The Benefits and Risks of Cannabis and Cannabinoids

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Disclosures

- Consulting
  - Pfizer, Forest, Eli Lilly, Pierre Fabre, Cypress Biosciences, Wyeth, UCB, AstraZeneca, Merck, J & J, Nuvo, Jazz, Abbott, Cerephex, Iroko, Tonix, Theravance, IMC, **Zynerba**, Sammumed, Aptinyx, **Lundbeck**
- Research support
  - Pfizer, Cypress Biosciences, Forest, Merck, Nuvo, Cerephex
- Testifying on behalf of State of Oklahoma against opioid manufacturers
- Went to the University of Michigan in the 1970's

How useful do you feel cannabinoids are for medicinal use?

0 — 10

Worthless — Wonderful

Benefits and Risks of Cannabinoids

- Definitions and Background
- Benefits of Cannabinoids
- Risks of Cannabinoids
- Role in Treating Chronic Pain
- Summary

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Definitions

- Cannabis – A genus of flowering plants with three different species: indica, sativa, and ruderalis
  - Can be bred to have low amounts of psychoactive compounds (e.g. THC) that are used to make hemp, or high amounts that are used for recreational/medicinal purposes
  - Sativex is a oral spray that is a cannabis extract
- Cannabinoid – Compounds that act at cannabinoid receptors
  - Endocannabinoids – endogenous ligands produced naturally that bind to CB1 and CB2 receptors
  - Phytocannabinoids – plant origin (cannabis/marijuana)
    - At least 80 different cannabinoids in cannabis
  - Synthetic cannabinoids

CB, cannabinoid receptor; THC, tetrahydrocannabinol

Pertwee RG. Handb Exp Pharmacol. 2005;(168):1-51.

Endocannabinoid system - I

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

- **Receptors** – G-coupled protein receptors (the most abundant in CNS in man) on presynaptic membrane of cells in peripheral and central nervous system
  - CB1 – Primarily in central nervous system (but not in medulla in man) these act primarily to inhibit release of neurotransmitters
  - CB2 – Largely found in periphery on immune and nerve cells (although some in CNS on microglia and DRG)
  - Other receptors can bind these ligands because there is activity in CB1/CB2 knockouts (TRPV1, GPR55)

CB, cannabinoid receptor; CNS, central nervous system, DRG, dorsal root ganglion

Pertwee RG. Handb Exp Pharmacol. 2005;(168):1-51.

