PHARM OR FABLE:
CONTEMPORARY CLINICAL CONSIDERATIONS OF CANNABIS

C W FETROW, PHARMD

SENIOR CARE CONSULTANT GROUP, LLC

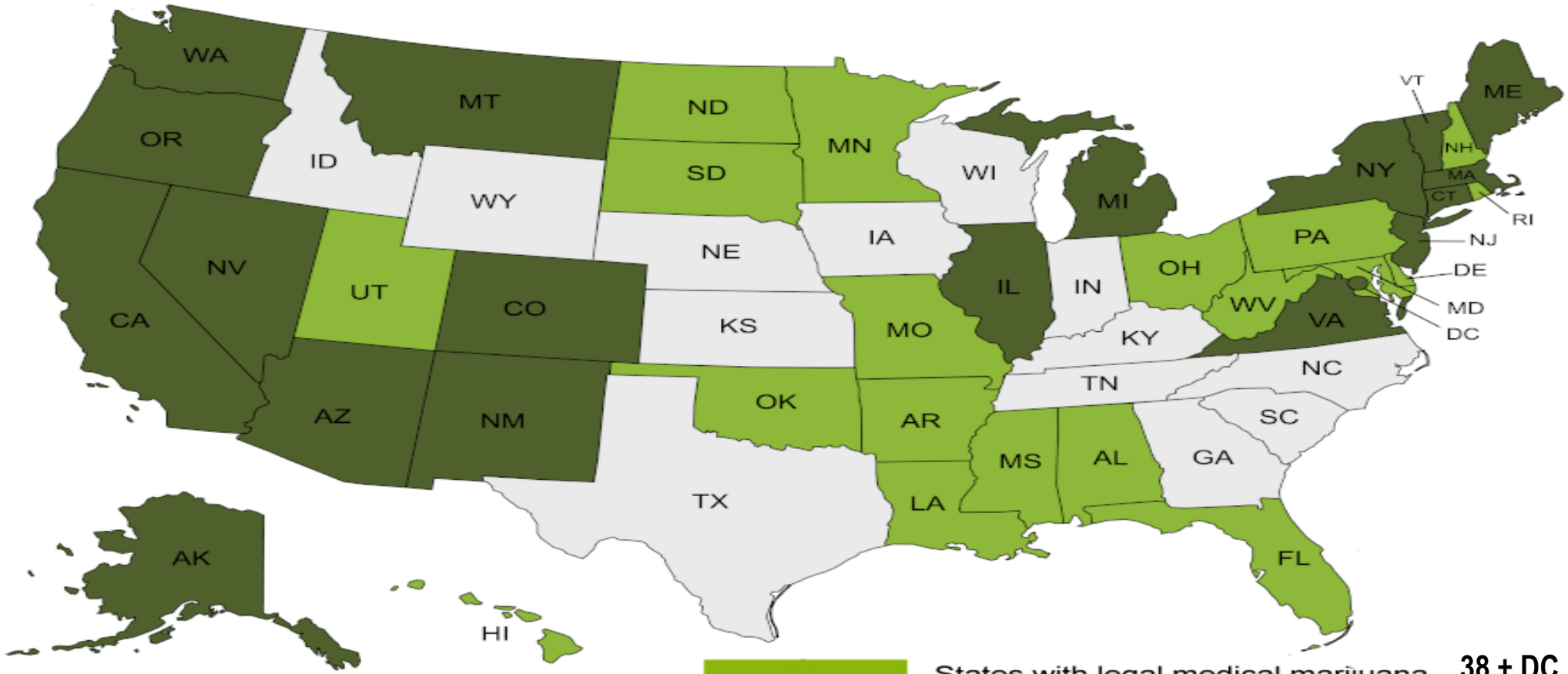
High time for an . . .

UPDATE

OBJECTIVES

UNDERSTAND	UNDERSTAND GENERAL CONCEPTS RELATING TO DIFFERENCES IN PHYTOCHEMICAL PHARMACOLOGY BETWEEN VARIETIES OF CANNABIS
COMPARE & CONTRAST	COMPARE & CONTRAST EXISTING PHARMACEUTICALS WHICH HAVE EVOLVED FROM CANNABIS
DESCRIBE	DESCRIBE RELEVANCE OF ENDOCANNABINOID SYSTEM & HOW IT RELATES TO MEDICINNAL CANNABIS
RECOGNIZE	RECOGNIZE LIMITATIONS OF PUBLISHED EVIDENCE SURROUNDING USE OF CANNABIS IN CERTAIN DISEASE STATES
REVIEW	REVIEW POTENTIAL RISKS ASSOCIATED WITH CANNABIS USE
EXPRESS	EXPRESS AN UNDERSTANDING FOR NEEDS OF FUTURE RESEARCH RELEVANT TO MEDICINNAL CANNABIS

Legal Medical & Recreational Marijuana States



Created with mapchart.net

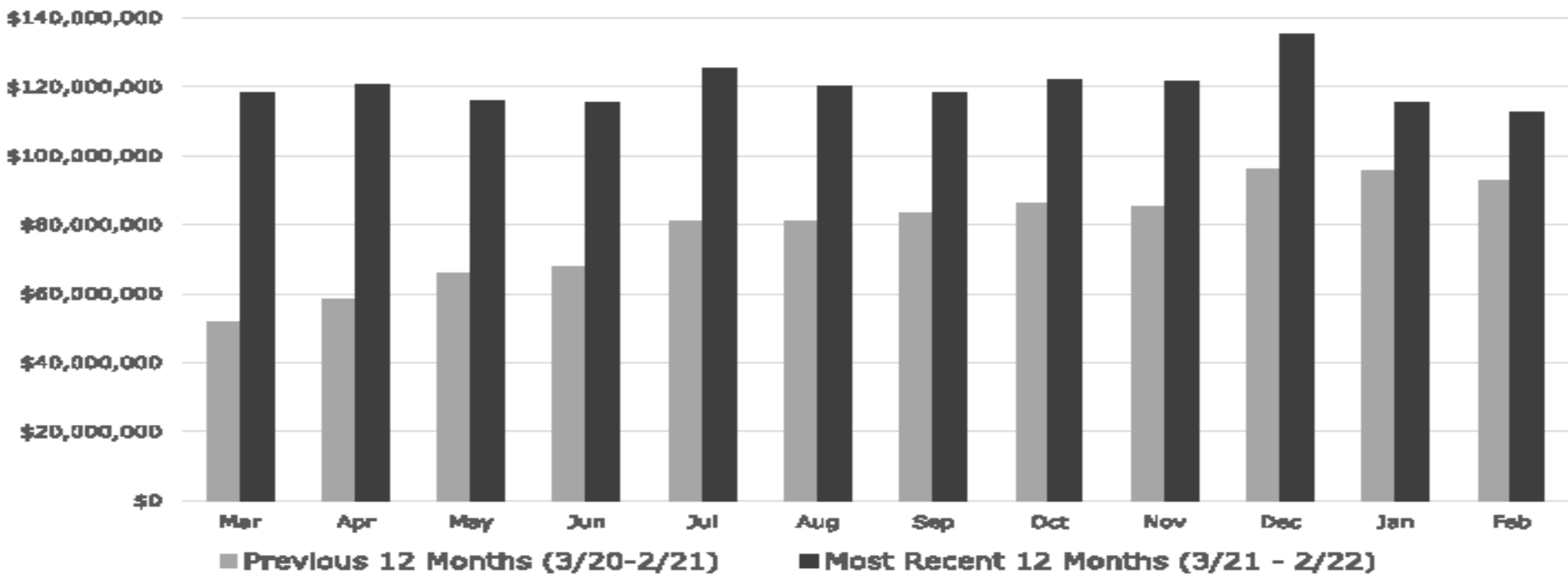
BRITANNICA PROCON.ORG | RELIABLE. NONPARTISAN. EMPOWERING.

Pennsylvania – (23) Approved Indications

- Amyotrophic lateral sclerosis
- Anxiety disorders
- Autism
- Cancer, including remission therapy
- Crohn's disease
- Damage to the nervous tissue of the central nervous system (brain-spinal cord) with objective neurological indication of intractable spasticity, and other associated neuropathies.
- Dyskinetic and spastic movement disorders
- Epilepsy
- Glaucoma
- HIV / AIDS
- Huntington's disease
- Inflammatory bowel disease
- Intractable seizures
- Multiple sclerosis
- Neurodegenerative diseases
- Neuropathies
- Opioid use disorder for which conventional therapeutic interventions are contraindicated or ineffective, or for which adjunctive therapy is indicated in combination with primary therapeutic interventions
- Parkinson's disease
- Post-traumatic stress disorder
- Severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain
- Sickle cell anemia
- Terminal illness
- Tourette syndrome

Medical Marijuana Program Update

Month on Month Dispensary Sales



pennsylvania
DEPARTMENT OF HEALTH

Consumer Prices for Marijuana

Prices for medical marijuana in Pennsylvania can cost more than twice as much as in Colorado or California, two states where outdoor cultivation of cannabis is legal. Prices shown here are average consumer costs for an **eighth of an ounce**, the most commonly offered amount, which can be rolled into about seven joints.

- Illinois $60.42
- **Pennsylvania** $58.86
- Massachusetts $56.81
- New Hampshire $50.33
- Alaska $50.30
- Connecticut $50.23
- Rhode Island $49.39
- Vermont $48.33
- Michigan $42.48
- Maine $41.55
- Oklahoma $31.14
- New Mexico $29.63
- Nevada $27.53
- Colorado $24.83
- California $24.55
- Arizona $23.58
- Oregon $21.88
- Washington $17.84
- DC $48.83

Chart: JOHN DUCHNESKIE / Staff Artist Source: Cannabis Benchmarks; Inquirer survey of Pa. growers and dispensaries in Philadelphia Inquirer Published 12/20/2020

Kentucky Health Issues Poll (Medical Marijuana)

"Do you favor or oppose the Commonwealth of Kentucky allowing patients to buy and use marijuana for medical purposes if their doctors recommend it?"

90% favor

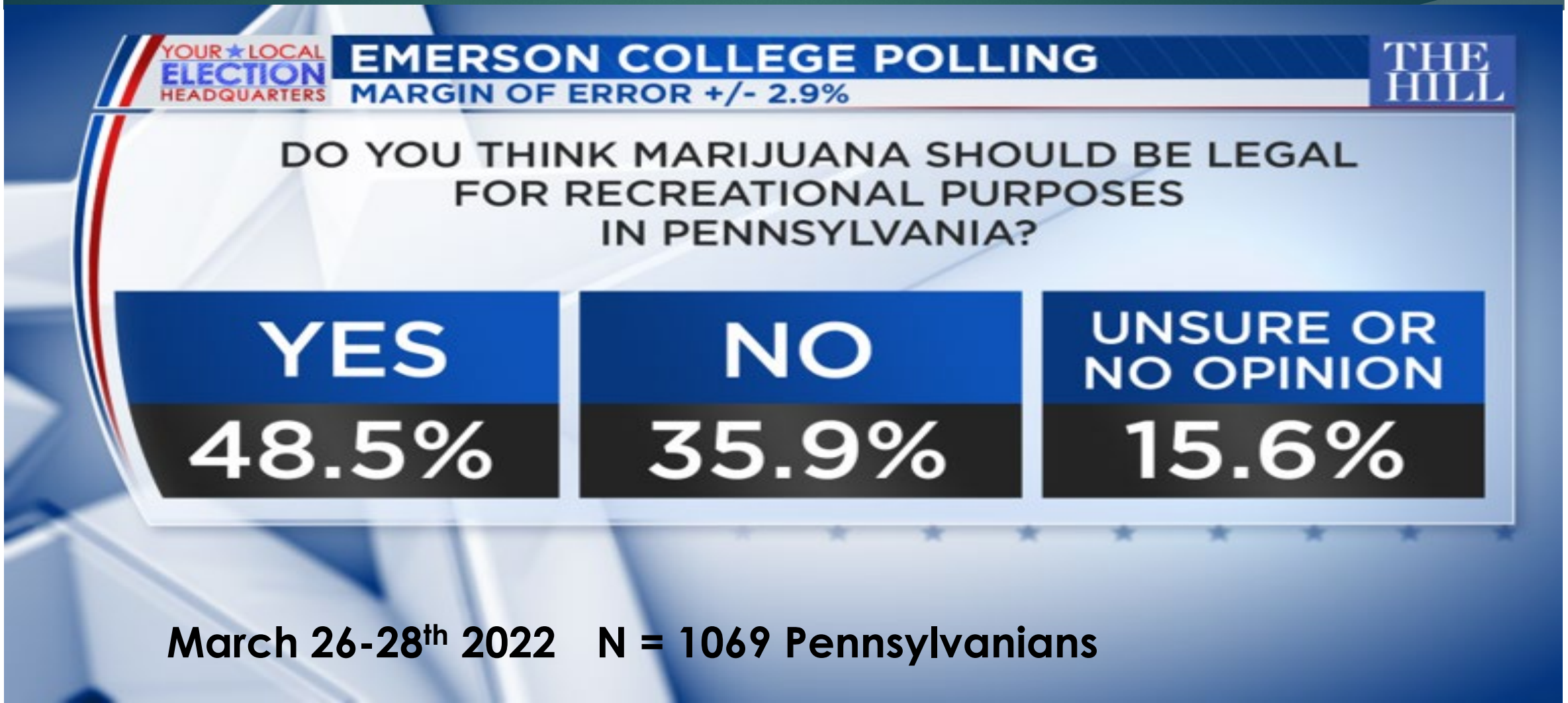
8% oppose

1 % neutral

Foundation for a Healthy Kentucky (conducted by the Institute for Policy Research at the University of Cincinnati)
N = 1559 adults throughout Kentucky, February 2020

WJET / WFXP / Emerson College Polling / The Hill

Recreational Marijuana



March 26-28th 2022 N = 1069 Pennsylvanians

Physician Perspectives on Medical Marijuana

PRO

"There is now promising research into the use of marijuana that could impact tens of thousands of children and adults, including treatment for cancer, epilepsy and Alzheimer's, to name a few. With regard to pain alone, marijuana could greatly reduce the demand for narcotics and simultaneously decrease the number of accidental painkiller overdoses, which are the greatest cause of preventable death in this country… Marijuana is a medicine, that should be studied and treated like any other medicine."

