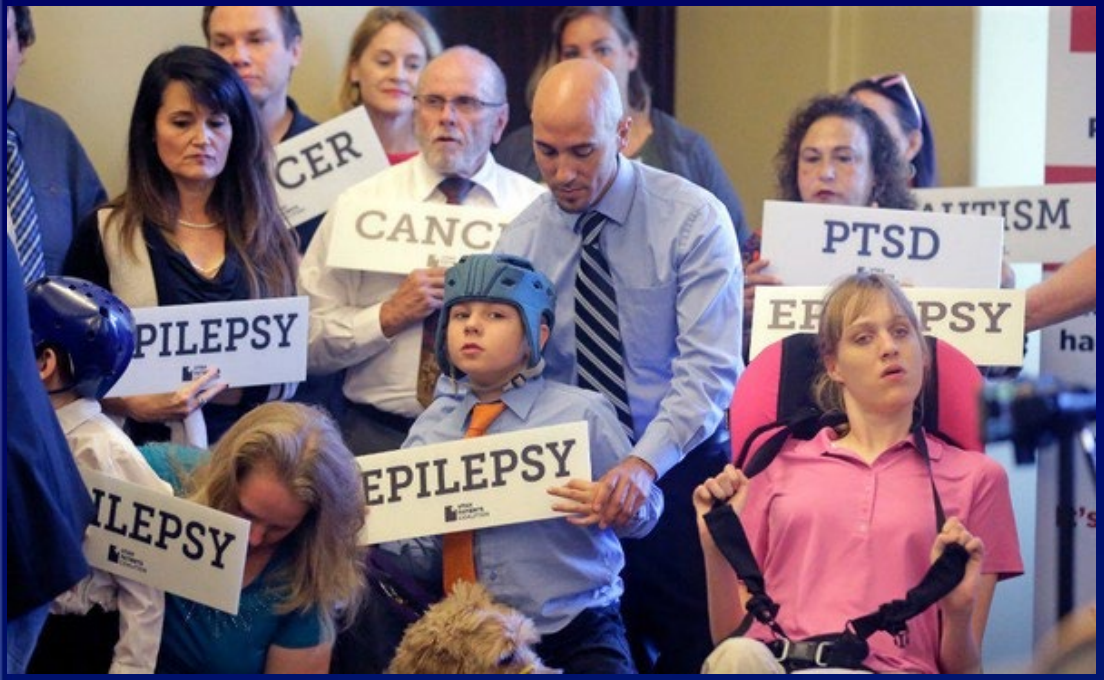
Adapted with permission from Dr. Daniel J. Clauw.

Disclosures

- None

http://66.media.tumblr.com/tumblr_mbkx10s2D51qapkmyo1_500.jpg



https://www.silive.com/news/2017/09/costly_medical_marijuana_pushe.html

http://blog.norml.org/2011/07/21/who-are-americas-medical-marijuana-patients/

https://www.leafly.com/cannabis-events/michigan-medical-cannabis-cup

Medical cannabis in US

https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881

Medical cannabis in Michigan

LARA
LICENSING AND REGULATORY AFFAIRS
CUSTOMER DRIVEN. BUSINESS MINDED.

Michigan Medical Marihuana Program
Application/Renewal Instructions and Checklist
www.michigan.gov/mmp
(517) 284-6400

Michigan Medical Marihuana Program
Application for Registry Identification Card

Instructions

- This application is for a person who is 18 years of age or older and a resident of Michigan.
- Type or print legibly when completing the application.

- Michigan Medical Marihuana Act of 2008:
  - Many conditions/symptoms covered
  - In 2017: 92.8% of the 269,553 patients in Michigan have their license for severe and chronic pain[1]
- When is cannabis appropriate to use?

1: 2017 Medical Marihuana Act Statistical Report, Michigan

PAIN NEWS NETWORK

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Big Decline in Opioid Use by Marijuana Users

March 23, 2016

RollingStone Medical Pot Is Our Best Hope to Fight the Opioid Epidemic

Medical Pot Is Our Best Hope to Fight the Opioid Epidemic

"There are direct reasons why [cannabis] could actually help people get off of opioids," says one leading marijuana researcher

It's time we start talking seriously about medical marijuana as a way to end the opioid epidemic

Vox EXPLAINERS POLITICS & POLICY WORLD

One way to fight the opioid epidemic? Medical marijuana.

An innovative, but evidence-based, idea.

By German Lopez | @germanrlopez | german.lopez@vox.com | Updated Jan 18, 2017, 1:10pm EST

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John Vizcaino / Reuters

Patients Are Ditching Opioid Pills for Weed

Can marijuana help solve the opioid epidemic?

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PUBLIC HEALTH

Could Medical Cannabis Break the Painkiller Epidemic?

A body of research suggests yes, but scientists are having to fight red tape to study whether medical marijuana could substitute for opioid drugs

Cannabis as an opioid substitute for chronic pain?

- Cannabis as a synergist with opioids[1,2]
- State-wide analyses[3-5]
  - Importance of Dispensaries in these studies (Powell et al, 2018)
- Cross-sectional[6-8] and longitudinal support[9-11]

1. Abrams et al, *Clinical Pharmacology and Therapeutics*, (2011) 2. Cooper, Ziva D., et al. *Neuropsychopharmacology* (2018) 3. Bachhuber MA et. al. JAMA Int Med (2014). 4. Bradford and Bradford *Health* Affairs, (2016) 5. Bradford and Bradford, *Health* Affairs (2017). 6. Boehnke, Kevin F., Evangelos Litinas, and Daniel J. Clauw. *The Journal of Pain* (2016). 7. Lucas et al, *Journal of International Drug Policy* (2017) 8. Reiman et al, *Cannabis and Cannabinoid Research* (2017). 9. Haroutounian et al,. *Clinical Journal of Pain* (2016). 10. Stith et al, *PLOSone* (2017) 11. Abuhasira et al, *European Journal of Internal Medicine*, (2018)

