

Medical Marijuana: What We Know and Don't Know

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Disclosures

- National Institute on **Drug Abuse**- NIH: 30 yrs of support
- Scientific Advisory Board: *Center for Medical Cannabis Research*, UCSD, State of California
- Consultation / DSMB: Tilray, Inc., GW Pharmaceuticals

*Don't Currently Use Cannabis - THC or CBD:
recreationally or therapeutically*

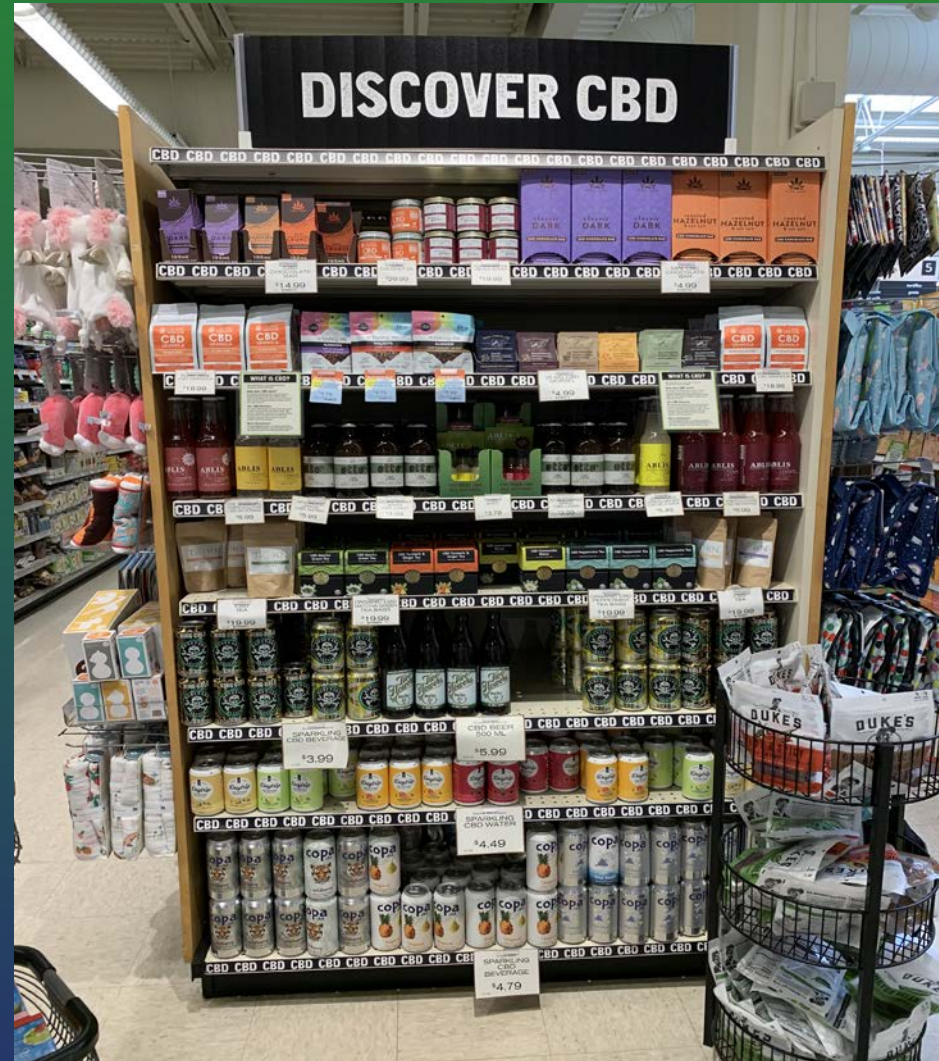
21st Century Reefer Madness

Legalization & New Products



21st Century Reefer Madness

Legalization & New Products



Aims for this Morning

1) Addictive Potential / Consequences of Cannabis Use

2) “Medical” Marijuana / Cannabis: Operationalize?

What are we talking about? Providers, Patients, Public

What are you approving (Providers)?

3) Data on Therapeutic Cannabis Products?

Scientific Literature, State Governments, Sales People?