- Sanjay Gupta, MD

Medical Correspondent for CNN
"It's Time for a Medical Marijuana Revolution," cnn.com
Apr. 20, 2016

CON

"[T]here really is no such thing as medical marijuana… The dangers and risks of marijuana use are well-known by the scientific community, even if they are downplayed by corporate interests wishing to get rich off of legalization. Apathy, lost productivity, addictive disease, deterioration in intellectual function, motor vehicle accidents, and psychosis are all among the negative outcomes. All from a product that has no demonstrated benefit. For nearly all conditions for which marijuana has purported benefits, we already have existing medications – safe medications – demonstrated to have value."

- Stuart Gitlow, MD, MPH, MBA

Former President of the ASAM Board of Directors
Testimony to the Senate Committee on the Judiciary
July 13, 2016

Species

Cannabis sativa

→

Grows 12 – 24 feet
Taller, narrow leaf

Content
CBD > THC
THC < 1%

Cannabis indica

←

Grows up to 6 feet
Shorter, broad leaf

Content
THC > CBD
THC upwards of 20%

Cannabis ruderalis

Thick & sturdy / only 1.5 -2 ft tall / flowers after 21-30 days / harvest ready 70-110 days from seed / Low THC

indica

sativa

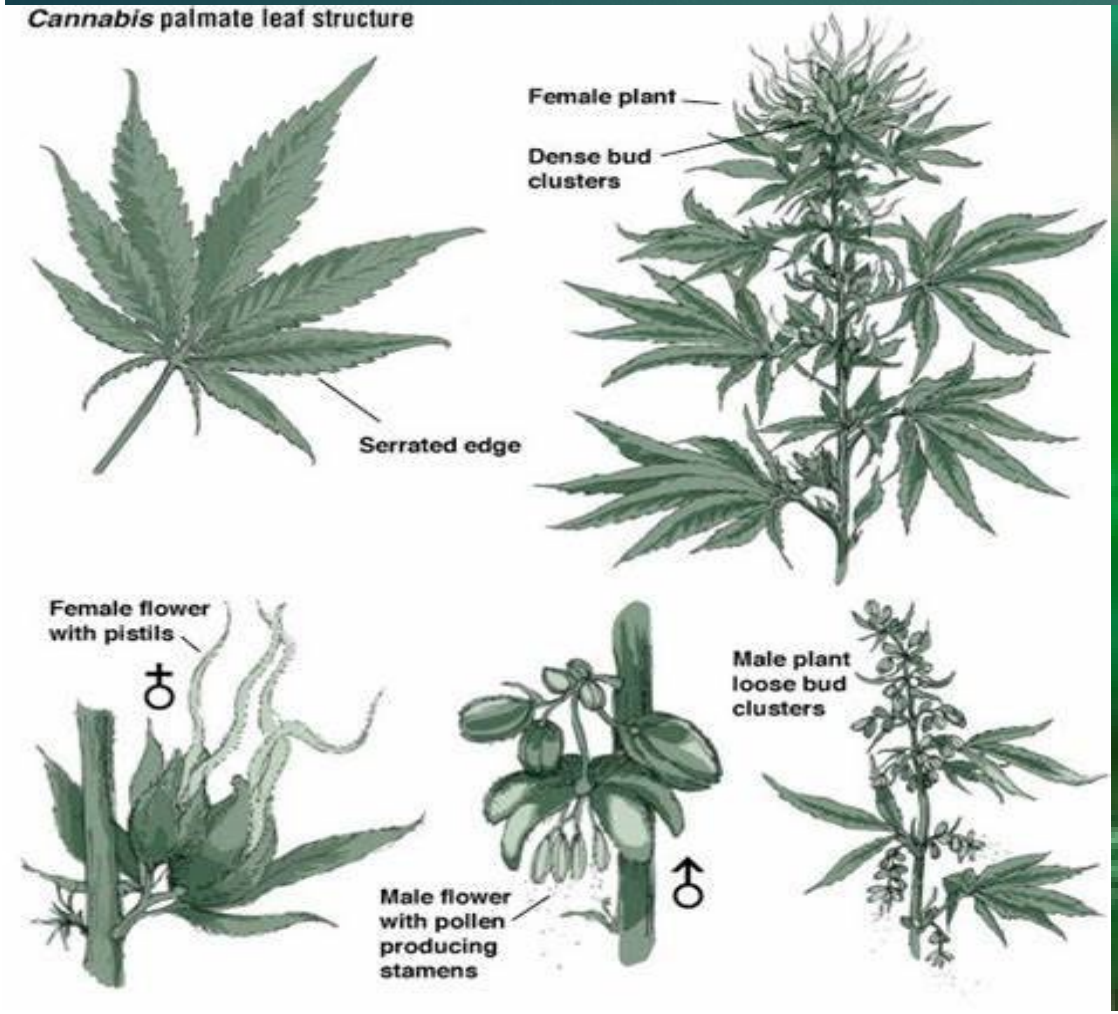
ruderalis

sativa

indica

ruderalis

Cannabis Celibacy



What's up, Bud ?

GLANDULAR TRICHOMES ON BUD

Plant Parts . . . .

THC (dry weight) concentrations

- **Fan Leaves** → 1 - 3 % THC
  Mature leaves → ↓↓ CBDs
- **Trim** → 2 – 6 % THC
- **Bud** → 5 – 20 % THC
- **Stems / Woody Parts** of Plant → Ø THC
- **Flower & Small Leaves** → 10 – 15 % THC
- Glandular **Trichomes** → ↑↑↑ THC

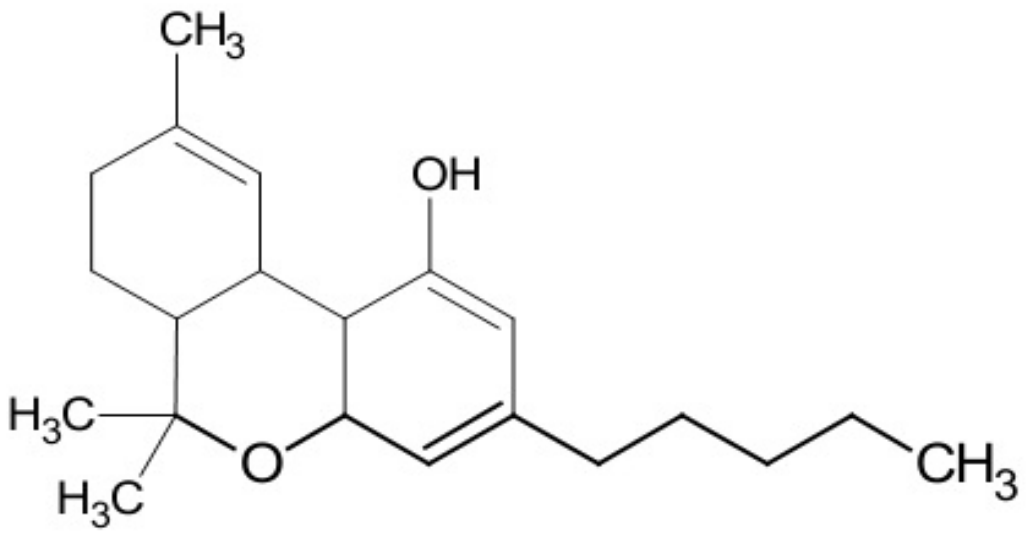
Cool, Dry Air most ideal for preservation of chemicals
Heat / Air **(Oxidation)** promotes degradation !!!

[↑ Temp / ↑ Light]

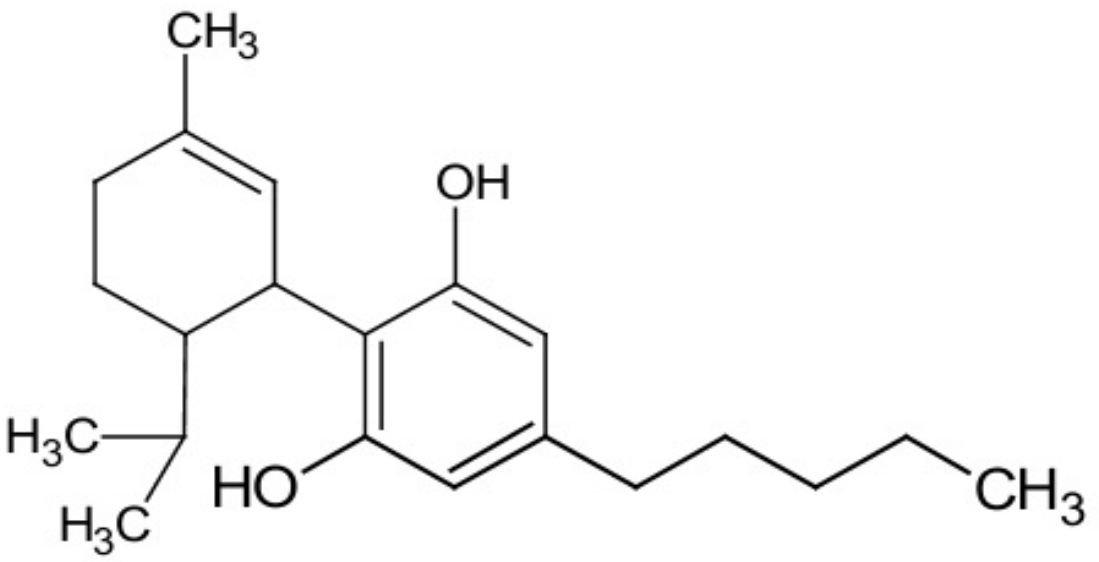
THCA → CONVERSION → THC

CBDA → [↑ TIME] → CBD

THCA (non-psychoactive)



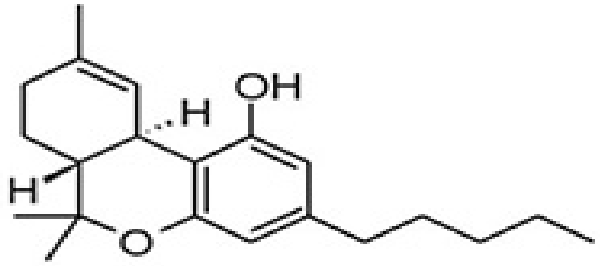
Tetrahydrocannabinol (THC)



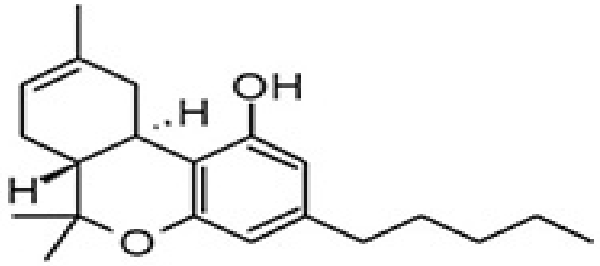
Cannabidiol (CBD)