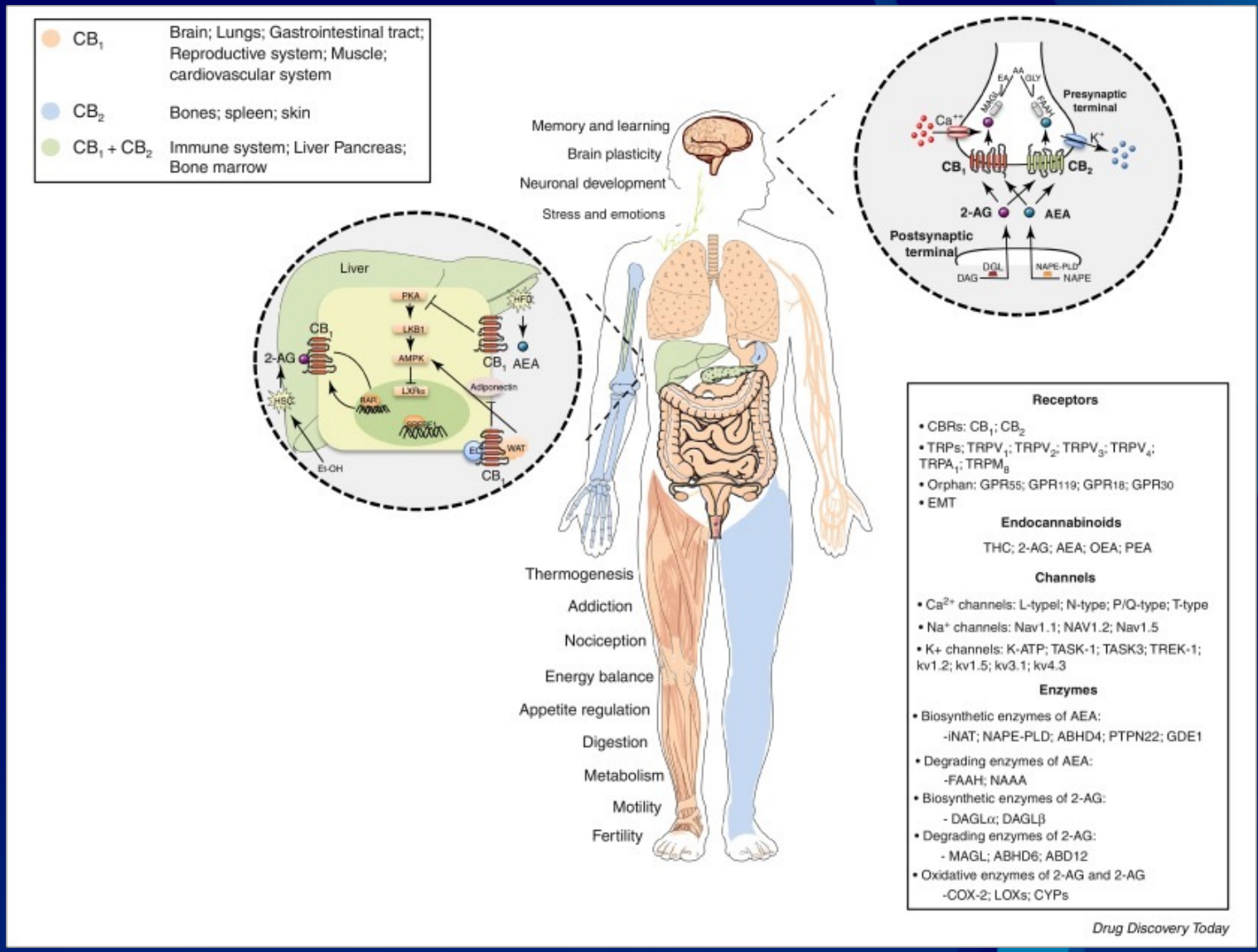
Endocannabinoid system - II

- **Ligands** – Endocannabinoids are eicosanoid lipid messengers that are the physiological ligands for the cannabinoid receptors:
  - ananamide (N-arachidonoylethanolamide, AEA)
  - 2-arachidonoylglycerol (2-AG)
  - PEA, virodamine, OAE
- **Enzymes** that synthesize and degrade the lipids endocannabinoids, such as fatty acid amide hydroxylase or monoacylglycerol lipase
  - Drugs being developed for pain that inhibit these enzymes

AEA, arachidonoylethanolamine PEA, palmitoylethanolamide; OAE, oleoylethanolamine

Pertwee RG. Handb Exp Pharmacol. 2005;(168):1-51.

Endocannabinoid system



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.

Commentary

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Hijacking the endogenous opioid system to treat pain: who thought it would be so complicated?

Daniel Clauw

In this issue, there is an especially interesting and important special review by Ballantyne and Sullivan entitled, "The discovery of endogenous opioid systems: what it has meant for the clinician's understanding of pain and its treatment".[1] This review adds to these authors' significant prior contributions to the pain field, as they are now proposing that many of the problems associated with opioid therapy can be understood mechanistically as being off-target effects on the endogenous opioid system. They describe how our emerging understanding of the endogenous opioid system might allow us to better understand how exogenous opioids can "hijack" this system to produce unexpected and undesired consequences, both when they are used for pain relief, and when they are misused or abused. They especially focus on how acute or chronic opioid therapy (COT) may impair some of the nonanalgesic functions of the endoge-

These issues of excess death and addiction, combined with a lack of any evidence of long-term efficacy,[3] have led many of us in the pain field to question whether opioid should ever be used to treat chronic nonmalignant pain. We know of some patients with chronic pain who are on long-term high-dose opioid therapy who are doing well (ie, have good pain control and good functional status), but these patients are exceedingly rare. Instead, we see large numbers of individuals who want to keep taking opioids, although after we assess them, we conclude that the long-term side effects of these drugs far exceed any benefit they are receiving.

This review highlights why we may see some of the more insidious problems that occur with COT, which are summarized below.

Individuals on COT may continue to "need" opioids to replicate the functions of endogenous opioids that are no longer being

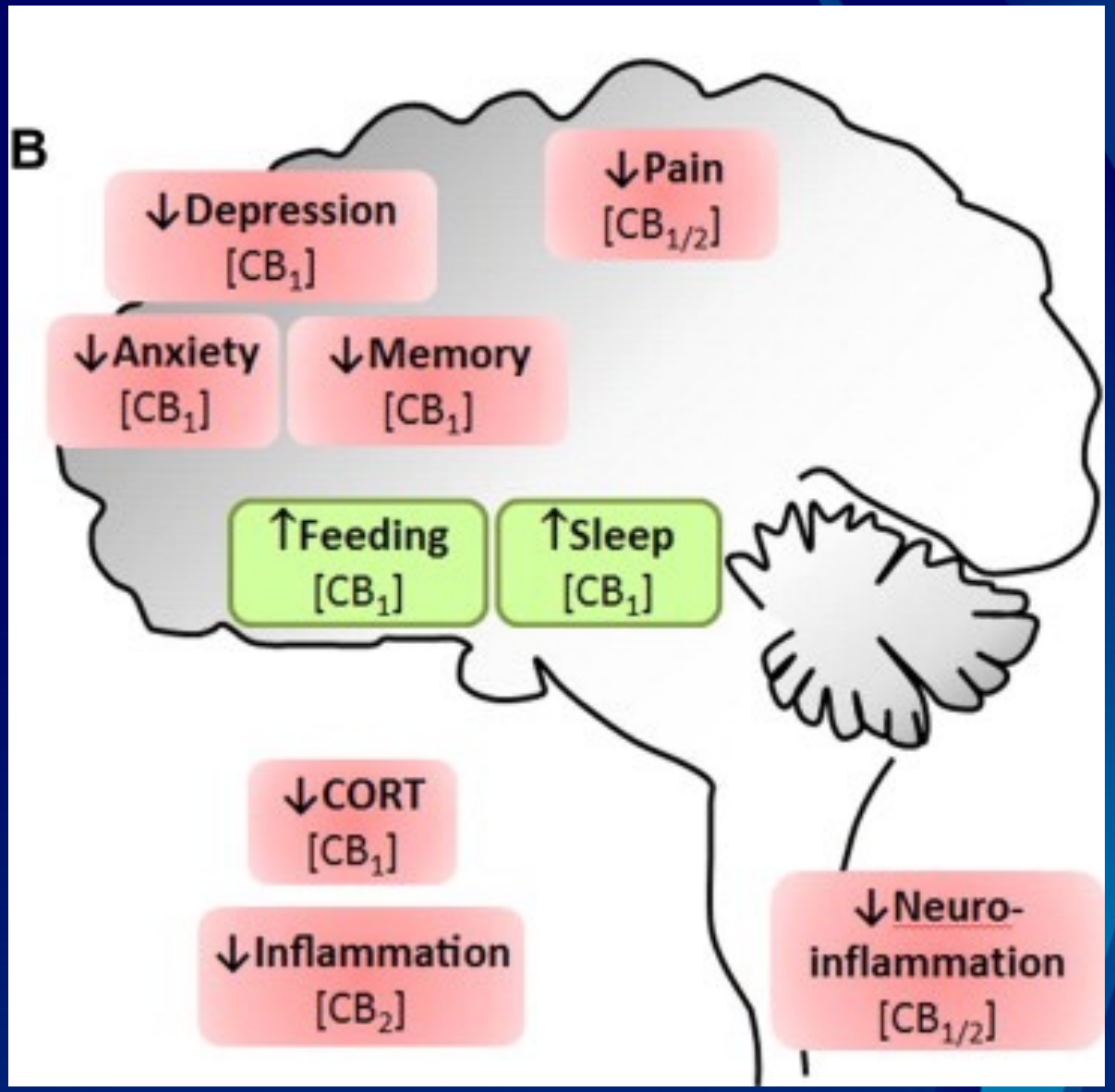
Endocannabinoid system - III

Some known functions of the endocannabinoid system in humans:

- **Memory** – Generally affect short term memory, may play adaptive role in extinction of old memories in hippocampus
- **Neurogenesis**
- **Appetite** – Act in hypothalamus to increase appetite, inversely related to leptin levels
- **Analgesia**
- **Immune function** – Generally inhibit immune function, generally mediated via CB2[1] but some evidence CB1 might play role in T-cell responses. May be upregulation of CB2 receptors in some inflammatory disorders
- **Stress** – Help habituate/reduce HPA axis activity during repeated stress[2]

CB, cannabinoid receptor; HPA, hypothalamic-pituitary-adrenal

1. Rom S, Persidsky Y. J Neuroimmune Pharmacol. 2013; 8:608-20. 2. Hill MN, et al. Proc Natl Acad Sci U S A. 2010;107:9406-11.



CB, cannabinoid receptor
Image source: © Crowe S, et al. Brain Behav Immun

Crowe S, et al. Brain Behav Immun. 2014;42:1-5.

Cannabis-derived cannabinoids

More than 80 known, with different strains having different relative concentrations

- **THC** (Synthetic forms include Dronabinol, Marinol, Nabilone)
  - The primary psychoactive cannabinoid in cannabis, and its metabolites are those assayed for in drug tests
  - Although it binds relatively equally to both the CB1 and CB2 receptors, most of its effects are associated with CB1 activity in brain
- CBD (cannabidiol)
  - Seems to be generally very well tolerated
  - Is not psychoactive and does not bind with any significant affinity to CB receptors, but yet has anticonvulsant and anti-inflammatory effects
  - Is actually thought to potentially protect against psychoactive effects of THC and hypothesized by some to be an effective anti-psychotic (although a recent Cochrane review concluded there was insufficient evidence of this)

CB, cannabinoid receptor; THC, Tetrahydrocannabinol

Pertwee RG. Handb Exp Pharmacol. 2005;(168):1-51.

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Potential Benefits of Cannabinoids

- Antiemetic[1] – Marinol is FDA-approved (Schedule III) for use in post-chemotherapy nausea/vomiting
- Anorexia – Marinol is FDA-approved for this use in AIDS-induced anorexia in US
- Anti-spasticity agent[2]
- Anticonvulsant[3] – Focus on CBD effects
- Neuroprotective
  - Being studied in Alzheimer's[4] because preclinical models show CB1/2 activation leads to reduction in beta-amyloid
  - Retrospective study of patients admitted with severe TBI showed significant reduction in death in those who had a positive drug screen for THC[5]
- Anti-tumor effects[6]

AIDS, acquired immune deficiency syndrome; CB, cannabinoid receptor; CBD, cannabidiol; FDA, Food and Drug Administration; TBI, traumatic brain injury; THC, tetrahydrocannabinol

1. Sharkey K, et al. Eur J Pharm. 2014; 722:134-46. 2. Koppel, et al. Neurology. 2014;82:1556-63. 3. Devinsky O. Epilepsia;2014:55:791-802.
4. Aso E, et. al. Front Pharmacol. 2014;5:37. 5. Nguyen BN. Am Surg. 2014;80:979-83. 6. Cridge B, Rosengren RJ. Cancer Manag Res. 2013;5:301-13.

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Risks of Cannabinoids

- Almost all available data is from long term recreational users so we probably have good “worst case” data
- Partly related to route of administration
  - Smoking cannabis may lead to chronic bronchitis and potentially cancer of the mouth, throat, lung
  - This is likely reduced or eliminated with use of vaporizers or e-cigarettes
  - Oral administration causes less “likability” than inhalation or smoking and presumably no risk of bronchitis or cancer
  - *Individuals using cannabis for medicinal purposes should probably be using an oral formulation but dosing is problematic*
- The few deaths associated with cannabis are generally due to severe paranoia or tachycardia associated with overdose via oral administration

Degenhardt L, Hall WD. CMAJ. 2008;178:1685-6.

Long Term Risks of Cannabinoids[1]