Cannabis and Cannabinoids

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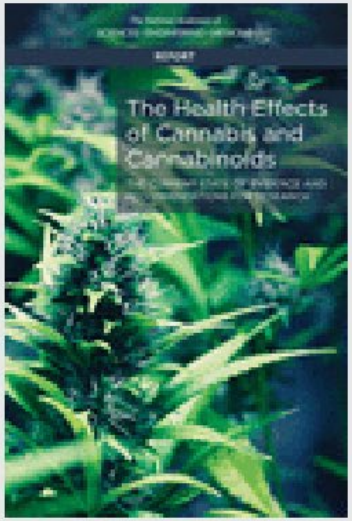

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

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DETAILS

486 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-45304-2 | DOI: 10.17226/24625

CONTRIBUTORS

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

Definitions

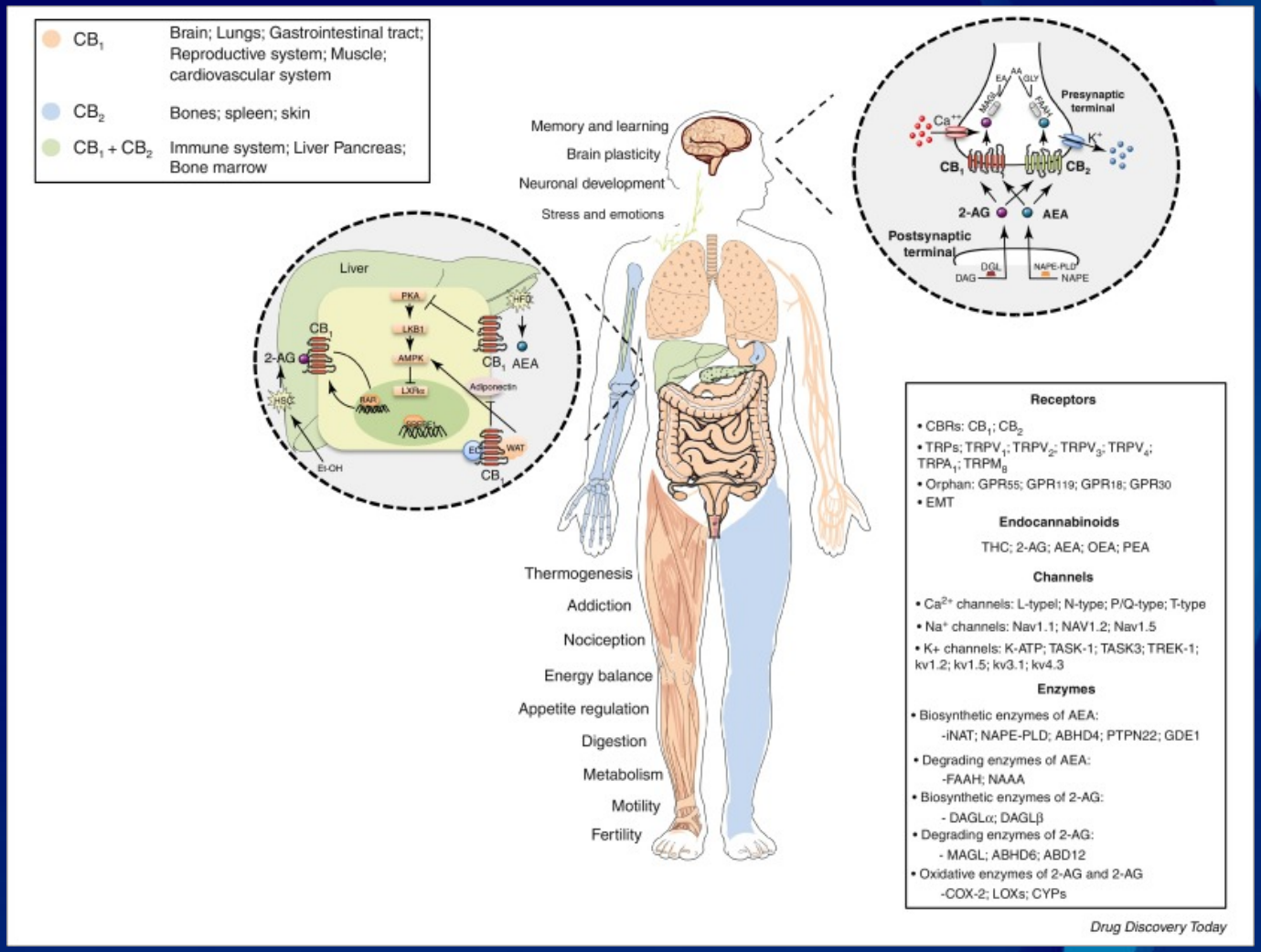
- Cannabis - indica, sativa, and ruderalis
- Cannabinoids:
  - Endocannabinoids
  - Phytocannabinoids – plant origin
  - Synthetic cannabinoids – e.g. dronabinol and Nabilone

https://upload.wikimedia.org/wikipedia/commons/2/23/Marijuana-Cannabis-Weed-Bud-Gram.jpg

https://en.wikipedia.org/wiki/Cannabis#/media/File:Cannabis_sativa_Koehler_drawing.jpg

Endocannabinoid system - I

A set of receptors and their naturally occurring ligands (endocannabinoids) and enzymes regulating control



Aizpurua-Olaizola, Oier, et al. "Targeting the endocannabinoid system: future therapeutic strategies." *Drug discovery today*22.1 (2017): 105-110. Fonseca et al, *Prostaglandins & other lipid mediators* 102 (2013): 13-30.