Cannabinoid Chemistry

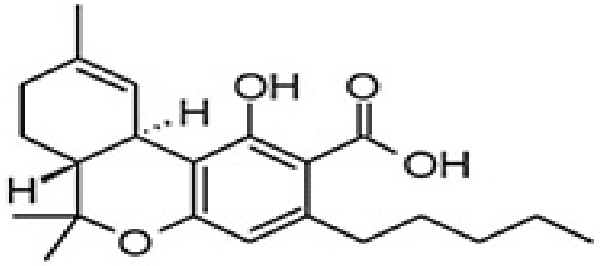
Cannabis Alkaloids



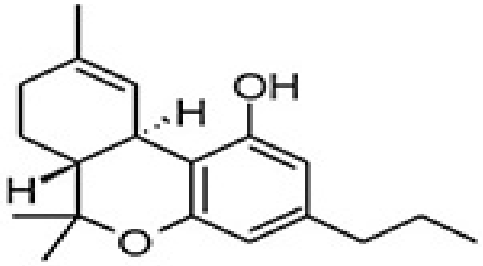
Δ9-Tetrahydrocannabinol
(Δ9-THC)



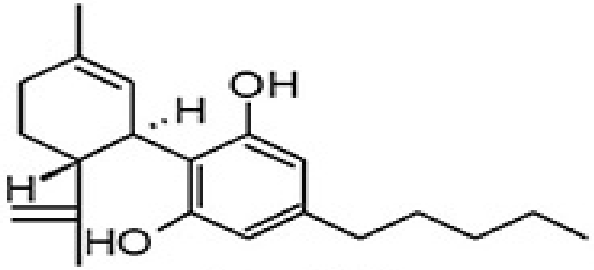
Δ8-Tetrahydrocannabinol
(Δ8-THC)



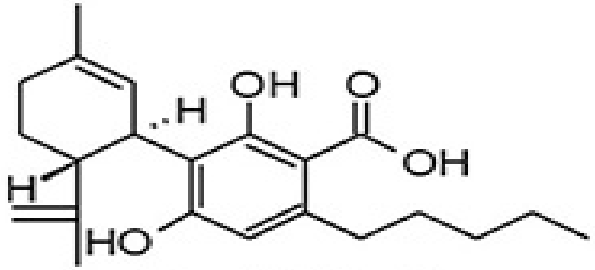
Δ9-Tetrahydrocannabinolic acid
(THCA)



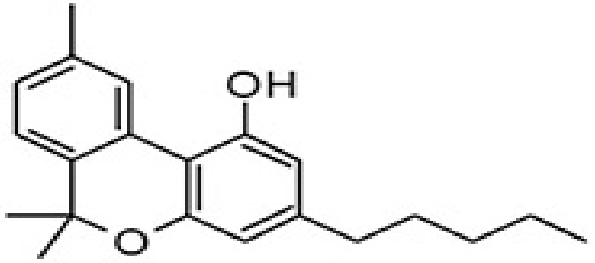
Tetrahydrocannabivarin
(THCV)



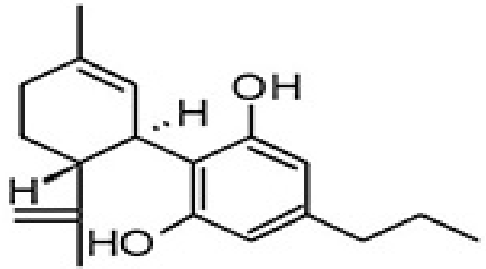
Cannabidiol
(CBD)



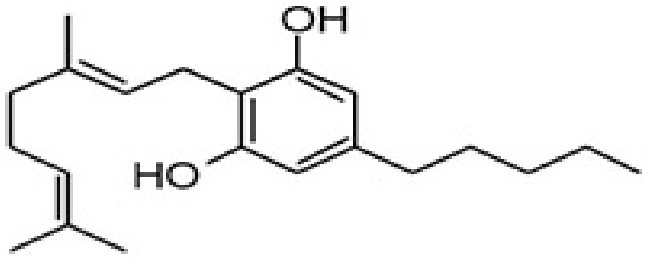
Cannabidiolic acid
(CBDA)



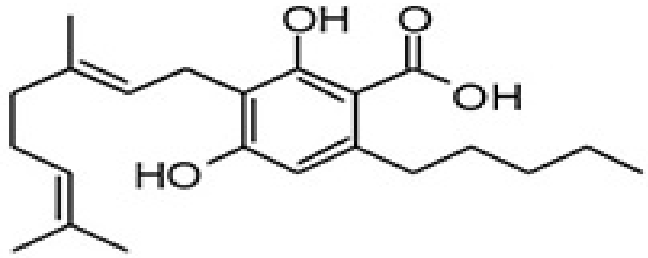
Cannabinol
(CBN)



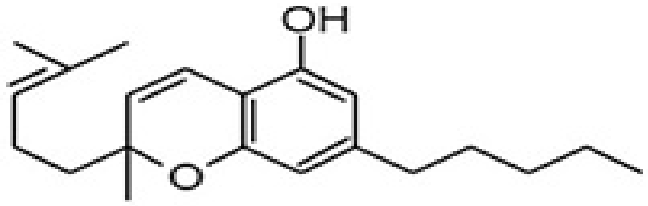
Cannabidivarin
(CBDV)



Cannabigerol
(CBG)



Cannabigerolic acid
(CBGA)



Cannabichromene
(CBC)

Constituents *(Phyto-chemicals)*

- **500+ different chemicals**

80-100 Cannabinoids

5 categories: THC (circa 1964) CBD(circa 1940) CBG, CBC, CBN

140 Terpenoids

ex: Myrcene, Limonene, Beta-caryophyllene, Linalool, Ocimene, Terpinolene …

23 Flavonoids

33 Fatty Acids

Linoleic 60%, Linolenic 25%, Oleic 15%

Numerous Carbohydrates

Mono-, Di-, & Polysaccharides, Sugar alcohols, Cyclitols, Amino Sugars

Cannabinoids

D9-THC (Delta-9 Tetrahydrocannabinol)
D8-THC (Delta-8 Tetrahydrocannabinol)
THCA (Tetrahydrocannabinol – Acid)
THCV (Tetrahydrocannabivarin)
THCVA (Tetrahydrocannabivarin – Acid)

CBD (Cannabidiol)
CBDA (Cannabidiol - Acid)
CBDV (Cannabidivarin)
CBDVA (Cannabidivarin - Acid)

CBC (Cannabichromene)

CBG (Cannabigerol)
CBGA (Cannabigerol – Acid)
CBGV (Cannabigerovarin)

CBN (Cannabinol)
CBNV (Cannabinovarin

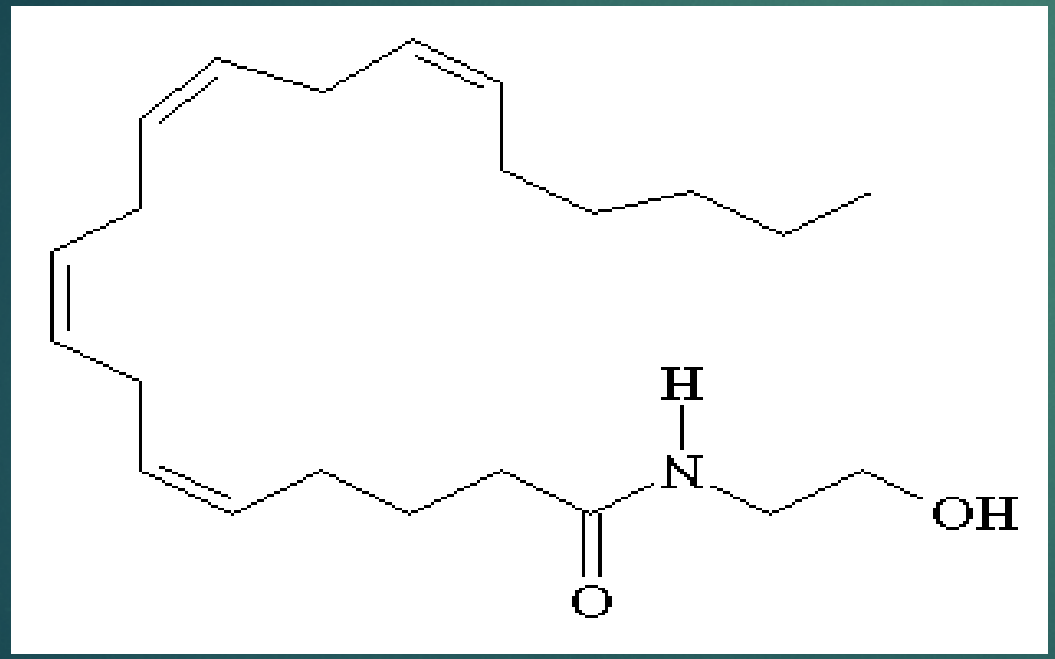
ENDOCANNABINOID SYSTEM

ENDOGENOUS (EICOSANOID) CANNABINOIDS

Identified 1980s

CB1 & CB2 receptors

Anandamide (arachidonylethanolamide)



CB1 receptors: Central Nervous System, WBCs & Testes

CB2 receptors: Peripheral Tissues
Skin, Bone Marrow, Immune System (Interleukins), Spleen, WBCs
RBCs, & Tonsils

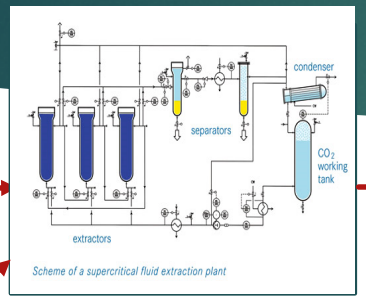
ANANDAMIDE - Arachidonic acid derivative

2-ARACHIDONOYLGLYCEROL (2-AG) → CB1

ENTITY	RECEPTOR INTERACTION	PHARMACOLOGIC EFFECT	QUALIFICATION
THC	CB1 / CB2 PARTIAL **AGONIST** (weak affinity)	ANALGESIA PSYCH (CB2) BRONCHODILATOR APPETITE STIMULANT ANTIEMETIC	NEUROPATHIC > SOMATIC THC 10MG ≈ CODEINE 60MG*
CBD	CB1 / CB2 **ANTAGONIST** (high affinity)	ANTIEPILEPTIC ANXIOLYTIC	DECREASES SEIZURE FREQUENCY / INTENSITY
THCV	CB2 PARTIAL AGONIST CB1 ANTAGONIST (↓ CONCS) CB1 AGONIST (↑ CONCS)	ANTI-NOCICEPTION	
Rimonabant	CB1 ANTAGONIST	ANTI-DOPAMINERGIC	REDUCES REWARD EFFECT OF COCAINE
HU-210	Synthetic CB1 / CB2 Agonist		
UR 144	Synthetic CB1 / CB2 Agonist CB2 > CB1 Affinity		

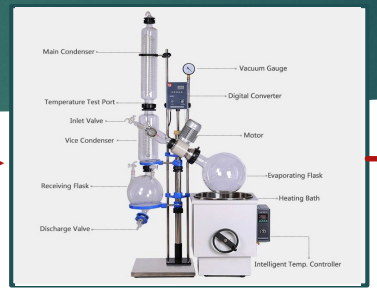
FARM TO PHARMACEUTICAL

HARVEST



SUPERCRITICAL CO2 EXTRACTOR

WINTERIZATION & SEPARATION
Refrigerate x 48 hrs



SHORT PATH DISTILLATION / CONDENSATION

Purified CO_2 Oil

DRY ICE KEIF

BUTANE / PROPANE EXTRACTOR

OVEN SOLVENT EVAPORATION
100°C - 125°C for 60 mins

SHATTER

HEAT CONVERSION (OIL)

INJECTION INTO VAPE CARTRIDGE

FROZEN DRY STORAGE

VAPE OIL FROM KEIF
5gm KEIF + 20mL Polyethylene Glycol + 20mL Vegetable Glycerin
HEAT to dissolution
Evaporate solvent to concentrate Oil

NOTES:
Vaping Solution: (Inhalation) Chronic Pain, Spinal Cord Injury, Multiple Sclerosis, ALS, PTSD, Glaucoma, HIV

(BHO→Wax→Budder→Honeycomb→ Shatter)

↑ing Appeal

*** Crude Inconsistent Dosage Forms**

Med MJ Dosage Forms

- LEAF (whole plant parts)
- PILLs & CAPSULEs
- TINCTURE
  (plant parts steeped in 5-20% ethanol or glycerin)
- AEROSOL (oral, buccal, inhalation)
- TOPICALs (Creams, Ointments, Transdermal)
- EDIBLEs (foods, candies, liquids, etc.)
- "DABBABLEs" [wax, shatter, rosin, crumbles, etc. (smoke via glass pipette)]
- VAPE OIL (elaborate electronic device)

Low-dose vaporized cannabis significantly improves neuropathic pain

J Pain 2013 Feb;14(2):136-48

- 39 cannabis-naive subjects w/ central & neuropathic pain

  R, DB, PLAC, Crossover design

- **Inhalation: Low (1.29% THC) or Med (3.53% THC) vs PLAC**
  - Volcano® Vaporization (0.8g cannabis above NaCL soln) collected into bag w/ mouthpiece
  - Visual Analog Scale to measure pain intensity / Neuropsych & performance tests
  - Assessments @ baseline and hourly x 6 hrs