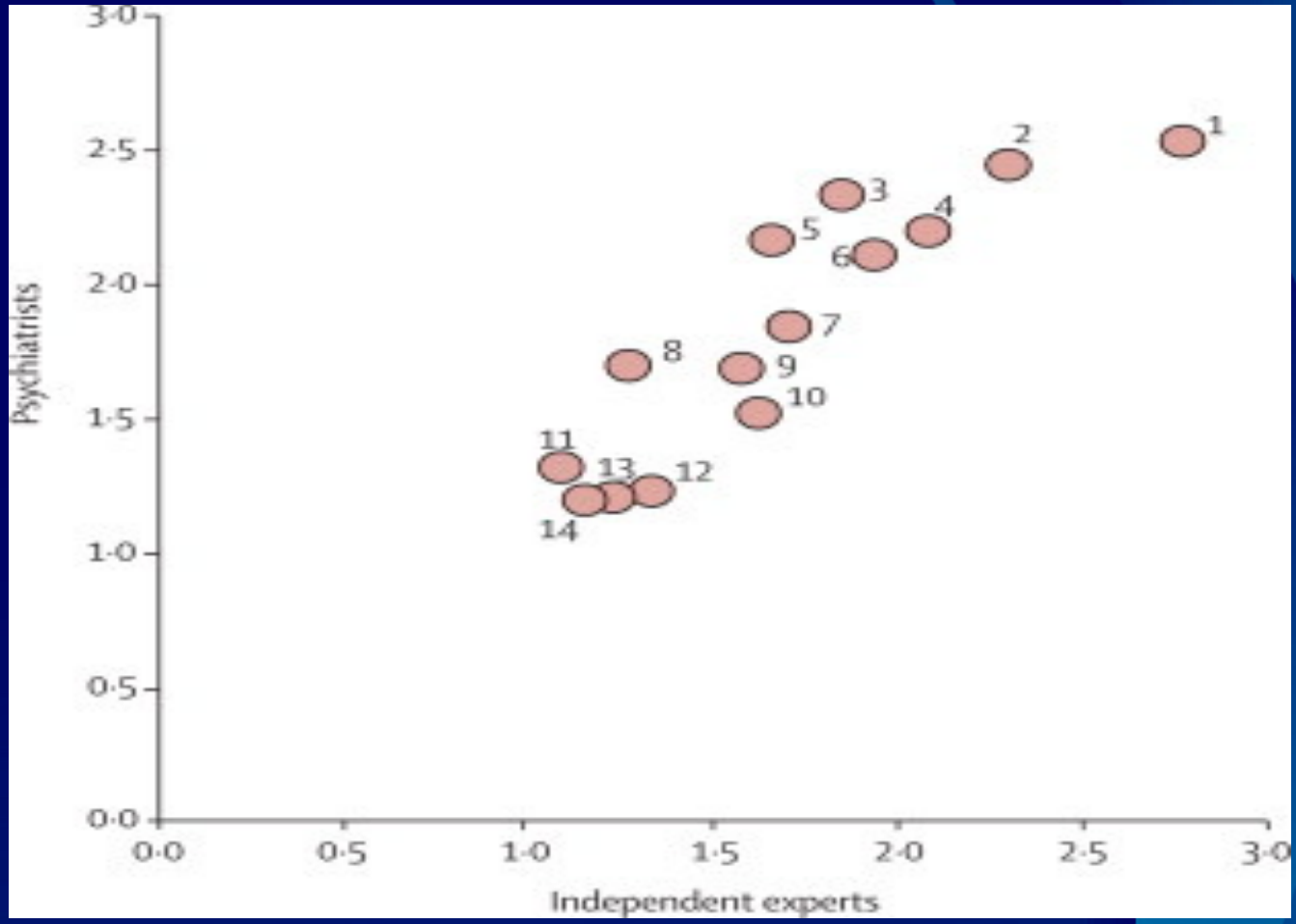
- Psychotic illnesses
  - It is now generally accepted that individuals who begin smoking cannabis prior to age 25 have 1.5 – 2.4X the rate of developing a psychotic illness[2]
  - This risk is modified by childhood trauma, family history of a psychotic illness, and perhaps genetic polymorphisms
- Long term effects on memory and brain structure
  - Both neuropsychological testing, and functional and structural neuroimaging studies, have suggested that individuals who use cannabis recreationally beginning in adolescence have decreased cognitive performance[1,3]
  - These studies have significant methodological issues because of other common exposures (e.g. alcohol or other illicit drugs) and behavioral issues in these individuals[3]

1. Hall W. Drug Test Analysis 2014:6:39-45 2. Radhakrishnan R. Front Pharmacol. 2014:5:1-6. 3. James A, et al. Psychiatry Res. 2013;214:181-9.
3. Batalla A. PLOSone 2013;8:e55821.

Risks of Cannabinoids[1]

- Respiratory
- Dependence
  - Occurs in approximately 9% of individuals who use cannabis, but is about double in those who begin using in adolescence
  - This is lower than almost all other drugs of abuse (nicotine 32%, opioids 23%, alcohol 15%)
  - Highest risk in those with poor academic achievement, deviant behavior in childhood, poor parental relationships, family history of substance abuse
  - Physical addiction and withdrawal are much less common/severe than other drugs of abuse

1. Hall W. Drug Test Analysis 2014:6:39-45 2. Radhakrishnan R. Front Pharmacol. 2014:5:1-6. 3. James A, et al. Psychiatry Res. 2013;214:181-9.



Comparison of classification systems for the harms and risks of drug abuse in the development of the multi-category Nutt rational scale

Correlation between mean scores from the independent experts and the specialist addiction psychiatrists 1=heroin. 2=cocaine. 3=alcohol. 4=barbiturates. 5=amphetamine. 6=methadone. 7=benzodiazepines. 8=solvents. 9=buprenorphine. 10=tobacco. 11=ecstasy. 12=cannabis. 13=LSD. 14=steroids

Nutt D, et al. Lancet. 2007 Mar 24;369(9566):1047-53.

Is there a link between marijuana and cancer?

- Smoked marijuana delivers THC and other cannabinoids to the body, but it also delivers harmful substances to users and those close by, including many of the same substances found in tobacco smoke, which are harmful to the lungs and cardiovascular system.
- Researchers have found limited evidence of an association between current, frequent, or chronic marijuana smoking and testicular cancer (non-seminoma-type

National Academies of Sciences E, and Medicine. (2017). The health effects of cannabis and cannabinoids.