4) Industry Impact? Koop Institute – Public Health Issues



- Drink Alcohol Regularly (one drink or more)
- Intoxicated (more than 4 drinks) past yr
- Why do you drink alcohol
- Use Marijuana/Cannabis (currently)
- Use Cannabis (past)
- Use CBD
- Think Alcohol Causes More Harm than Cannabis
- Why don't you currently use Cannabis

Addictive Potential of Cannabis

Cannabis (**thc-laden**) is more similar than dissimilar to other substances that are considered “substances of abuse”

Like other substances, cannabis is used primarily for its positive (and negative) reinforcing effects

A subset of those who use will develop problems (10-30%)

Problems will range from mild to severe

Hasin et al., (2016); Haney et al. (2009)

U.S. NSDUH Survey 2017

Prevalence of Cannabis Use Disorder (CUD)

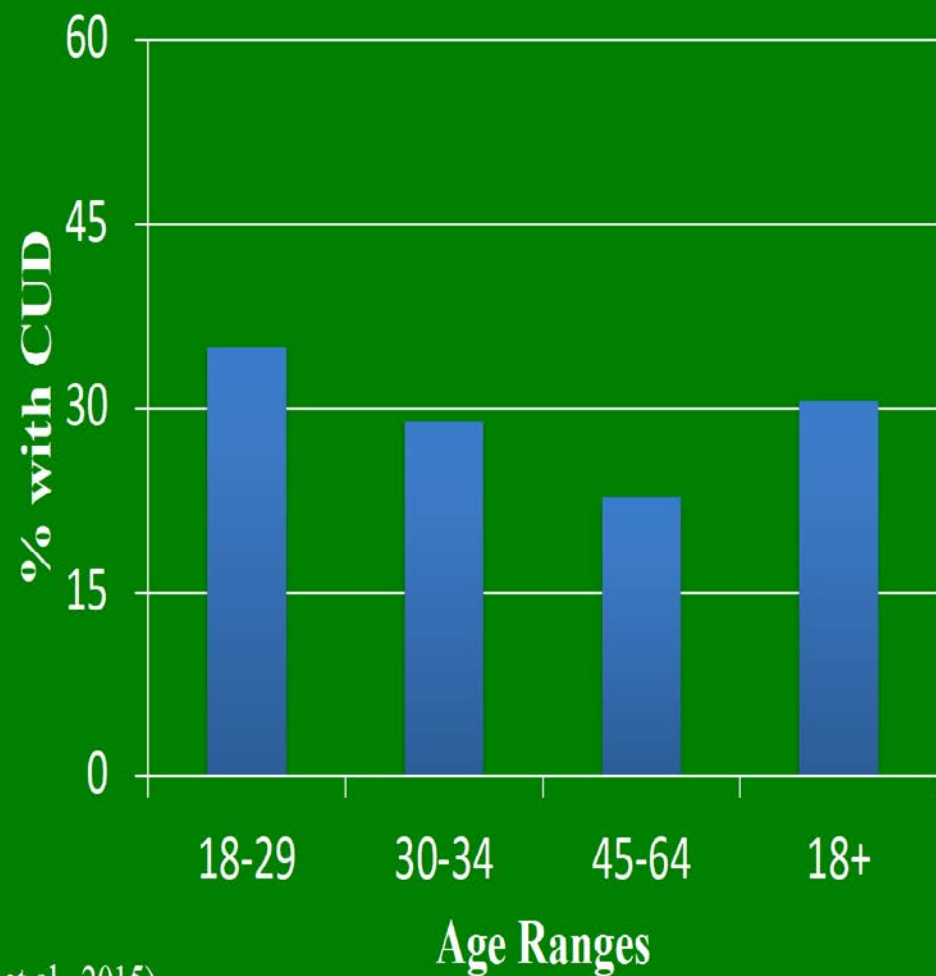
12 -17 years: 2.2%

18-25 years: 5.2%

26 + years: 0.8%

NESARC 2012

Conditional Probability of Past Year CUD



(Hasin et al., 2015)

NSDUH 2011

Conditional Probability of Past Year CUD



(Hasin et al., 2014)

Cannabis Use Disorder (CUD)

- *DSM-5: “Cannabis Use Disorder”*
 - *ICD 11: “Cannabis”*
 - *“Hazardous Use”*
 - *“Harmful Use” (single episode, episodic, continuous)*
 - *“Cannabis Dependence”*
 - *Cannabis Withdrawal Disorder*
- ** CUD manifests much the same as other types of Substance Use Disorders (Budney 2006, Shmulewitz, 2016)**

Substance (Cannabis) Use Disorder Criteria

Impaired Control

- (1) Longer / larger
- (2) Quit / Control
- (3) Time Spent
- (4) Craving

Social Impairment

- (5) Neglect roles, obligations
- (6) Continued use despite associated interpersonal problems
- (7) Reduced or Discontinued Activities

Substance (Cannabis) Use Disorder Criteria

Risky Use

(8) Use in Hazardous Situations

Physical/Psychological Consequences

(9) Continued use despite medical or psychological problems

Physiological/Pharmacological

(10) Withdrawal

(11) Tolerance

Cannabis Withdrawal?