Results:

No difference between two active treatment groups

NNT was approx. 3 (subjects) to **achieve 30% pain reduction**

Cannabis produced a general cognitive decline on all tests over time

Greatest effect on learning and memory tests – those effects sizes considered small to moderate

Cannabis in Orthopedics

Systematic Review:

33 ortho studies (**21 primary trials** / 12 reviews)

21 trials (6 controlled / 15 lacked control group)

- Wide variation in study design across trials

Trials **w/o control** group supported cannabis while those **w/ control** achieved mixed results

Trials supporting cannabis **employed higher doses** which also **increased side effects**

Madden K, et al. Cannabis for pain in orthopedics: a systematic review focusing on methodology Can J Surg 2019;62: (6):369-80

Cannabis as Analgesic: Key Points

- Cannabinoids are both centrally-acting **and** peripheral acting analgesics
- Thought to effect arachidonic acid pathway &/or CB-1 receptor stimulation

Anti-inflammatory effect ≈ NSAIDs but less potent THCA / CBGA / CBDA inhibit COX-1 & THCA / CBGA / CBG inhibit COX-2

- ***Pain studies have focused on THC / CBD combinations. Human data on CBD (alone) lacking***
- ***Modest, at best results in acute pain*** *Cannabis Cannabinoid Res 2020 Dec 15;5(4):290-7*
- ***Appears most beneficial for certain states of chronic pain (neuropathy & some cancer pain studies)***
- ***Cannabis not recommended as first line Rx by any guideline***
- ***Synergy with opiates***
- ***Does not cause respiratory depression***
- ***Does not impair gut motility***
- ***THC = Narrow Therapeutic Concentration Range***

Martin-Sanchez E, et al Pain Med 2009 & Lynch ME, et al. Br J Clin Pharmacol 2011

Systematic reviews of Cannabis in analgesia

NEUROPATHIC PAIN ☺

- "short term and intermediate term therapy with cannabinoids can be considered in select patients with chronic neuropathic pain after failure of 1st line or 2nd line therapies"
- "Inhaled cannabis appears to provide short term relief for approx. 1 in 6 subjects (> 30% reduction)"

CANCER PAIN ☹

- "due to sparse amount of data, not possible to support cannabis products for cancer pain"

RHEUMATOLOGIC PAIN ☹

- "recommend against use of medical cannabis in pain associated with rheumatologic conditions (including OA and Low Back) owing to lack of evidence and known harms"

Medical cannabis for treatment of chronic pain: CADTH July 2019:1-43

In combination w/ Opiates . . .

- Cannabis "***augments analgesic effect of opiates***"

  Clin Pharmacol Ther 2011;90:844-51

- Cannabis can ***re-potentiate opiate analgesia***

  Reducing need for dose escalation Life Science 2004;74-1317-24

- **Naloxone** (opiate antagonist) **blocks** . . .

  Cannabinoid-mediated reward (rat data)

  Analgesic enhancement effect of cannabinoid (Δ-9 THC) on opiate analgesia

  J Pharmacol Exp Thera 2003;304:1010-15

Customize therapy w/ THC . . .

NARROW THERAPEUTIC CONCENTRATION RANGE

- Therapeutic window demonstrated in human trials

  Wallace M et al. Anesthesiology. 2007;107:785-796

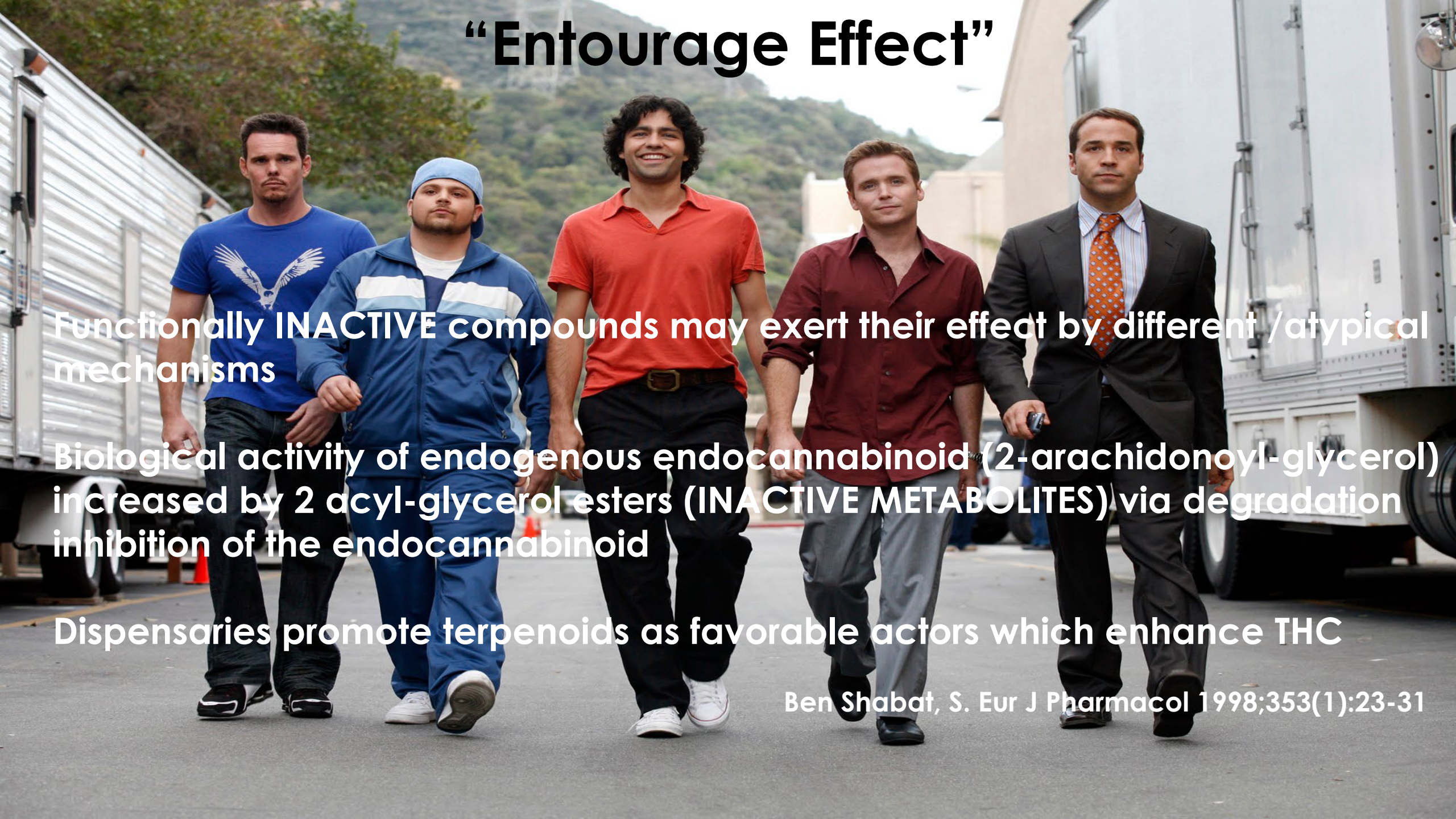
- Low doses →[pleasure]
- High doses →[aversion]

  Braida D et al. *Neuroscience*. 2001;104:923-926

- THC plasma concs **5 - 15 ng/mL** therapeutic for analgesia

  Dissipates at > 15 ng/mL

“Entourage Effect”



Functionally INACTIVE compounds may exert their effect by different /atypical mechanisms

Biological activity of endogenous endocannabinoid (2-arachidonoyl-glycerol) increased by 2 acyl-glycerol esters (INACTIVE METABOLITES) via degradation inhibition of the endocannabinoid

Dispensaries promote terpenoids as favorable actors which enhance THC

Ben Shabat, S. Eur J Pharmacol 1998;353(1):23-31

Surgical Considerations around Cannabis use

Summary:

Cannabis use within 72 hours of general anesthesia is not advisable

Has caused airway obstruction & need for ↑ anesthetic dosages to place laryngeal airways

- Use ↑ cardiac workload / ↑ myocardial oxygen demand
- Has caused strokes & MI in young chronic users

Use causes pulmonary complications similar to that of a tobacco smoker

- Case report of severe laryngospasm following extubation

Contradictory reports of both anti-thrombotic (↓PLT activation / aggregation) and pro-thrombotic effects exist

Hudson HB et al. Heliyon 2018:4:1-19

Major Peri-operative Findings in Cannabis Users

New Users

- Tachycardia and systolic hypertension (within 2 hours from consumption)
- Malignant arrythmias (Vfib, Vtach, Brugada pattern, Afib)
- Coronary spasm in pre-existing CADz
- Airway Hyperreactivity or Uvulitis

Chronic Users

- Bradycardia → Tachycardia
- Postural / Orthostatic Hypotension
- Sinus arrest
- Hyperreactive airway
- Intraoperative hypothermia
- Coronary vasospasm / myocardial infarction

Echeverria-Villalobos M et al. J Clin Anesthesia 2019;57:41-49

CBD and Anxiety / PTSD

BACKGROUND

- *Cannabis folklore suggests cannabis functions therapeutically as an anxiolytic*
- Use of **whole plant (smoked)** appears to have **no benefit for PTSD or can even *worsen* PTSD** and/or anxiety
- Rodent data supports anxiolytic effect but suggests value lies with the CBD component and not THC

RETROSPECTIVE CHART AUDIT

11 adult psychiatric patients who experimented with oral CBD administration over 8 weeks.

All subjects followed by mental health professional and used CBD in conjunction with routine psych care and current psych medications

Ten of 11 patients experienced a reduction in PTSD symptom severity as measured by a 20-question survey (PCL-5).

PCL-5 score decreased average of 28% over the 8-week period. No subject discontinued treatment during the study period.

Elms L, et al. Cannabidiol in the treatment of Post Traumatic Stress Disorder: A case series 2019;25(4):392-397

CBD (alone) may prove to be useful in scenarios of Anxiety or PTSD **(might be beneficial ☺)**

CBD "expectancy" encourages sedating effects Psychopharmacology 2021;238:1965-77

CBD and other mental illnesses

Systematic Review of Applications in Psych D/O

Khan et al. **J Cannabis Research** 2020:2:2:1-21

- Level 2 evidence from 8 RCTs of 23 total studies reviewed
- Level 3 evidence in 5 open-label / clinical trials
- Level 4 evidence in case reports and case series

CBD & Nabiximols (antipsychotic, neuroprotective, anxiolytic and sedating properties)

- Higher CBD doses (> 1200 mg / daily) may be effective for schizophrenia & Parkinson's psychosis

  ** Not valuable in treatment resistant psychosis / Benefits occur via amelioration of "positive" symptoms

- **Nabiximols may be effective in reducing tics relating to Tourette's syndrome**

No credible evidence for use in ADHD ☹

Sarris et al. BMC Psychiatry 2020;20(24)1-14

Lowe et al Eur Arch Psychiatry Clin Neurosci 2019;269:1:107-120

EFFECTS ON SLEEP

BACKGROUND

- ***CB1 receptors*** in pons and basal forebrain may be involved in sleep induction
- ***Serotoninergic*** transmission in the dorsal raphe nucleus involved in the modulation of the sleep-wake cycle

SHORT TERM administration **(may be beneficial)**☺

- Improved sleep consolidation, decreased time to sleep onset, increased total sleep time

LONG TERM administration **(detrimental)**☹

- Decreased slow wave sleep, increased sleep disruption, reduced total sleep time

- **CBD (alone) may be preferable in scenarios of underlying Anxiety-induced Insomnia**
- Cannabis withdrawal syndrome (CWS) often characterized by insomnia / sleep disturbances

Neurotherapeutics 2021;18:217-27

Dementia (?)