Cannabis and motor vehicle accidents

- Driving while impaired by any substance, including marijuana, is dangerous. Marijuana, like alcohol, negatively affects a number of skills required for safe driving:
  - Marijuana can slow your reaction time and ability to make decisions.
  - Marijuana use can impair coordination, distort perception, and lead to memory loss and difficulty in problem-solving.
- The risk of impaired driving associated with marijuana in combination with alcohol appears to be greater than that for either by itself.
- Latest statistics in states that have legalized cannabis suggests very small increase in MVA (3%) but no increase in fatalities

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Systematic reviews with meta-analysis on cannabis-based medicines for chronic pain: a methodological and political minefield

Winfried Häuser[a], Nanna B. Finnerup[b,c], R. Andrew Moore[d]

Public interest in cannabis products for medical purposes has been widely advocated, with legalization for recreational and medical use in North America and some European countries.[6,8] Legalization of cannabis-based medicines (CBMs) (medical cannabis, plant-based cannabinoids [tetrahydrocannabinol, cannabidiol, and combinations], and synthetic tetrahydrocannabinol analogues) has bypassed usual drug regulatory procedures.[6] Systematic reviews with meta-analyses of randomised controlled trials (RCTs) with CBM for chronic pain conditions help determine "post hoc" whether the preconditions of drug agencies for approval were met and to guide physicians and patients.

A systematic review of systematic reviews on CBM highlighted the uncertainty about whether CBMs improve pain, with only low or very low quality evidence available.[1] Individual systematic reviews generally avoided issues of trial quality, usually had some flaws, and included different drugs, doses, durations, conditions, and outcomes. Most reviews agreed that there was no, or no clinically relevant, effect.

In this issue of *PAIN*, Stockings et al.[12] provide the most comprehensive systematic review with meta-analysis of RCTs and observational studies with CBM, including 47 RCTs with 4271 patients with chronic noncancer pain. Study duration ranged between 1 day and 26 weeks. The authors avoid some methodology flaws of some of the systematic reviews mentioned above. They included "gray" literature and used all studies providing data in quantitative analyses. Average pain intensity, 30% and 50% or more pain relief, emotional and physical

There remains a methodological minefield, through which we need to step carefully. For example:

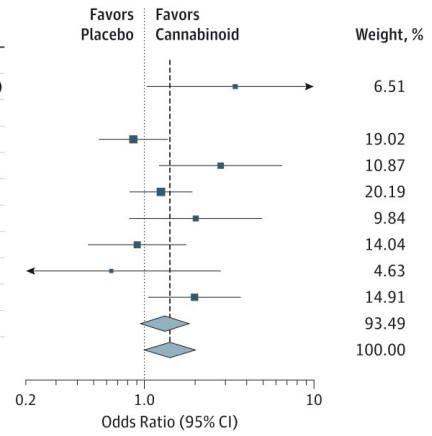
(1) Most studies analysed are of low methodology quality.
(2) Most studies included fewer than 50 patients per treatment arm. Small CBM studies are often the most positive.
(3) Short-duration experimental studies (hours, a single day) were included, unhelpful in judging longer-term efficacy.
(4) Lumping all chronic pain syndromes together does not help in managing individual patients, given the heterogeneity of chronic pain and its mechanisms. Even the importance of subgroup analyses is limited: cancer pain might have nociceptive and/or neuropathic components; neuropathic pain can have many dimensions, and drugs might be effective for some dimensions of neuropathic pain but not for others.[3] Whether heterogeneity of pain mechanisms is relevant for the efficacy of CBM, which are nonspecific centrally acting drugs is, however, unknown.
(5) Lumping together all CBMs, including experimental drugs unavailable for clinical use, limits the clinical relevance of combined results.
(6) There is the risk of overestimating the effects of CBM for pain relief because of unpublished studies, for example, with nabilone for chronic neuropathic pain.[10]
(7) Long-term risk and severe but rare side effects are not captured in small, short-duration trials.

What can patients, clinicians, trialists, drug companies, and

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)	Weight, %
Tetrahydrocannabinol (smoked)						
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)	6.51
Nabiximols						
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)	19.02
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)	10.87
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)	20.19
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)	9.84
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)	14.04
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)	4.63
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)	14.91
Subtotal $I^2 = 44.5\%$, ($P = .0.94$)	241	660	209	660	1.32 (0.94-1.86)	93.49
Overall $I^2 = 47.6\%$, ($P = .0.64$)	254	685	215	685	1.41 (0.99-2.00)	100.00



- Limited: short length and small sample size
  - Many used THC alone or THC + CBD
- Most support for use of cannabinoids in neuropathic pain (THC+CBD).
- Increased risk of short term AEs (mostly minor) for study participants

Whiting, Penny F., et al. *Jama* 313.24 (2015): 2456-2473.
Nugent, Shannon M., et al. *Annals of internal medicine* 167.5 (2017): 319-331.