Cannabis Withdrawal Syndrome (DSM-5)

3 or more within approximately 1 week:

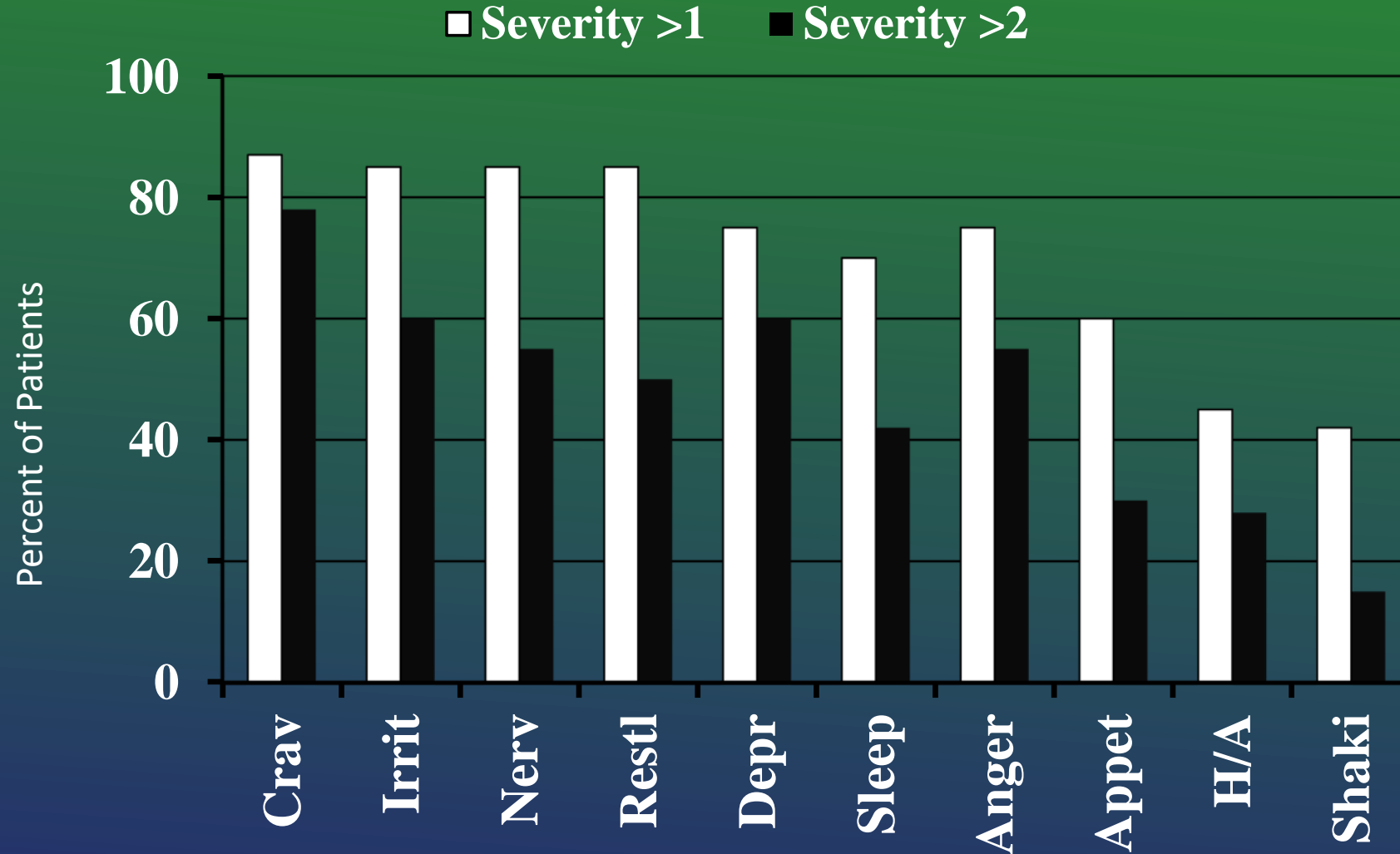
- Irritability, anger, or aggression
- Nervousness or anxiety
- Sleep difficulty (e.g. insomnia, disturbing dreams)
- Decreased appetite or weight loss
- Restlessness
- Depressed mood
- At least 1 of the following physical symptoms cause significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills or headache