Systematic review of 12 trials

- 4 of 12 studies found treatment of patients with dementia using medial cannabis resulted in improvements in a range of neuropsychiatric behaviors associated with dementia

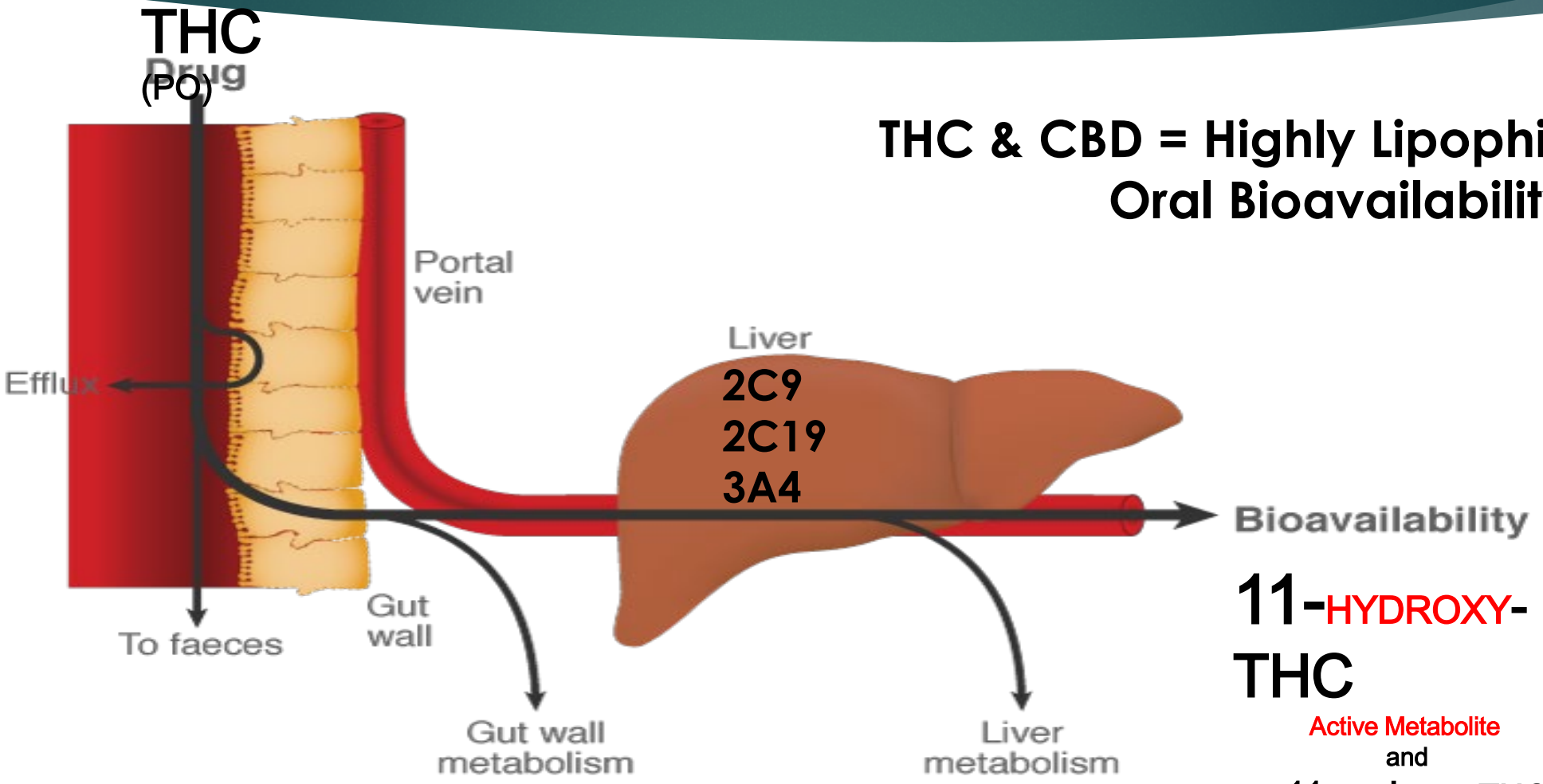
CADTH 2019; July:1-24

***Pilot study using oil (THC 7.6 mg /CBD 13.2 mg) in chocolate cake* (N = 11)**

- Upwards titration over 2 months to 9 mg THC / 18 mg CBD
- **May be effective for treating behaviors associated with dementia** (ie; agitation, disinhibition, irritability, aberrant vocalization, aberrant motor behavior, nocturnal behavior disorder)
- Limited improvement in rigidity and cognition via MMSE
- **Provided for the reduction or cessation of other psychotropic meds in 50% of subjects**

Broers B et al. Med Cannabis Cannabinoids 2019;2(1):56-9

Extensive First Pass Hepatic Metabolism



THC & CBD = Highly Lipophilic
Oral Bioavailability ≈ 6%

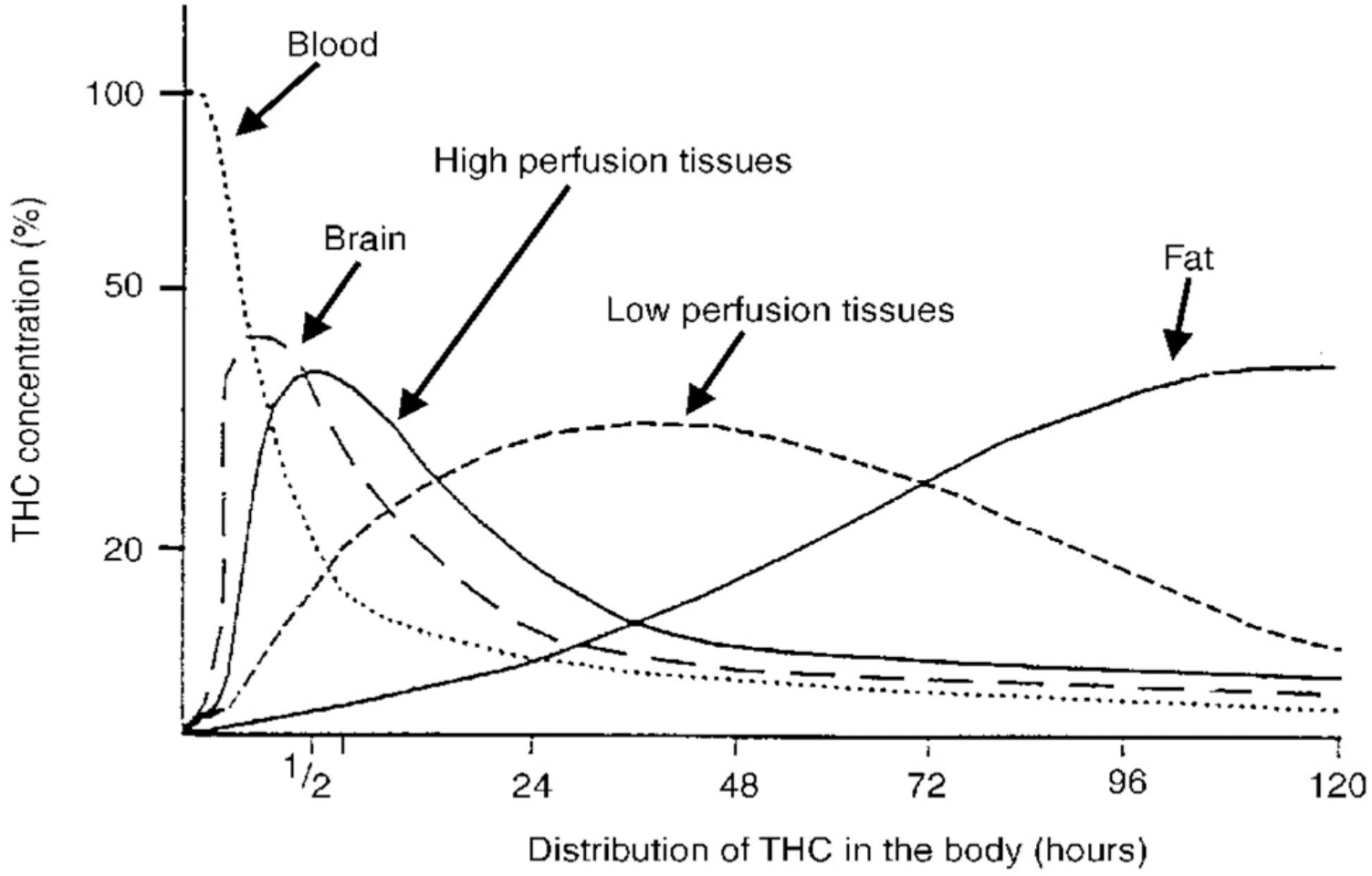
11-HYDROXY-THC

Active Metabolite

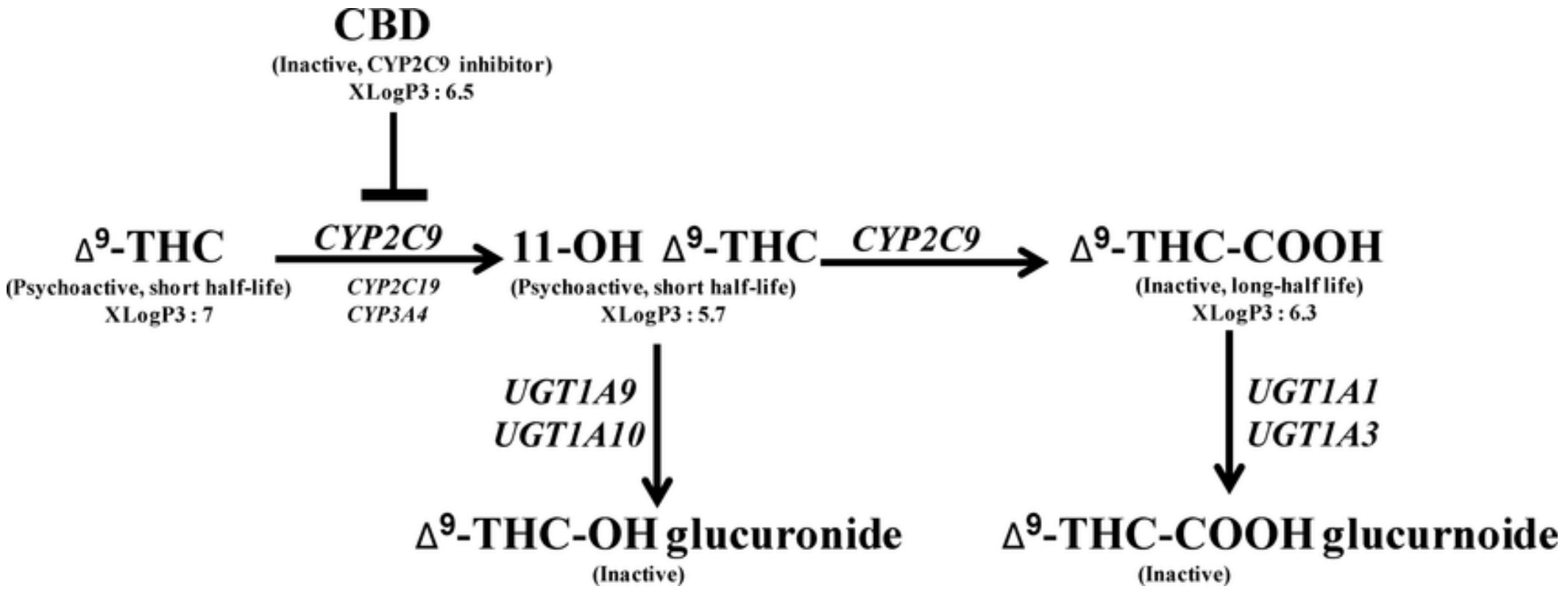
and

11-carboxy-THC

Distribution Kinetics of THC



Nahas, G. G. (1975) Marijuana: toxicity and tolerance. In Medical Aspects of Drug Abuse (ed. Richter, R. W.), pp. 16–36. Baltimore, MD: Harper & Row.


CBD
(Inactive, CYP2C9 inhibitor)
XLogP3 : 6.5
Δ9-THC
(Psychoactive, short half-life)
XLogP3 : 7
CYP2C9
CYP2C19
CYP3A4
11-OH Δ9-THC
(Psychoactive, short half-life)
XLogP3 : 5.7
CYP2C9
Δ9-THC-COOH
(Inactive, long-half life)
XLogP3 : 6.3
UGT1A9
UGT1A10
UGT1A1
UGT1A3
Δ9-THC-OH glucuronide
(Inactive)
Δ9-THC-COOH glucurnoide
(Inactive)

Marinol® (Dronabinol)

Synthesized Δ-9 Tetrahydrocannabinol

- **Pharmacokinetics:** 2.5mg, 5mg & 10mg capsules
  - 90-95 % absorption PO – Effect Onset 0.5 – 2hrs

    (20-45 % absorption INHALED – max CNS concs @ 15mins)

    High first pass metabolism → 10-20% reaches systemic circulation
  - Large Vd – approx. 10 L/kg (highly lipophilic)

    97% protein binding – approx. 3 % free concs

    Cross placenta / penetrates breast milk
  - Hepatic (Hydroxylation) Metabolism
    - $T½_{\alpha}$ = 4 hrs $T½_{\beta}$ = 25-36 hrs
    - **Highly active / psychoactive metabolite (11-OH-Δ-9 THC) and inactive metabolites**
  - Elimination
    - Fecal-Biliary & Renal excretion of metabolites
    - < 5 % unchanged THC in feces

BID (PO)	Cmax ng/mL (SD)
2.5mg	1.32 (0.62)
5mg	2.96 (1.81)
10mg	7.88 (4.54)

THC (Marinol®) Side Effects

Adverse Reactions

- Dose-related "High" (easy laughing, elation, and heightened awareness)
- **CNS effects (33%)**

  ADRs > 1% (≈ 3-10%)

  - Palpitations, **tachycardia**, vasodilation/facial flushing, **headache**
  - Abdominal pain, **nausea, vomiting**, **dry mouth**, **diarrhea**
  - Amnesia, anxiety, nervousness, ataxia, **confusion**, depersonalization, **dizziness**, euphoria, hallucinations, psychosis, paranoid reaction, **somnolence**, sedation, abnormal thinking, cognitive impairment, dysphoria, depression, **insomnia**
  - **Asthenia**, Increased risk of falls (Sativex® for Spasticity), **lightheadedness**
  - Increase in appetite **AND** decrease in Appetite

THC (Marinol®) Side Effects

Adverse Reactions

ADRs < 1%

- Hypotension, myalgias, conjunctivitis, fecal incontinence, depression, nightmares, speech impairment, **tinnitus**, **blurred vision**
- ADRs <<<1% Chills, **headache**, malaise, **anorexia**, elevated LFTs, cough, rhinitis, sinusitis, **sweating**
- **Sudden Death, Arrhythmia, ↑ risk MI / CVA**

Cannabidiol Oil (CBD 100mg/mL)

Hx: (Charlotte's Web)

R, PC, Compassionate Use Trial (n = 171)

Add on Rx: EPIDIOLEX 20 mg/kg/day vs PLAC

Endpt: ↓ Median SZR Frequency ≥ 50%
(44% Rx vs 22% PLAC, P < 0.005)

Effect maintained thru 12, 24 & 48 weeks

ADRs (86% experienced mild-moderate ADR)
diarrhea, somnolence, pyrexia, decreased appetite, and vomiting

CBD inhibits Clobazam & Valproic Acid metabolism – dose reductions warranted

Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomized, double-blind placebo-controlled phase 3 trial. Published online January 24, 2018 http://dx.doi.org/10.1016/S0140-6736(18)30136-3.