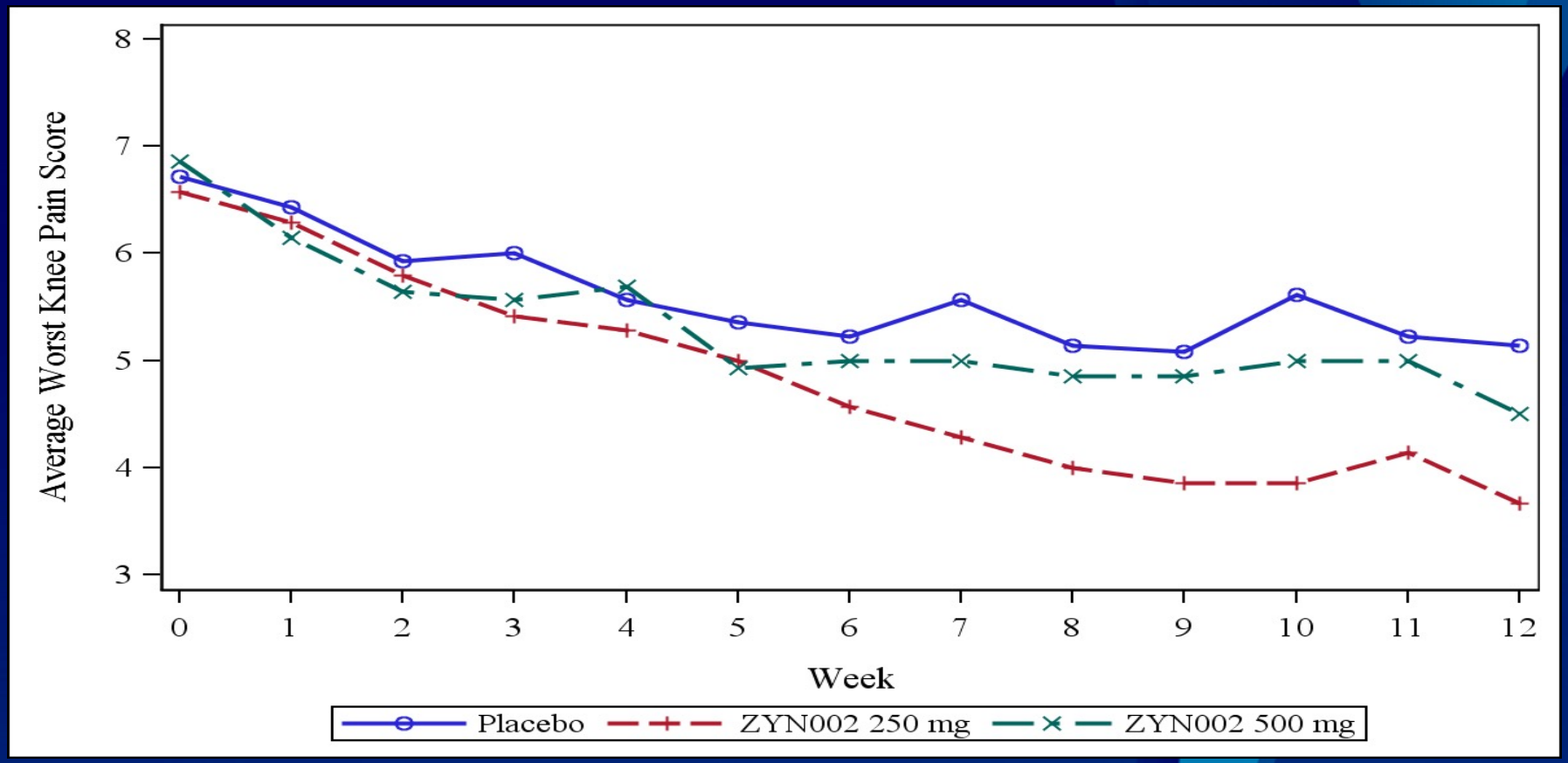
Anti-inflammatory effects of CBD

- There are many animal models where CBD has been demonstrated to have potent anti-inflammatory effects in a variety of models (including murine collagen arthritis and carrageenan models) but it is much less clear how those anti-inflammatory effects are being mediated
- Some evidence that anti-inflammatory effects might be occurring via CB2 (very high doses needed), adenosine receptors, arachidonic acid release (causes shift from cyclooxygenase to lipoxygenase pathway), via direct inhibition of cytokine production, or via binding to the GPR55 receptor (which has both inflammatory and nociceptive properties)

CB, cannabinoid receptor; CBD, cannabidiol; GPR55, G protein-coupled receptor 55

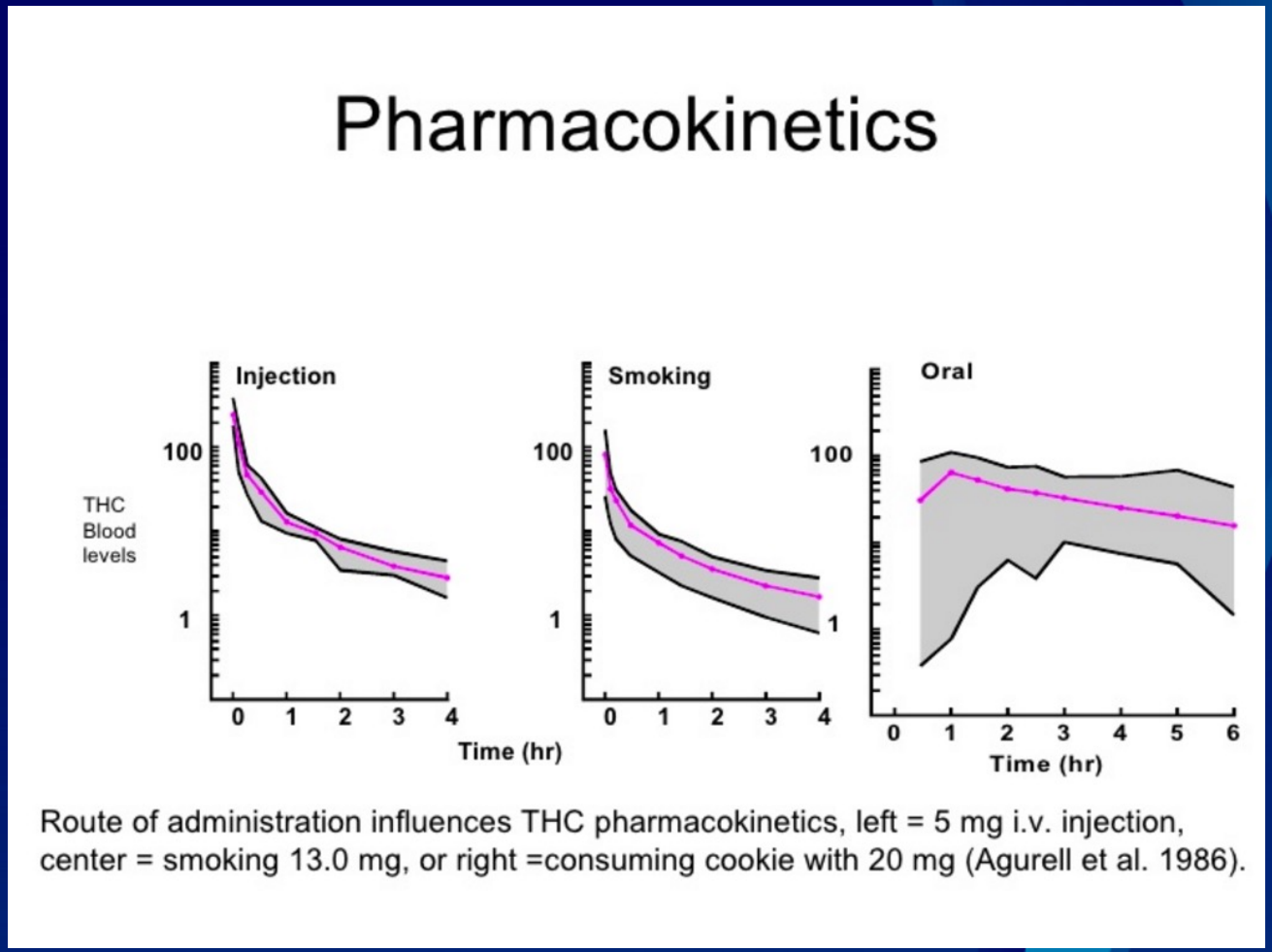
Burstein S. Bioorg Med Chem. 2015;23:1377-85.