Endocannabinoid system - II

Some known functions of the endocannabinoid system:

- Functions: “Relax, eat, sleep, forget, protect”
- Memory
- Neurogenesis
- Analgesia
- Immune function
- Stress
- Appetite

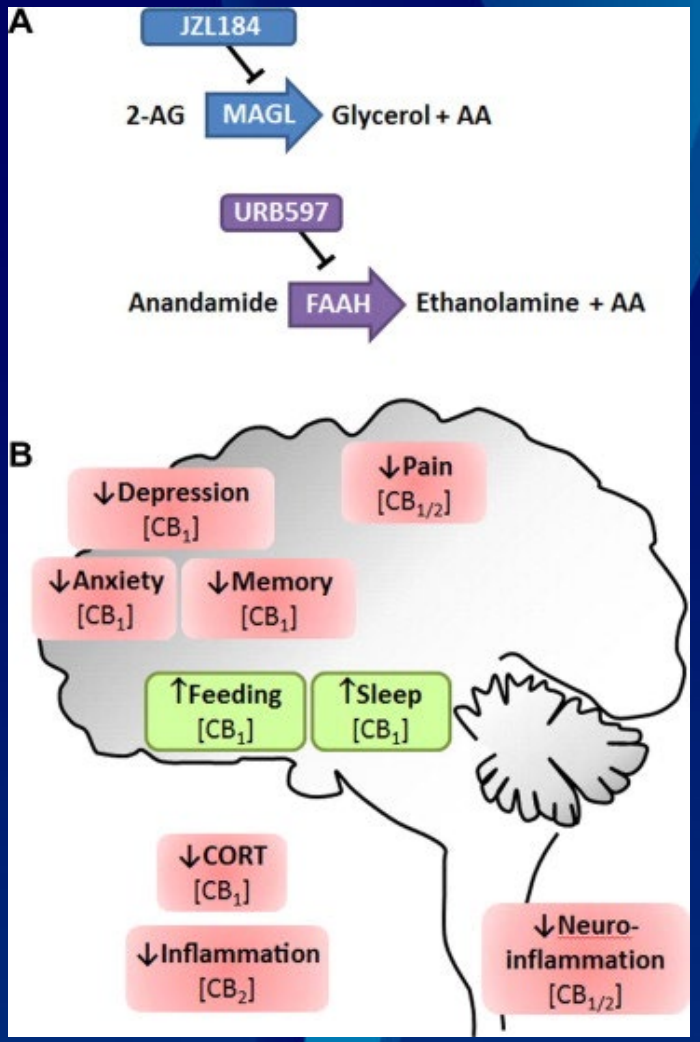


Figure from Crowe et al, 2014.

1. Rom S. Journal of Neuroimmune Pharmacology. 2013; 8(3): 608-620. 2. Hill et. al. PNAS 2010; 107(20) 9406–9411. 3. Crowe S et. al. Brain, Behavior, and Immunity, Volume 42, 2014, 1 - 5

Cannabis-derived cannabinoids

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CBD Biscuits

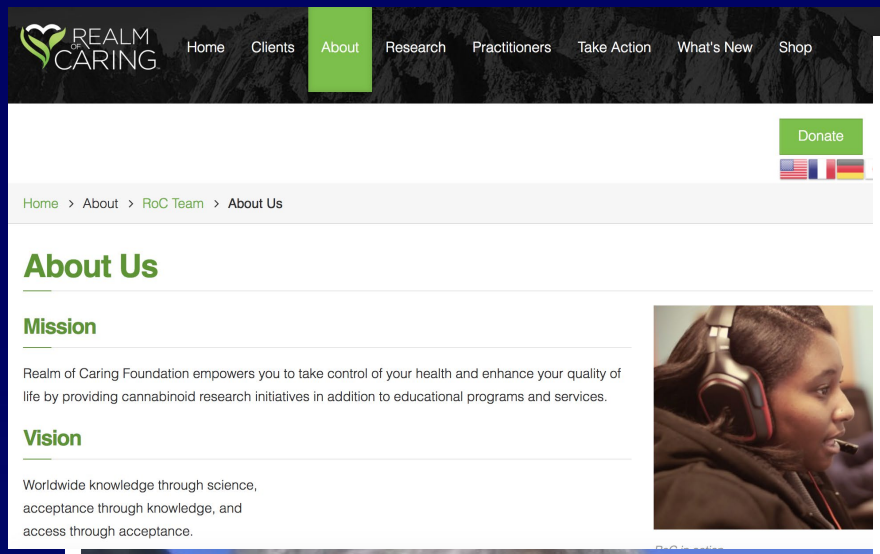
For small to medium dogs (9-44lbs)

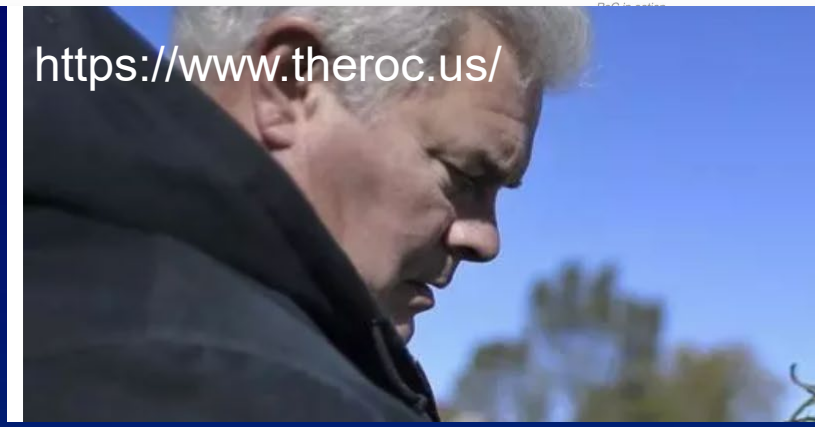
For medium to large dogs (45-120lbs)

CBD Extracts

journal of pharmacology 163.7 (2011): 1344-1364. 3. Devinsky, Orrin, et al. *New England Journal of Medicine* 376.21 (2017): 2011-2020.

Verifiable products, Hemp vs. Marijuana-derived cannabinoids





Certificate of Analysis

112803

Sample ID: BK51944
Customer: Ananda Hemp | Type: Oil | Instrument: HPLC-PDA | Submitted: 05/29/18
Test Site: Berkeley, CA | Test: Extended Cannabinoids | Method: SOP-024 | Reported: 05/31/18
Density: 0.98 g/mL

Compound Profile: Cannabinoids

Cannabinoid	mg/mL	mg/g
CBC	0.82 mg/mL	0.86 mg/g
CBCA	0.069 mg/mL	0.073 mg/g
CBD	30. mg/mL	31 mg/g
CBDA	1.36 mg/mL	1.43 mg/g
CBDV	0.31 mg/mL	0.33 mg/g
CBDVA	Not Detected	
CBG	0.45 mg/mL	0.47 mg/g
CBGA	Not Detected	
CBL	Not Detected	
CBLA	Not Detected	
CBN	0.26 mg/mL	0.27 mg/g
CBNA	Not Detected	
D8THC	Not Detected	
THC	2.9 mg/mL	3.0 mg/g
THCA	Not Detected	
THCAC4	Not Detected	
THCV	Not Detected	
THCVA	Not Detected	
Total Measured:	**36.2 mg/mL**	**37.4 mg/g**