JUNE 2018

FDA approves Epidiolex®

for Lennox-Gastaut & Dravet Syndrome

Re-Scheduled 9/2018 CS - V

CBD Side effects

Adverse Reactions

in ANIMALS (at higher doses weight to weight basis, than humans)

- Developmental toxicity, embryo-fetal mortality, CNS inhibition & neurotoxicity, hepatocellular damage, decreased spermatogenesis, organ weight alterations, male reproductive system alterations and hypotension

in HUMANS

- Hepatic abnormalities, insomnia, gait disturbance, diarrhea, infections (pneumonia), decreased appetite, weight loss, fatigue, lethargy, vomiting, suicidal thoughts & behaviors, sedation and somnolence

Huestis MA et al. Cannabidiol adverse effects and toxicity Current Neuropharmacol 2019;17:974-89

Brown JD & Winterstein AG. Potential ADRs and DDIs with CBD. J Clin Med 2019;8:989:1-14

Sophisticated . . . Pharmaceuticals

SATIVEX® (nabiximols)

- ≈ Equal ratio CBD / THC
- Available in 15 countries including UK
- Standardized Cannabis extract
- 2.5mg CBD & 2.7mg THC per mL
- Oral Spray

- Indicated for

  MS- Induced spasticity

  NDA - Phase III Trials in US for CA pain

MARINOL® (dronabinol)

- Δ -9 THC only
- Synthesized - not extraction
- Schedule III CS – US generic
- 2.5, 5 & 10mg capsules
- Indications

  CINV
  AIDS-associated Cachexia

- #60 5mg caps = $ 3300.00

(www.goodrx.com)

Pharmacogenomics

Incidence of CYP_{450} Metabolizers in the US

CYP2C9

- Poor Metabolizers (PM) – 3.4% of US population
- Intermediate Metabolizers (IM) – 28.2% of US population

CYP 2C19

- Poor Metabolizers (PM) – 2.3% of US population
- Intermediate Metabolizers (IM) – 25.4% of US population
- Rapid Metabolizers (RM) – 24.2% of US population
- Ultra Rapid Metabolizers (UM) – 3.5% of US population

CYP3A4

- Intermediate Metabolizers (IM) – 5.3% of Caucasians

Drugs Affected by CYP_{450} 2C9 Genetic Variation

CYP 2C9

Cardiology

- Warfarin (Coumadin®)
- Carvedilol (Coreg®)

Miscellaneous

- Phenytoin (Dilantin®) – seizures
- Ibuprofen (e.g. Motrin®) – pain relief
- Celecoxib (Celebrex®) – pain relief for arthritis
- Indomethacin (Indocin®) – pain relief
- Meloxicam (Mobic®) – pain relief for osteo- and rheumatoid arthritis
- Glyburide (Micronase®) – diabetes
- Glipizide (Glucotrol®) – diabetes
- Glimepride (Amaryl®) – diabetes

Drugs Affected by CYP_{450} 2C19 Genetic Variation

CYP 2C19

Anti-depressants

- Amitriptyline
- Doxepin (Silenor®)
- Imipramine
- Citalopram (Celexa®)
- Escitalopram (Lexapro®)
- Fluoxetine (Prozac®)
- Sertraline (Zoloft®)

Cardiology

- Clopidogrel (Plavix®)

Miscellaneous

- Clobazam (Onfi®) – certain types of seizures
- Diazepam (Valium®) – anxiety
- Carisoprodol (Soma®) – muscle relaxant
- Voriconazole (Vfend®) – anti-fungal
- Omerprazole (Prilosec®) – gastric reflux/ulcers
- Esomeprazole (Nexium®) – gastric reflux/ulcers
- Lansoprazole (Prevacid®) – gastric reflux/ulcers

Drugs Affected by CYP$_{450}$ 3A4 Genetic Variation

CYP 3A4

Anti-psychotics

- Aripiprazole (Abilify®)
- Quetiapine (Seroquel®)
- Risperidone (Risperidal®)

Cardiology

- Atorvastatin (Lipitor®)
- Lovastatin (Mevacor®)
- Simvastatin (Zocor®)
- Amiodarone (Cordarone®)
- Quinidine

Opioids

- Buprenorphine (e.g. Buprenex®)
- Fentanyl (Duragesic®)
- Oxycodone (Oxycontin®, Percocet®)

Miscellaneous

- Cyclosporine (Neoral®) – transplant anti-rejection medication
- Tacrolimus (Prograf®) – transplant anti-rejection medication
- Sirolimus (Rapamune®) – transplant anti-rejection medication
- Eszopiclone (Lunesta®) – sleep
- Trazodone (Oleptro®) – sedative and anti-depressant
- Alprazolam (Xanax®) – anxiety
- Buspirone (Buspar®) – anxiety
- Clonazepam (Klonopin®) – seizures, panic disorders, anxiety
- Saxagliptin (Onglyza®) - diabetes

Cannabis Drug Interactions

Concurrent Drug	Clinical Effect
Amphetamines, cocaine & other sympathomimetics	Additive hypertension, tachycardia, possible cardiotoxicity
Atropine, scopolamine, antihistamines & other anticholinergics	Additive or super-additive tachycardia, drowsiness
Amitriptyline, amoxapine, desipramine & other tricyclic antidepressants	Additive hypertension, tachycardia, drowsiness
Barbiturates, benzodiazepines, ethanol, lithium, opioids, buspirone, antihistamines, muscle relaxants, & other **CNS depressants**	Additive drowsiness and CNS depression
Barbiturates, rifampin & other **CYP 2C9, 2C19 & 3A4 inducers** (ie; carbamazepine, phenytoin, rifabutin, SJWort, primidone) **Clobazam**	Ex: Rifampin ↓ THC & CBD concs by 40% & 20%, respectively **(drug induces metabolism of cannabinoids)** **↑ Clobazam concs from CYP 2C19 inhibition via CBD**
Disulfiram **(CYP 2C9 inhibitor)**	Reversible hypomanic Rxn in 28 yo man, confirmed by dechallenge & rechallenge
Fluoxetine **(CYP 2C9 inhibitor)**	21 yo female w/ depression & bulimia receiving 20mg/day fluoxetine x 4wks became hypomanic after smoking marijuana; symptoms resolved after 4 days
Warfarin **(3A4 substrate) – (THC / CBD = 3A4 inhibitors)**	4 Case reports of stable INR increased to supratherapeutic INRs during cannabis smoking
Voriconazole / ketoconazole (Azole antifungals) & other **CYP 2C9, 2C19 & 3A4** inhibitors (numerous)	Decreased hepatic clearance of THC or CBD via competitive inhibition of metabolism when CYP 450 enzyme pathway is shared. Drug with greater affinity for enzymes dominates and will be preferentially metabolized.
Theophylline & other **CYP 1A2** substrates (ie; caffeine, clozapine, duloxetine, estradiol, flutamide, fluvoxamine, frovatriptan, lidocaine, mexiletine, mirtazapine, olanzapine, propranolol, ramelteon, melatonin, ropinirole, tizanidine, rasagiline, triamterene, zolmitriptan)	Increased theophylline metabolism reported with smoking marijuana – similar to smoking tobacco **(regular smoking induces CYP1A2 enzyme)**

Pharmacologic Tolerance

Known to develop with Cannabinoids

Likely associated with a change in expression of CB1 receptors

Down-regulation of CB1 receptors (THC = weak CB1 agonist)

THC: Physiologic & Subjective tolerance develops with repeated exposure to CB-1 agonist (Benowitz & Jones 1981)

Evidence suggests a **down-regulation** of CB receptors occurs at least within the CNS = *Physiologic "Adaptation"*

Up-regulation of CB1 receptors (CBD = CB1 antagonist)

CBD: CB-1 antagonist "blocking" effects dissipate with chronic, repeated administrations (up-regulation ?)

"Phenomenon can be reversed within 30 days of abstinence"

Cannabis Withdrawal Syndrome (CWS)

Criterion in Diagnostic and Statistical Manual of Mental Disorders 5th ed. of Cannabis Use Disorders

- Mood and behavioral symptoms of light to moderate intensity

CRAVING (Cannabis), IRRITABILITY, ANXIETY, AGGRESSION, RESTLESSNESS, ANGER, SLEEP DIFFICULTY, STRANGE DREAMS, DEPRESSION, ↓ APPETITE, SWEATING, TREMORS, HEADACHES, STOMACH PAINS, NAUSEA

Women > Men (nausea and stomach pain)

- 61-96% report using cannabis to alleviate CWS during abstinence

Mirtazapine possibly useful / Venlafaxine worsens

Gabapentin and ∆-9 THC analogues (?) promising

Substance Abuse and Rehabilitation 2017;8:9-37

Marijuana-induced Psychiatric Illness

- Evidence suggests **primarily THC** **(not CBD)** consumption leads to **earlier diagnosis** of psychosis / schizophrenia in genetically-susceptible / at risk individuals

  (some data suggests CBD treats positive symptoms of schizophrenia)

THC use also exacerbates existing psychosis symptoms, causes relapses and hospitalizations

Dose correlates with risk

- Psychosis risk increases 4-fold in heavy users and 2-fold in average users versus non-users
- Daily use high potency THC increases risk of psychosis by as much as 5-fold