ZYN002 - Median Weekly Average Worst Knee Pain Score over Time - Males



Route of administration is very important

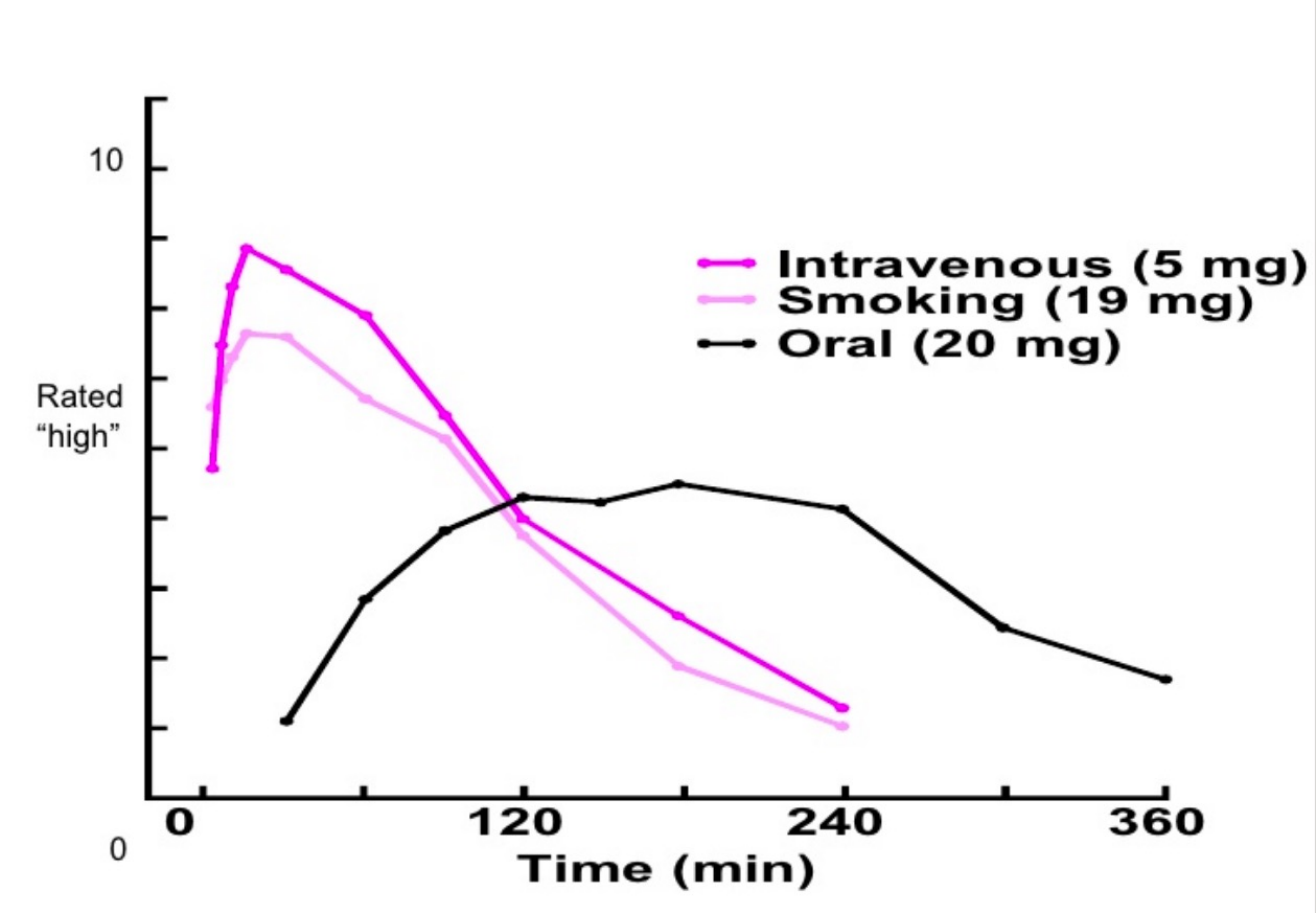
Pharmacokinetics



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).