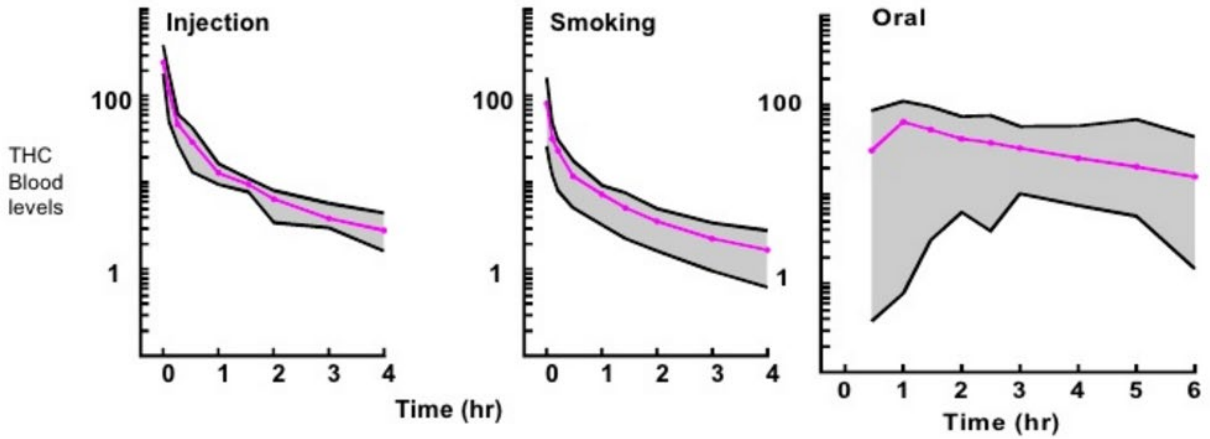
Decarboxylated Values

Cannabinoid	Equation	Value
THC	THCA x 0.877 + THC	2.9 mg/mL
CBD	CBDA x 0.877 + CBD	31 mg/mL

https://www.anandahemp.com/coa-lookup-tool/

Pharmacokinetics

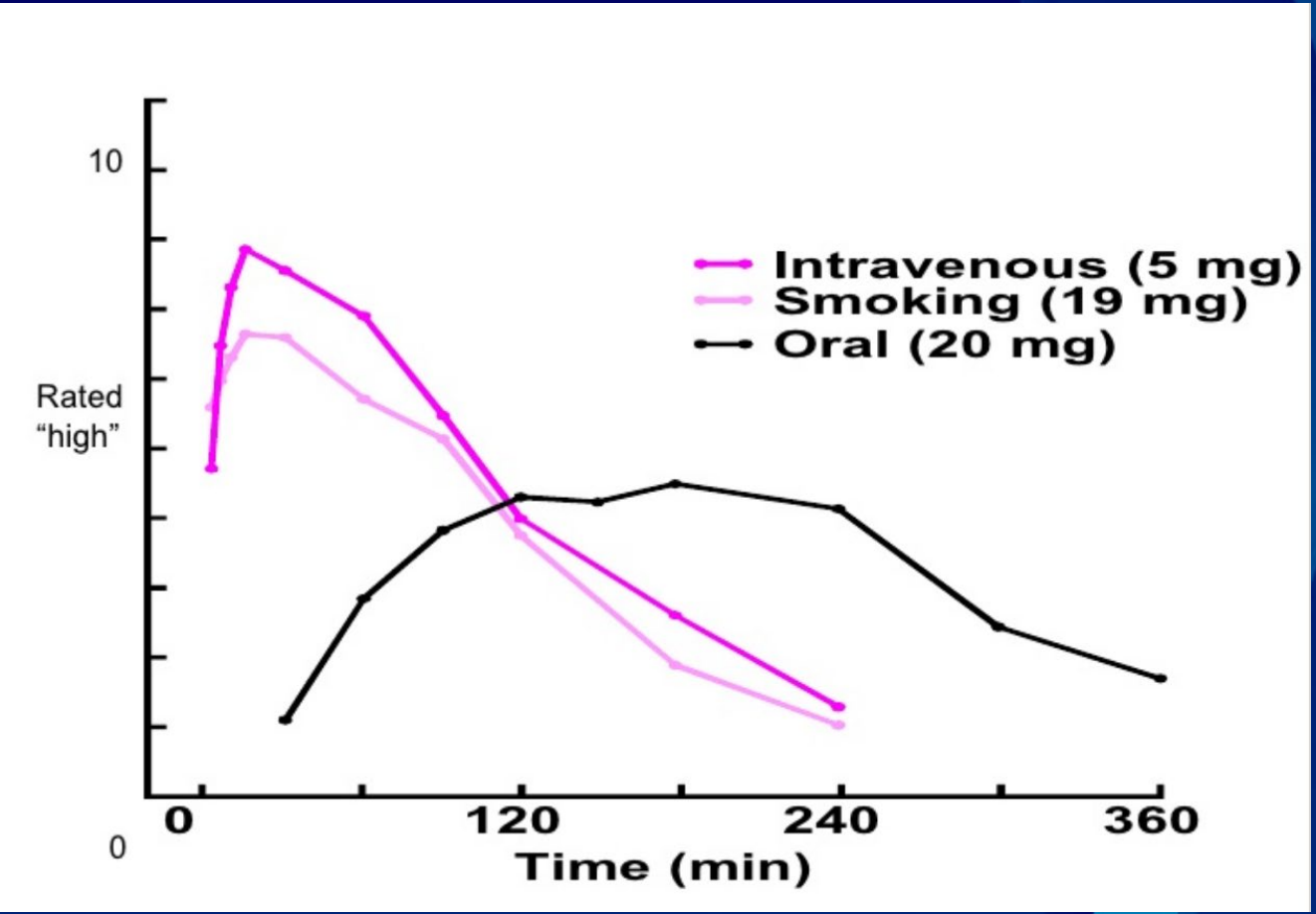
Pharmacokinetics



Route of administration influences THC pharmacokinetics, left = 5 mg i.v. injection, center = smoking 13.0 mg, or right =consuming cookie with 20 mg (Agurell et al. 1986).