Studies support a genetic predisposition to schizophrenia

2020 Patel et al. Cureus 12(7): e9309. DOI 10.7759/cureus.9309

Cannabis Smoking & CVDz

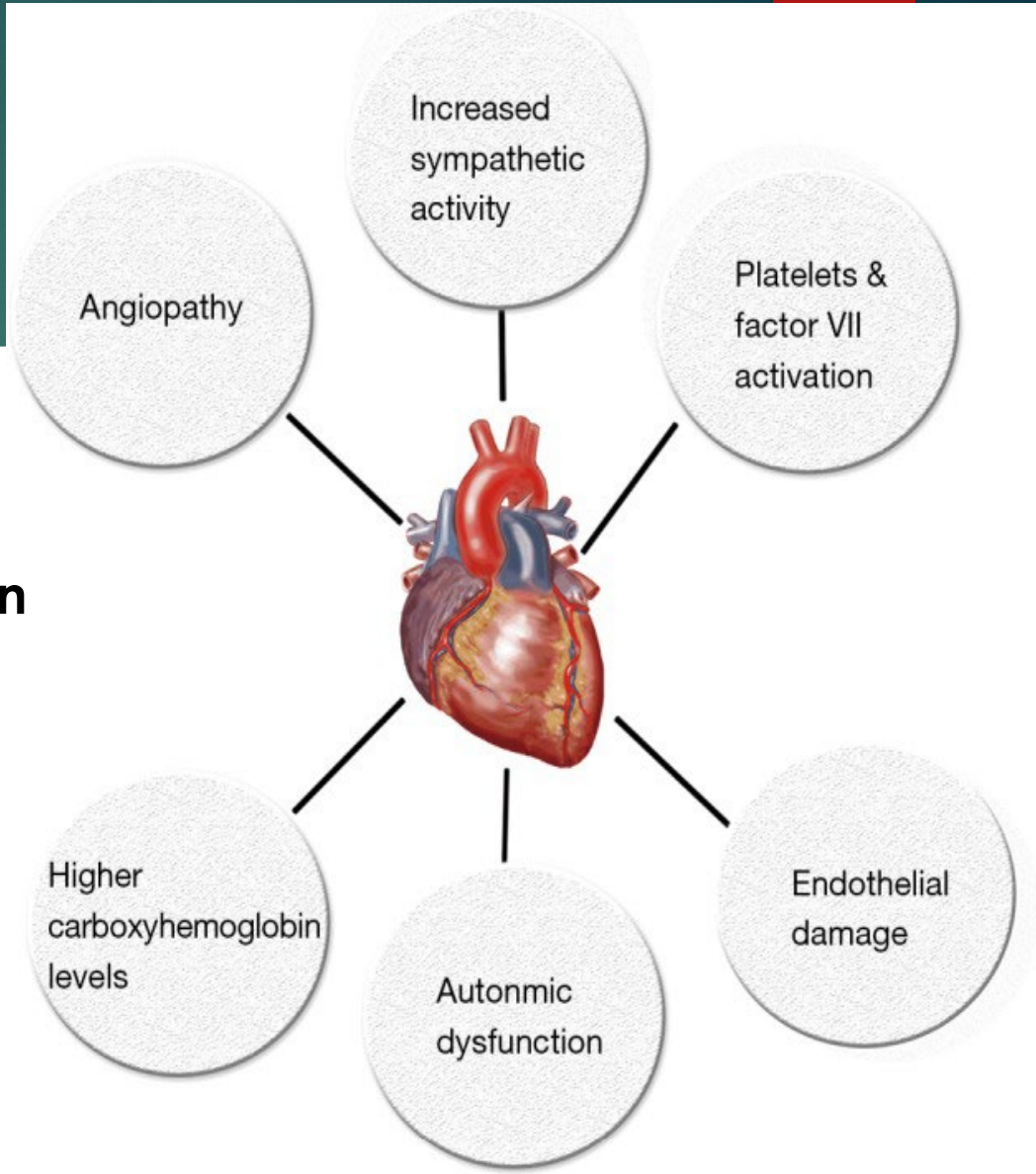
Case Reports:

Sudden Death, Arrhythmia (VT) ↑ risk MI / Stroke
Myopericarditis w/ low positive troponins
↑ Blood Pressure & Tachycardia & Ortho Hypotension

Hypotensive effects (CBD) in states of stress

Exacerbated by . . .

Physical Exertion / Stress
Cigarette Smoking
During 1st few hours



J Thorac Dis 2017 Jul; 9(7):2079-92 & Int J Mol Sci 2020;21:6740:1-49

Discourage Use in Adolescents

- **Hangover Effect**
  - Potentially detrimental neurocognitive effects lasting **24 hours post consumption**

    Some data suggests effects persist for 30 days
- **Detrimental Neurocognitive effects (adolescents)** ☹
  - Decline in IQ and higher risk of mental illnesses seen with regular cannabis use in adolescents
  - Heavy adolescent cannabis use is associated with poorer educational outcomes and increased depression

    Curr Addict Rep 2019;6(4):532-46
  - Adolescent smokers less likely to finish high school than peers ($P < 0.001$)

    - More likely to develop dependence, use other drugs or attempt suicide
  - Structural & functional changes seen in adult "heavy users" may be related to consumption at an early age
  - "Cannabis abuse accelerates brain aging by 2.8 yrs . . . every brain area suffers reduced blood flow"

    J Alzheimers Dis 2018(65):4:1087-92
  - 2x ↑ risk of FATAL motor vehicle accidents in adolescents under influence of Cannabis

    (although adolescents at ↑ risk MVA regardless)

    J Dev Behav Pediatric 2015;32(2)115-23

Cannabis Use Disorder (CUD) DSM-5

- THC – responsible for abuse related properties of Cannabis
  - Indirectly influences dopaminergic activity in midbrain
  - CB1 agonism mediates "high" associated with cannabis (effects curtailed by Rimonabant CB1 blocker)

- **Progression to CUD seen 1 in 10 of "regular" users and 1 in 3 of daily users**

- USA: CUD (average) use 6.2 out of every 10 days over a year

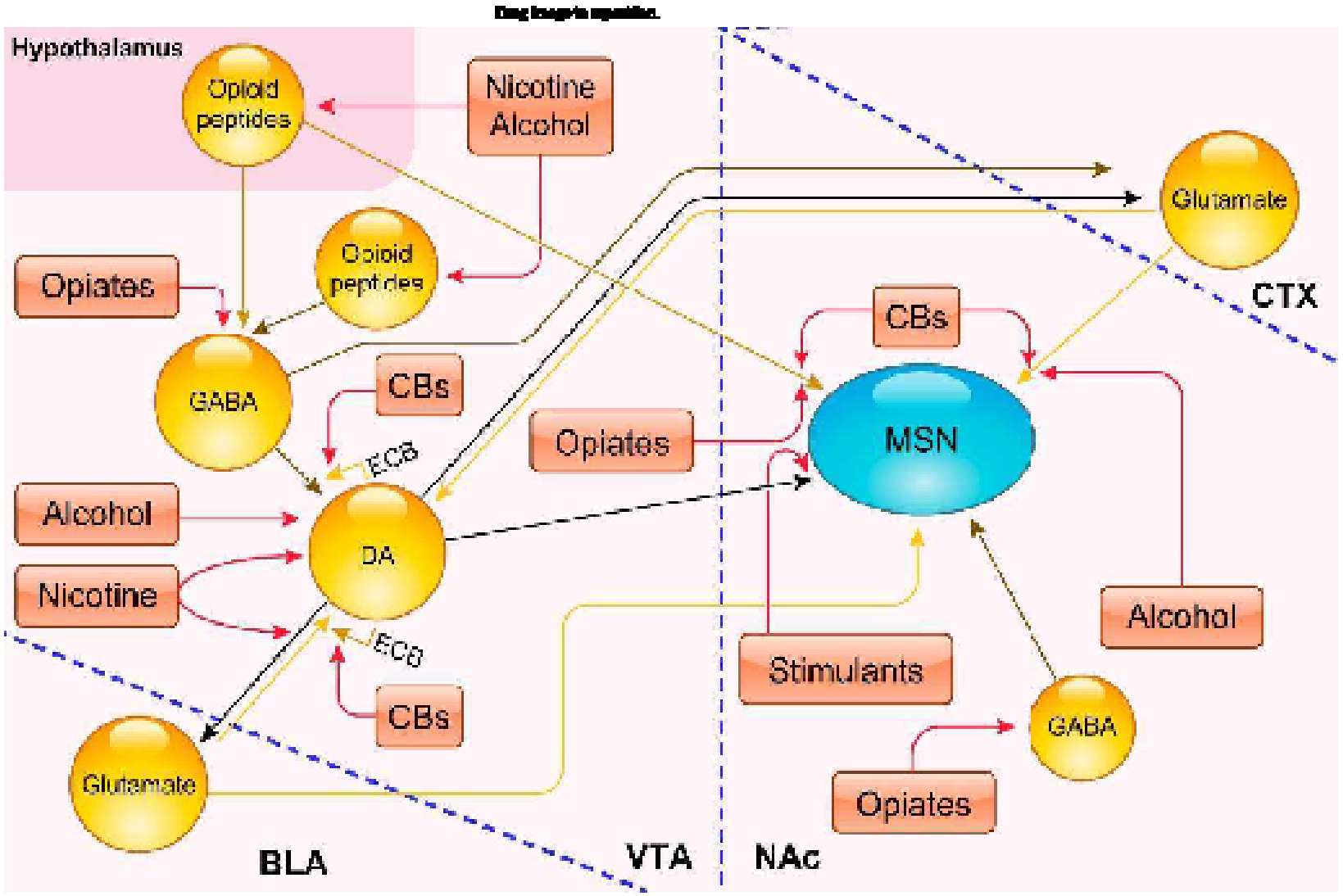
  6x more likely to have ETOH disorder

  9x more likely to have other drug disorder

Neuroimaging Studies

Pharmacology and Therapeutics 2019:195:132-161

- **Alters brain structure**
  - Chronic THC administration (or CB1 agonists) down regulates dopamine receptors in limbic system & neocortex (post-mortem)
  - Chronic users exhibit significantly smaller volumes in the hippocampus, orbitofrontal cortex and lateral cortex
  - Anatomical changes appear more modest and less than those created by alcoholism
- **Disrupts emotional processes**
  - Behavioral impairments in recognition of facial affect
  - Decreases in blood oxygen level dependent response in cingulate, frontal cortex and amygdala during negative emotional stimuli
- **Impairs executive function**
  - Reductions in prefrontal cortex function and blood flow
  - Negative effects across learning and memory including impaired recall
- **Subverts reward function** (reduced motivation / apathy) Psychopharmacology 2014;231(11):2251-59
  - **Chronic cannabis users may have a lower capacity to synthesize dopamine**
  - PET studies evaluate dopamine synthesis capacity in 14 “regular users”
  - **Inverse correlation of dopamine synthesis versus apathy (all subjects) regardless of criteria abuse/dependence**
  - In contrast, another study found hypersensitivity to monetary reward
  - **“At least partial support for link between cannabis use and decreased motivation”** Psychol Addict Behav 2018;32(5):497-507



NAc = nucleus accumbens, CTX = prefrontal cortex, BLA = basolateral amygdala, VTA = ventral tegmental area, MSN = Medium spiny neurons

Volkow ND, Michaelides MM, Baler R Neuroscience of drug reward and addiction Physiol Rev 2019;99:2115-2140

ACUTE Cannabinoid CATATONIA

- **Accidental ingestion of large doses of Cannabis ?**

  22 Cookies (≈ 1300 mg THC) led to 10 hour period of catatonia (eyes open, non-responsive to pain)

  Vitals stable throughout and slowly returned to normal over several hours

- Symptoms: from severe immobility to psychomotor agitation (malignant catatonia)
- Most often: decreased motor activity, unresponsiveness & posturing
- Often associated with other psychiatric, neurological and medical diagnoses
- Med-Psych emergency: severe rigidity, autonomic nervous system instability, altered mental status can be fatal

- Rx: Benzodiazepines (esp. lorazepam)
- Rx: Electroconvulsive therapy (if BZD refractive)

Mekala H, Malik Z, Lone J, et al. (June 13, 2020) Cannabis-Induced Catatonia: A Case Series. Cureus 12(6): e8603. DOI 10.7759/cureus.8603

Cannabis Hyperemesis Syndrome

Previously rare, now in as many as 1/3 of chronic heavy cannabis consumers

Theorized to involve Endocannabinoid receptors in GI tract

Frequent cyclic bouts of acute nausea, vomiting and moderate to severe abdominal cramping

"SCROMITING" – screaming while vomiting

Universally relieved by Hot Shower or Bath (Heat activates Vanilloid receptors → Substance P)

CHS **refractive to typical antiemetics** - ondansetron, promethazine, prochlorperazine, etc.