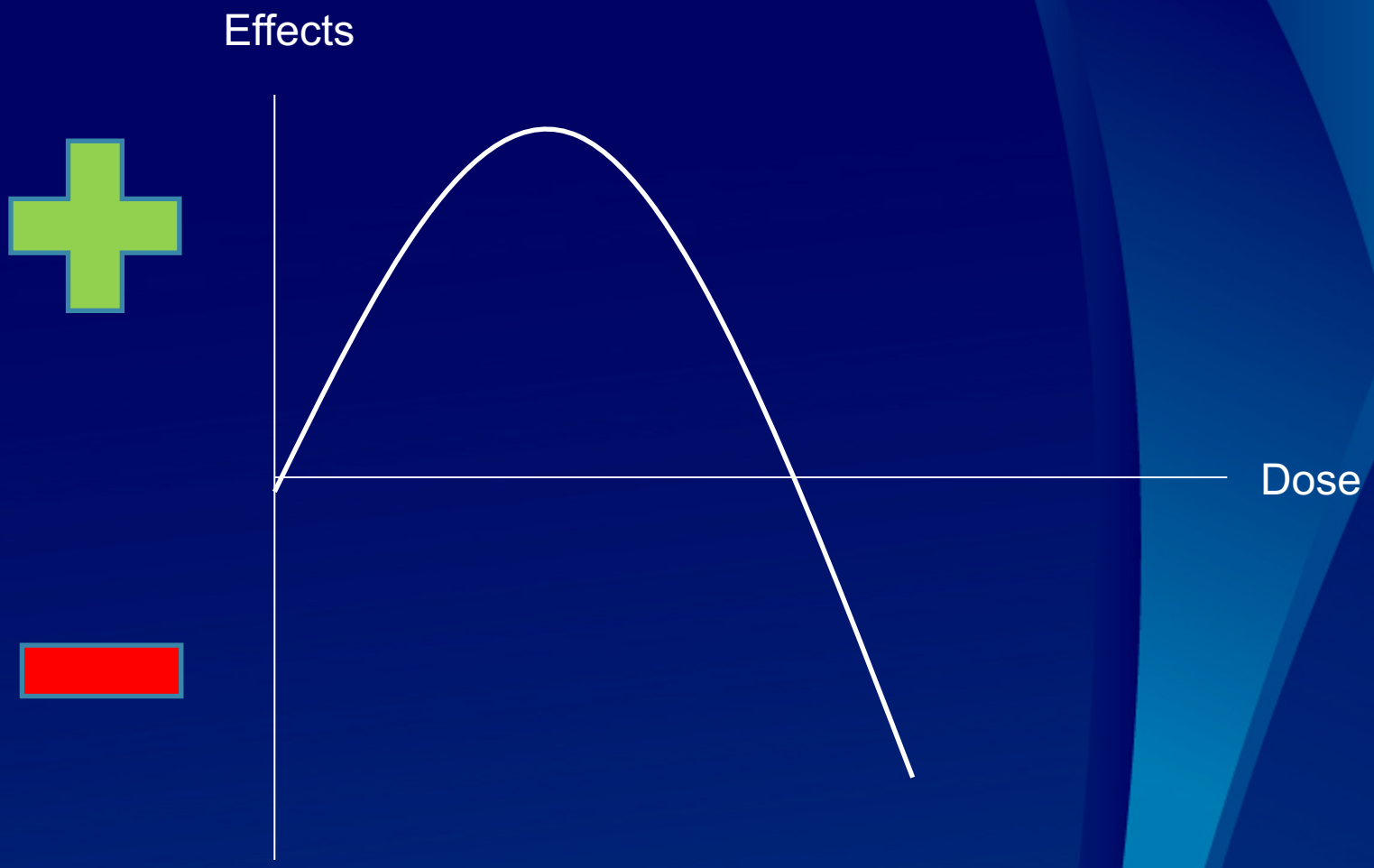
Agurell, Stig, et al. *Pharmacological Reviews* 38.1 (1986): 21-43.

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.

Mechanistic Characterization of Pain
Variable degrees of any mechanism can contribute in any disease

	Nociceptive	Neuropathic	Centralized
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (i.e. dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory and/or mood difficulties as well as history of previous pain elsewhere in body
Screening tools		PainDETECT	Body map or FM Survey
Treatment	NSAIDs, injections, surgery, ? opioids	Local treatments aimed at nerve (surgery, injections, topical) or CNS-acting drugs	CNS-acting drugs, non-pharmacological therapies
Classic examples	Osteoarthritis Autoimmune disorders Cancer pain	Diabetic painful neuropathy Post-herpetic neuralgia Sciatica, carpal tunnel syndrome	Fibromyalgia Functional GI disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain syndrome

CNS, central nervous system; FM, fibromyalgia; GI, gastrointestinal

Clauw DJ. The taxonomy of chronic pain: Moving towards more mechanistic classification. In: Wallace DJ & Clauw DJ, editors. Fibromyalgia and other central pain syndromes. Philadelphia: Lippincott, Williams & Wilkins; 2005. p.10-16.

Treating Based on Mechanisms

Any combination may be present

	Peripheral (nociceptive)	Neuropathic	Centralized Pain
NSAIDs	+	-	-
Opioids	+	+	-
Surgery/ Injections	+	+	-
Tricyclics	+	+	+
SNRIs	+	+	+
Gabapentinoid	-	+	+
CBD	+	-	-
THC	-	+	+

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. Elikottil, Jaseena, et al. *Journal of opioid management* (2009). 2. Abrams et al, *Clinical Pharmacology and Therapeutics*, (2011). 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)

Proposed marketing program for medical cannabis

Cannabis plant talking to opium producing poppy plant

At least we don't kill people

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Pragmatic Advice for Using Cannabinoids in 2022

- Where possible use a cannabinoid or cannabinoid extract of consistent and known potency
- Start with CBD alone 10 – 20mg and go as high as 200mg per day
- If CBD alone ineffective consider adding low dose of low THC:high CBD strain (5-10mg of THC), and go up slowly
- Emerging evidence of U-shaped curve
- Oral dosing better once stable dose and strain identified
- The strongest recommendation based on current benefit: risk data is for the use of cannabinoids instead of opioids for neuropathic or centralized pain states
- Use with caution in individuals under age 25

CBD, cannabidiol; THC, tetrahydrocannabinol