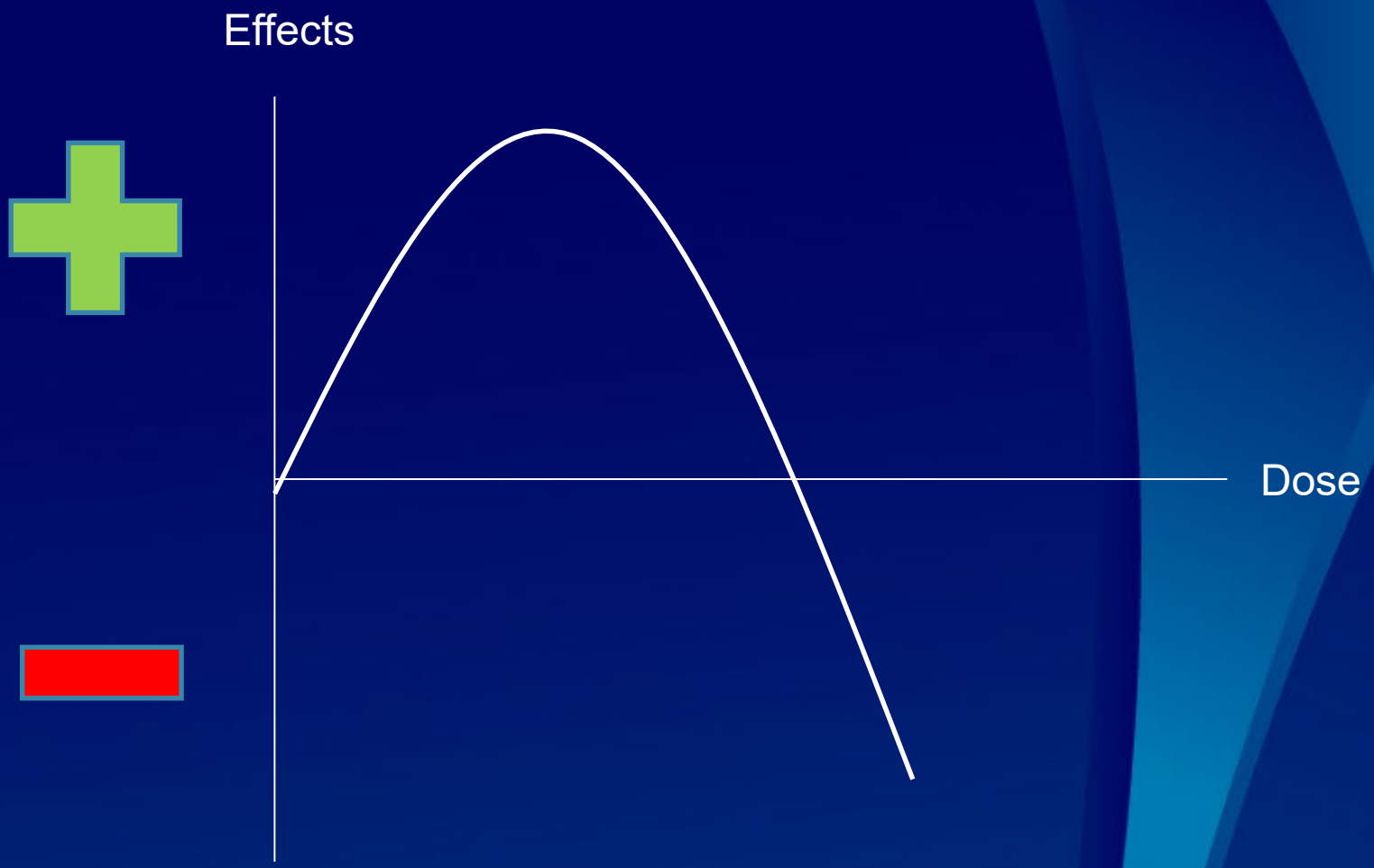
Agurell, Stig, et al. *Pharmacological Reviews* 38.1 (1986): 21-43.

Feelings of ‘high’ from different administration routes



Agurell, Stig, et al. *Pharmacological Reviews* 38.1 (1986): 21-43.

U-Shaped Curve for cannabis effects



1. Hill KP. Jama. 2015;313(24):2474. 2. Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, et al. Anesthesiology. 2007;107(5):785–96. 3. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. J Pain. Elsevier Ltd; 2012;13(5):438–49.

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Known benefits of Cannabinoids

- Antiemetic and
  dronabinol and
  approved (Sche
- Nabiximols: Ant
  used for MS[4,5,6]
- Sleep: In contex
- Analgesia[6]: Stro
  chronic neuropa
  - Recent trial of

DEA Reclassifies Plant-Derived Marijuana Medicine To Schedule V

October 5, 2018 Staff Health and Fitness 0 Comments

(Source: Daily Beast)

- Epilepsy: CBD found to reduce seizure frequency in Dravet Syndrome, Lennox-Gastaut, and other epileptic disorders

http://www.floridamarijuanainfo.org/marinol-the-prescription-thc-pill/

https://www.medycznamarihuana.com/glejak-kannabidiol-cbd-moze-hamowac-rozwoj-raka-mozgu/

1. Sharkey K. et. al. Eur J Pharm 2014; 722:134-146. 2. Machado Rocha, Francisco C., et al. *European journal of cancer care* 17.5 (2008): 431-443. 3. FDA:http://www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-emc0004-04.pdf 4.Collin C, et al. Neurol Res. 2010;32(5):451-459. 5. Collin C et al. Eur J Neurol. 2007;14(3):290-296.128. 6. Whiting, Penny F., et al. *Jama* 313.24 (2015): 2456-2473. 7. National Academies of Sciences, engineering, and medicine. Health effects of cannabis and cannabinoids (2017).