- IM Haloperidol or IM Olanzapine – DOC / also benzodiazepines, ondansetron, metoclopramide

Abstinence is longest lasting treatment

Cannabis effects on male virility

Background

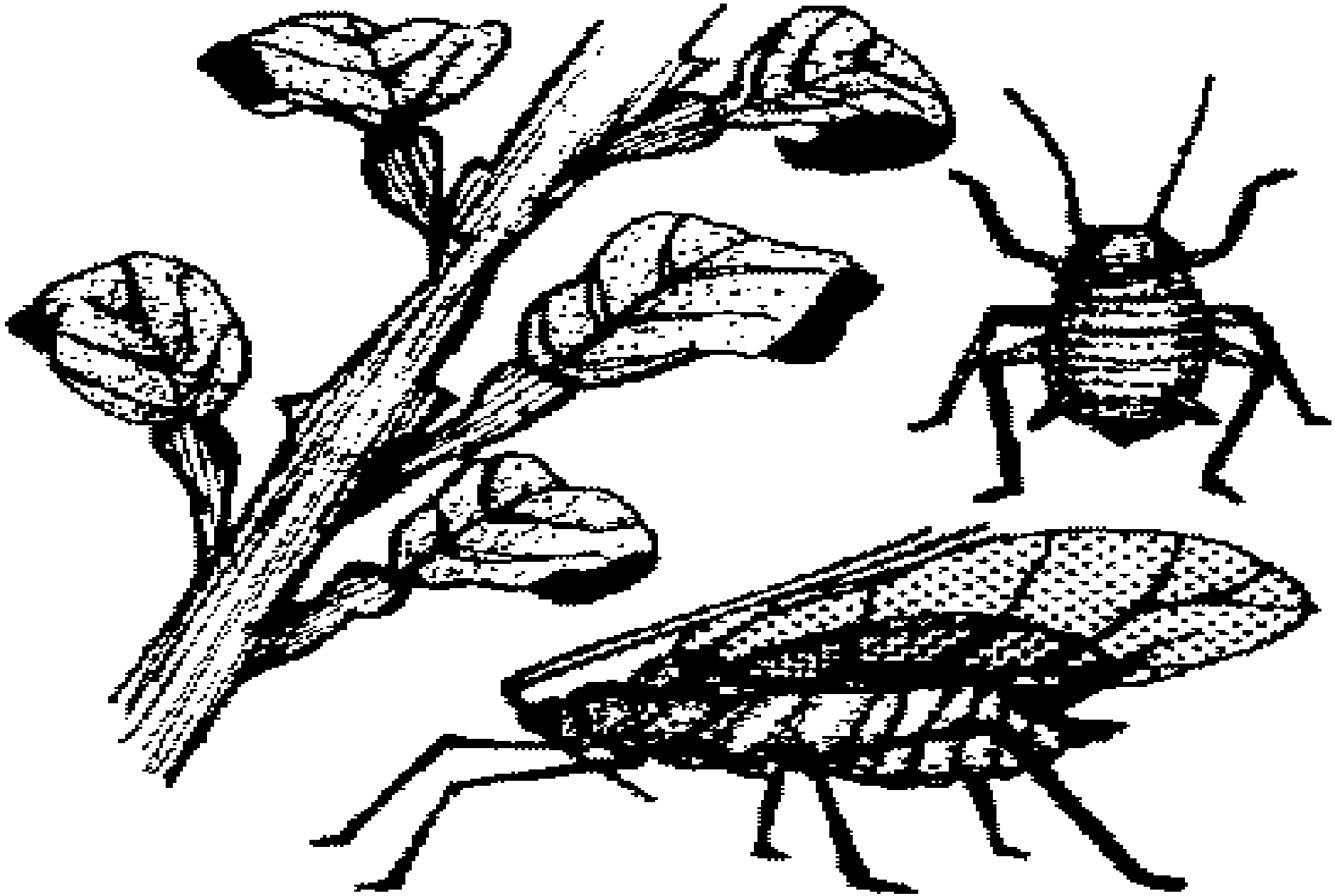
Alcohol, opiates and anabolic steroids reduce testosterone production in males

Nicotine & amphetamines alter spermatogenesis inducing oxidative stress & apoptosis in testicular tissue

Evidence appears also to be negative for cannabis . . .

- Evidence associates cannabis use with **lower sperm concentrations**
- Data suggests ≈ 4x ↑ risk of ED in cannabis users vs controls ≈ 70% of cannabis users (N =1035)

AM J Mens Health 2019;13;6;1-7



Potential Problems with Plant-based Medicines

- **Adulteration** (Intentional & Unintentional)
- **Contamination** (Herbicide residue / Pesticide residue)
- **Extracts have many active components**
- **Inadequate / Unknown stability**
- **Mislabeling**
- Misidentification of plant
- Selection of wrong part of plant

Edibles

- Cannabis / Δ9 - THC available as edibles (brownies, cookies, gummies, drinks, etc)
- **THC potency range (1-90%)**
- Case Series: Pediatric patients more severe symptoms & longer hospital stays. Majority presented with leukocytosis and elevated lactic acid levels
- Efforts should increase awareness in regard to potential hazards of "edibles" resembling commercially available foods
- Ann Emerg Med. 2018 Mar;71(3):306-313. doi: 10.1016/j.annemergmed.2017.09.008. Epub 2017 Nov 3

Vaping

www.cdc.gov/lunginjury

As of February 18, 2020, **2807 hospitalized** e-cigarette or vaping, product use associated lung injury reported by all 50 states

Among 2022 hospitalized patients with information on substances used in e-cigarette, or vaping, products

- **82%** reported using **THC-containing products**, with or without nicotine-containing products
  - 16% acquired products only from dispensaries or smoke shops
  - 78% acquired products only from friends & family, dealers, on-line or other sources
  - 6 % acquired products from both
- **33%** reported exclusive use of **THC-containing products**
- 57% reported using nicotine-containing products
- 14% reported exclusive use of nicotine-containing products

** Vitamin E acetate **
may interfere with normal lung fxn when inhaled

68 deaths confirmed in 29 states and District of Columbia (Highest #s: TX & IL, then NY & CA)
Median age of patients who have died is 49.5 years (15 to 75)

https://www.cdc.gov/tobacco/basic _information/e-cigarettes/severe-lung-disease.html#latest-information

Delta (Δ)-8 THC = "LIGHT WEED / DIET WEED"

THC ≈ Δ-9 THC

Increasing reports of poisonings / intoxications (as per CDC Health Advisory: 9/14/2021)

Available at Vape Stores / On-line / Hemp Sales

(HEMP = any part of cannabis plant containing less than 0.3% THC)

Δ-8 THC usually only present in small quantities in plant

Not as well studied

50-75% as psychoactive as Δ-9 THC

≈ toxicity (lethargy, slurred speech, ↓BP, dyspnea, ↑HR↓, incoordination, sedation)

CDC Health Alert Network HAN Archive - 00451 | Health Alert Network (HAN) (cdc.gov)

Laboratory Testing (Pennsylvania)

www.health.pa.gov/topics/Documents/Programs/Medical%20Marijuana

- Cannabinoids which require quantitation
- Terpenes
- Pesticide residue analysis*
- Residual solvents (processed products which use organic solvents for extraction)
- Heavy metals
- Microbiological Testing
- Moisture content & water activity
- Stability testing (6 mo & 1 yr)

*** List of known pesticides**

Abamectin Cyfluthrin Hexythiazox Piperonyl Butoxide Acephate Cypermethrin Imazalil Prallethrin Acequinocyl Daminozide Imidacloprid Propiconazole Acetamiprid DDVP Kresoxim-methyl Propoxur Aldicarb Diazinon Malathion Pyridaben Azoxystrobin Dimethoate Metalaxyl Spinetoram Bifenazate Dimethomorph Methiocarb Spinosad Bifenthrin Ethoprophos Methomyl Spriromesifen Boscalid Etofenprox Methyl parathion Spirotetramat Carbaryl Etoxazole Mgk-264 Spiroxamine Carbofuran Fenhaxamid Myclobutanil Tebuconazole Captan Fenoxycarb Naled Thiacloprid Chlorantraniliprole Fenpyroximate Oxamyl Thiamethoxam Chlorfenapyr Fipronil Paclobutrazol Trifloxystrobin Chlorpyrifos Flonicamid Permethrins Clofentezine Fludioxonil Phosmet

Ethical Issues

- **Growers have artificially enhanced samples prior to testing**
- **Labs "incentivized" to report "better" numbers in areas of strong competition / low business**
- **Re-processing occurs when products don't meet standards**

PA State Dept Health Mandatory Recall

February 4 2022

HARRISBURG, Pa. — The Pennsylvania Department of Health announced Friday that it is **recalling** certain medical marijuana **vape products** that it says contain ingredients **not approved for inhalation** by the U.S. Food and Drug Administration.

The department said that while some of the added ingredients may be considered safe in other non-inhaled products, it is issuing the recall because "patient safety is the top priority of the Medical Marijuana Program."

The mandatory recall affects 600 vape products, including names like Curaleaf, Modern Flower, and Moxie Liquid Distillate.

Pa. Department of Health recalls 500 marijuana vape products | fox43.com

Common Sense Contraindications

CONTRAINDICATIONS

- Hx of Psychiatric Disorders (ie; depression, mania, schizophrenia, anxiety(?), panic attacks, personality disorders)
- Hx of Drug Abuse
- Adolescent age / Developing minds
- Pulmonary Disease
- Immunocompromised / At risk of malignancy (inhalation of carcinogens)
- Cardiovascular Disease
- Pregnant or Nursing
- Allergy to cannabis or components
- Walking into dispensary without a reasonable education on cannabis

Benefit vs Risk Evaluation

- Consider cannabis Rx only after a careful evaluation of individualized **benefit vs risk**
- Important to *attempt* to **separate facts from folklore** FYI: "The GNC store employees wear white coats, too !"
- **Insufficient evidence** to suggest Cannabinoids slow or halt progression of any disease

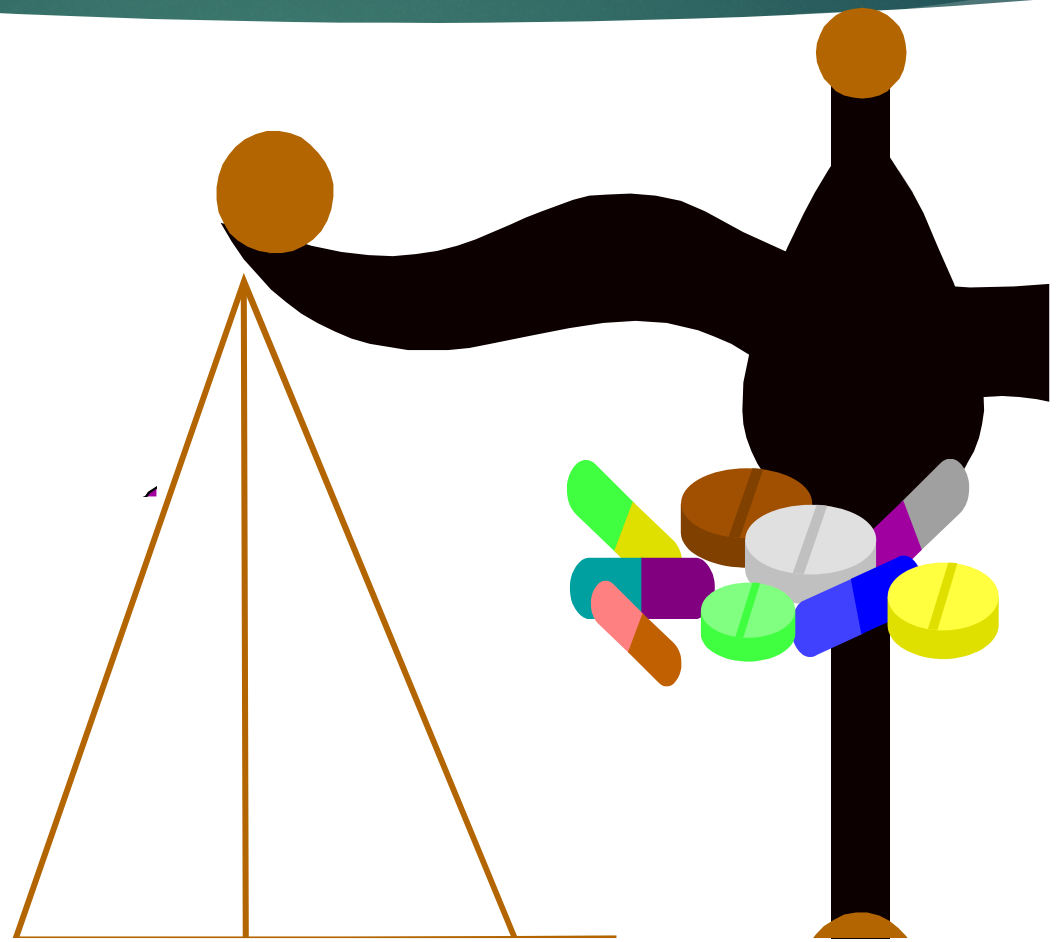
  Delay in time to implement proven strategies may be costly and potentially harmful
- **Consensus AND standardization lacking** on dose, dosage form, frequency, stability, efficacy, toxicity and monitoring . . . .
- Lack of GMPs – possible exposure to **unknown compounds & unnecessary contaminants**
- **Adverse Reactions may be insidious** and difficult to detect / recognize
- Cannabis - **drug Interactions primarily theoretical** w/ little practical experience in this realm
- Cannabis – disease **contraindications not well characterized / studied**
- Realize (often) **all data** points are **not known**

Help patients make Informed Decisions

- Familiarize yourself with Cannabis in particular disease state(s).
- Discuss body of evidence illuminating potential benefit vs risk scenario
- Mandate patient disclose ALL medications
- Reinforce “self-empowerment” towards health improvement
- Discuss REASONABLY ACHIEVABLE & MEASUREABLE GOALS with patient
- Explain how to self-monitor and what to do in emergency
- Align with dispensary that offers standardized, titratable dosage forms
- Assess clinical success, adverse effects, impact on quality of life
- Maintain appropriate documentation in patient’s medical record

QUESTIONS ?

C W Fetrow, PharmD
FetRx, LLC
fetrowcw@yahoo.com
561-601-4951



"All substances are poisons; there is none which is not a poison… the right dose differentiates a poison from a remedy."

PHILIPPUS AUREOLUS THEPHRASTUS BOMBASTUS VON HOHENHEIM-PARACELSUS

(PHYSICIAN-ALCHEMIST 1493-1541)