Contraindications of medical cannabinoids

- Poor data available on herbal cannabis
- Dronabinol contraindications:
  - Disulfiram or Metronidazole use in past 14 days
  - History of substance abuse
  - Pregnancy
  - Psychiactric disorder
  - Cardiovascular disease
  - History of seizures
- Nabiximols contraindications:
  - Known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil,
  - Patients with significant hepatic or renal impairment
  - Patients with serious cardiovascular disease such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure,
  - Patients with a history of schizophrenia or any other psychotic disorder,
  - Children under 18 years of age;
  - Women of child-bearing potential not on a reliable contraceptive or men intending to start a family, and in pregnant or nursing women.

Approval for Sativex with conditions. Bayer, 2005. Epocrates Online, Marinol

Risks of cannabinoids (recreational)

Long term:

- Respiratory effects
- Dependence and addiction
- Psychotic illnesses:1.5-2.4x rate developed under age of 25
- Long term effects on memory and brain structure

Acute:

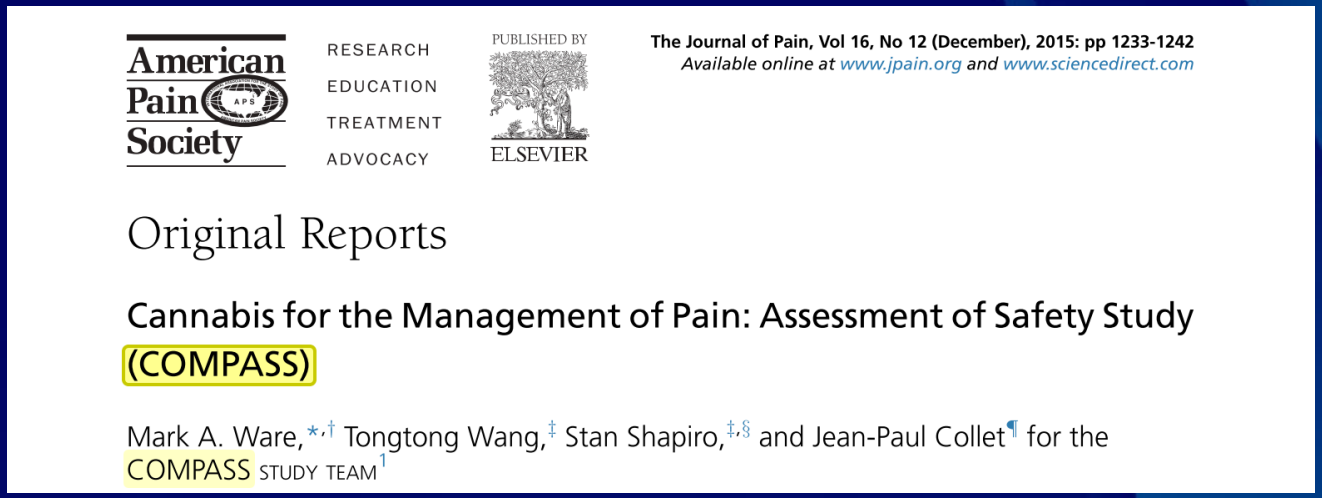
- Common: Dizziness, somnolence, euphoria, light-headedness, anxiety, and others
- Uncommon: Vomiting, hallucinations, paranoia, seizures
- Uncertain quality of herbal preparation[4]
- Vehicle accidents

http://arts.bio/en/products/budrot-mildew-rust-control

http://www.clker.com/cliparts/6/4/b/1/13234884051988079243joint-hi.png

1. Hall W. Drug Test Analysis 2014:6:39-45 2. Radhakrishnan R. Frontiers in Psychiatry 2014:5(54):1-6. 3. James et. al. Psychiatry Research: Neuroimaging 2013; 214:181-9. 4. Russo, Ethan B. *Frontiers in Pharmacology* 7 (2016). 5. National Academies of Sciences, engineering, and medicine. Health effects of cannabis and cannabinoids (2017).

Risks of cannabinoids (medical)



American Pain Society
RESEARCH
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TREATMENT
ADVOCACY

PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 16, No 12 (December), 2015: pp 1233-1242
Available online at www.jpain.org and www.sciencedirect.com

Original Reports

Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS)

Mark A. Ware,*,† Tongtong Wang,‡ Stan Shapiro,‡,§ and Jean-Paul Collet¶ for the COMPASS STUDY TEAM[1]

- Much fewer data on risks of medical use
- In observational trial of smoked medical cannabis: Increased minor adverse events, no increase in serious adverse events [1]
- Similar risk profile in elderly adults as younger medical users. [2,3]

1. Ware, Mark A., et al. *The Journal of Pain*16.12 (2015): 1233-1242. 2. van den Elsen, Geke AH, et al. *Ageing research reviews* 14 (2014): 56-64. 3. Abuhasira, Ran, et al. *European Journal of Internal Medicine* (2018).

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Role of Cannabinoids in Pain Management

- Mechanisms of pain
  - Preclinical models, mechanisms of action
- Clinical trials in chronic pain states
  - Efficacy

Mechanistic Characterization of Pain

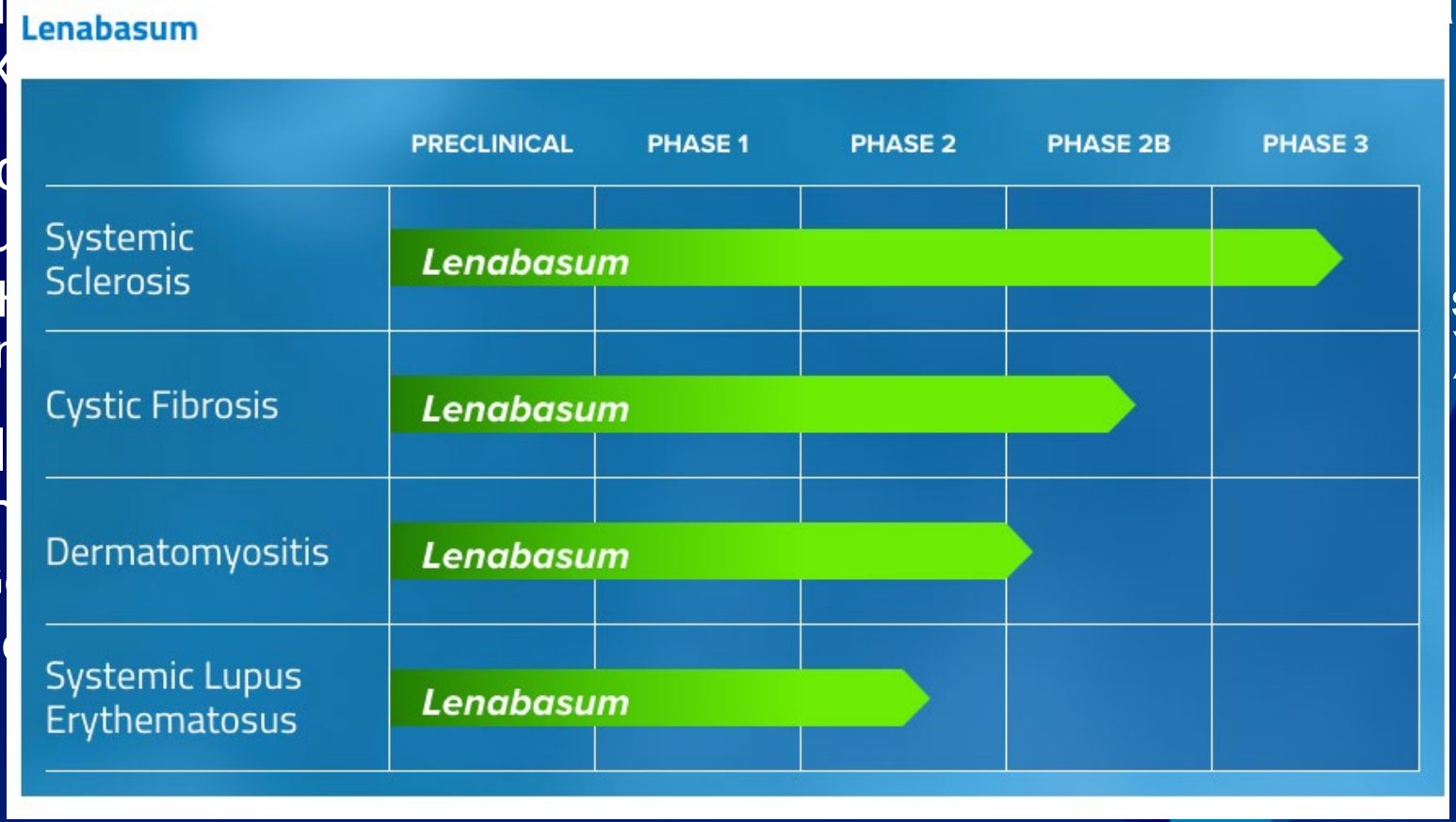
Any combination may be present in a given individual

Peripheral (nociceptive)	Peripheral Neuropathic	Centralized Pain
▪ Inflammation or mechanical damage in tissues ▪ NSAID, opioid responsive ▪ Responds to procedures	▪ Damage or dysfunction of peripheral nerves ▪ Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCA's, neuroactive compounds) pharmacological therapy	▪ Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia) ▪ Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission
▪ Classic examples ▪ Acute pain due to injury ▪ Osteoarthritis ▪ Rheumatoid arthritis ▪ Cancer pain	▪ Classic examples ▪ Diabetic neuropathic pain ▪ Carpal tunnel ▪ Sciatica	▪ Classic examples ▪ Fibromyalgia ▪ Irritable bowel syndrome ▪ TMJD ▪ Tension headache

Mixed Pain States

Preclinical models of pain

- Ani[illegible] and mix
- Bec[illegible] cau
  - TH[illegible] s, ar[illegible])
- Sel[illegible] con
  - G[illegible]
  - N[illegible]



https://www.corbuspharma.com/pipeline/lenabasum

1. Woodhams, Stephen G., et al. *Neuropharmacology* 124 (2017): 105-120. 2. Walker, J. Michael, and Susan M. Huang. *Pharmacology & therapeutics* 95.2 (2002): 127-135. 3. Henstridge, Christopher M. *Pharmacology* 89.3-4 (2012): 179-187. 4. Aghazadeh Tabrizi, Mojgan, et al. *Chemical reviews* 116.2 (2016): 519-560.

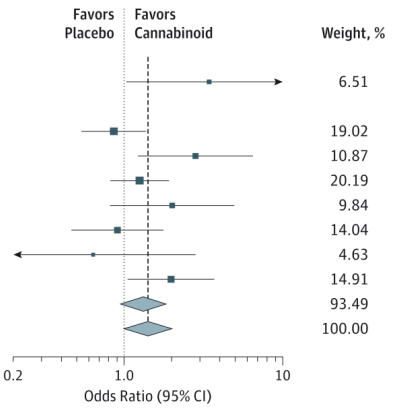
Role of Cannabinoids in Pain Management

- Preclinical models
- Mechanisms of action
- Clinical trials in chronic pain states
  - **Efficacy**

Cannabis clinical trials for chronic pain

Figure 2. Improvement in Pain

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal I^2 = 44.5%, (P = .0.94)	241	660	209	660	1.32 (0.94-1.86)
Overall I^2 = 47.6%, (P = .0.64)	254	685	215	685	1.41 (0.99-2.00)



- Limited: short length and small sample size
  - Many used THC alone or THC + CBD
- Most support in neuropathic pain (THC+CBD).
- Increased risk of short term AEs (mostly minor) for study participants
- Recent clinical trials suggest that CBD may be useful in nociceptive pain[3] but not centralized pain[4]

1. Whiting, Penny F., et al. *Jama* 313.24 (2015): 2456-2473. 2. Nugent, Shannon M., et al. *Annals of internal medicine* 167.5 (2017): 319-331. 3. Hunter, D., et al. *Osteoarthritis and Cartilage* 26 (2018): S26. 4. van de Donk, Tine, et al. *Pain* (2018).

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Cannabis and Mental Health

- Poor quality evidence across the board
  - Few clinical trials
  - Most studies examining harms – funding bias
  - Recreational vs. medical

Chapter Highlights
• Cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use the greater the risk. • In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks. • Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder. • For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than non-users. • Heavy cannabis users are more likely to report thoughts of suicide than non-users. • Regular cannabis use is likely to increase the risk for developing social anxiety disorder.

Cannabis and PTSD

REVIEW

Annals of Internal Medicine

Benefits and Harms of Plant-Based Cannabis for Posttraumatic Stress Disorder

A Systematic Review

Maya E. O'Neil, PhD; Shannon M. Nugent, PhD; Benjamin J. Morasco, PhD; Michele Freeman, MPH; Allison Low, BA; Karli Kondo, PhD; Bernadette Zakher, MBBS; Camille Elven, MD; Makalapua Motu'apuaka, BA; Robin Paynter, MLIS; and Devan Kansagara, MD, MCR

Background: Cannabis is available from medical dispensaries for treating posttraumatic stress disorder (PTSD) in many states

reported insufficient evidence to draw conclusions about benefits and harms. The observational studies found that compared

- "Limited evidence that cannabis or cannabinoids are effective for improving symptoms of PTSD" based on one small trial (n=10) of nabilone only
- Several ongoing clinical trials with PTSD and vaporized or smoked cannabis
- Most evidence in favor of cannabinoids is anecdotal or from observational studies for use

Betthauser, Kevin, Jeffrey Pilz, and Laura E. Vollmer. *American Journal of Health-System Pharmacy* 72.15 (2015): 1279-1284.

Cannabis and Anxiety/Depression

- Anxiety: “Limited evidence that cannabidiol are effective for improving anxiety symptoms” based on a small clinical trial (n=11) with a public speaking test
  - CBD also found to reduce subjective anxiety[1] with dosing efficacy following the u-shaped curve[2]
- Depression: “There is limited evidence that cannabis or cannabinoids are *ineffective* for reducing depressive symptoms in individuals with chronic pain or MS”

1. Crippa, José Alexandre S., et al. *Journal of Psychopharmacology* 25.1 (2011): 121-130. 2. Linares, Ila M., et al. *Brazilian Journal of Psychiatry* AHEAD (2018).

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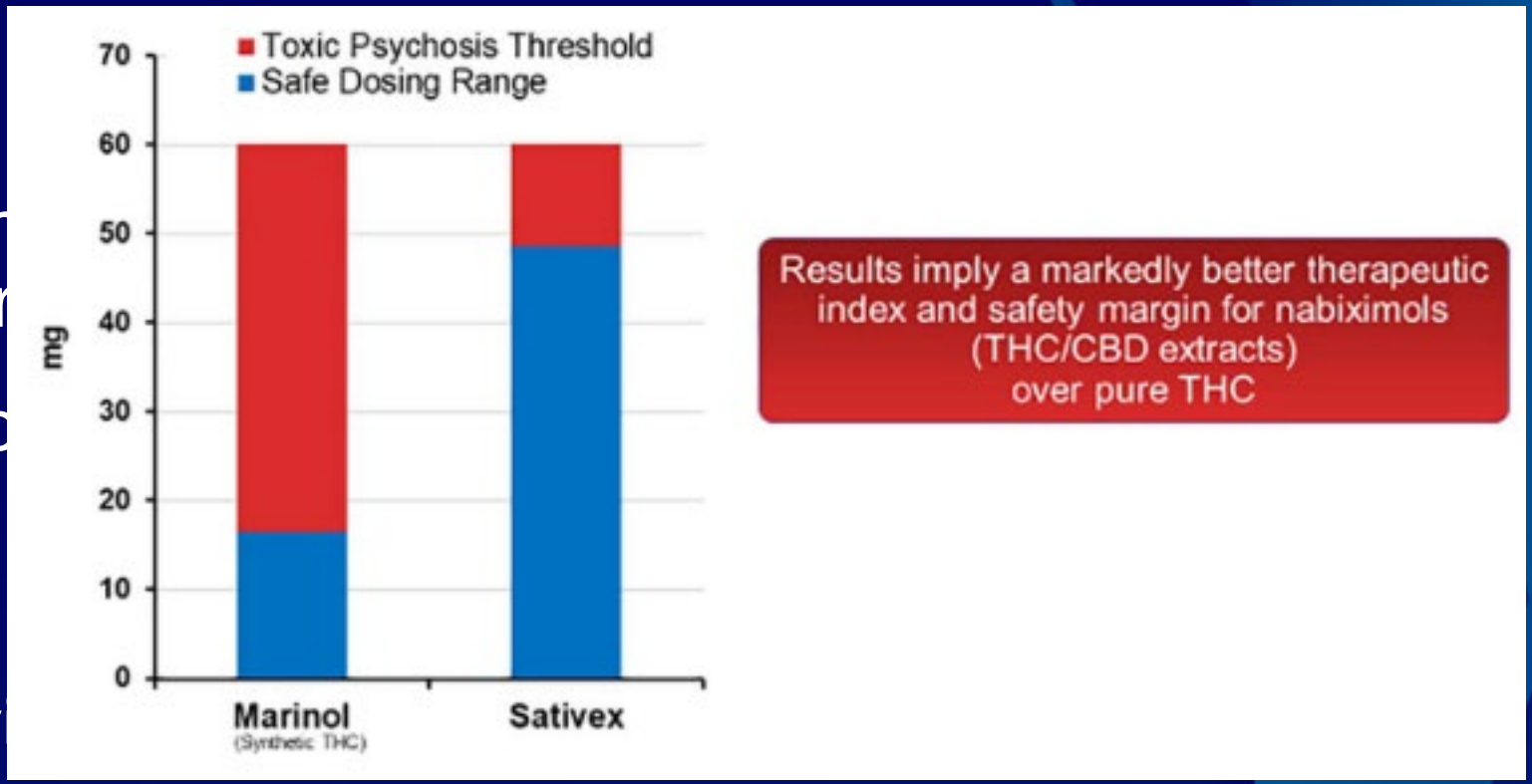

- If planning to use cannabis/cannabinoids:
  - "Start low, go slow"[1]
  - Use verifiable source with credible third party testing
  - Minimize harm by avoiding smoking

1. MacCallum, Caroline A., and Ethan B. Russo. "Practical considerations in medical cannabis administration and dosing." *European journal of internal medicine* (2018).

Questions?