Cannabis Withdrawal Syndrome

- Similar to other substance withdrawal syndromes
- Clinically important
- Only a subset experience withdrawal and there are substantial individual differences
- No **serious** medical or psychological symptoms

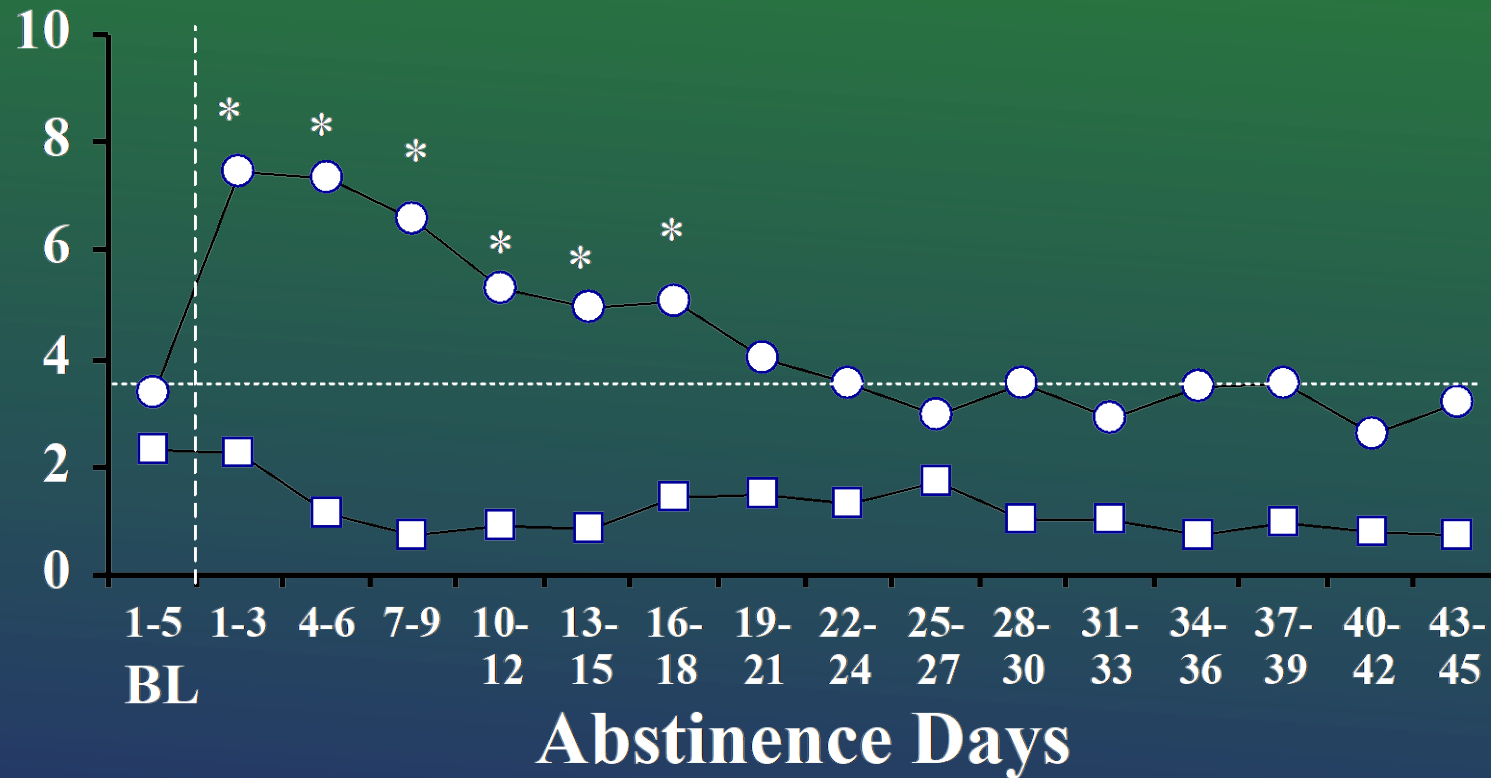
(Budney et al., 2004, 2006; APA, 2013)

Self-reported Withdrawal Symptoms in CUD Adult Outpatients (Budney et al., 1999)

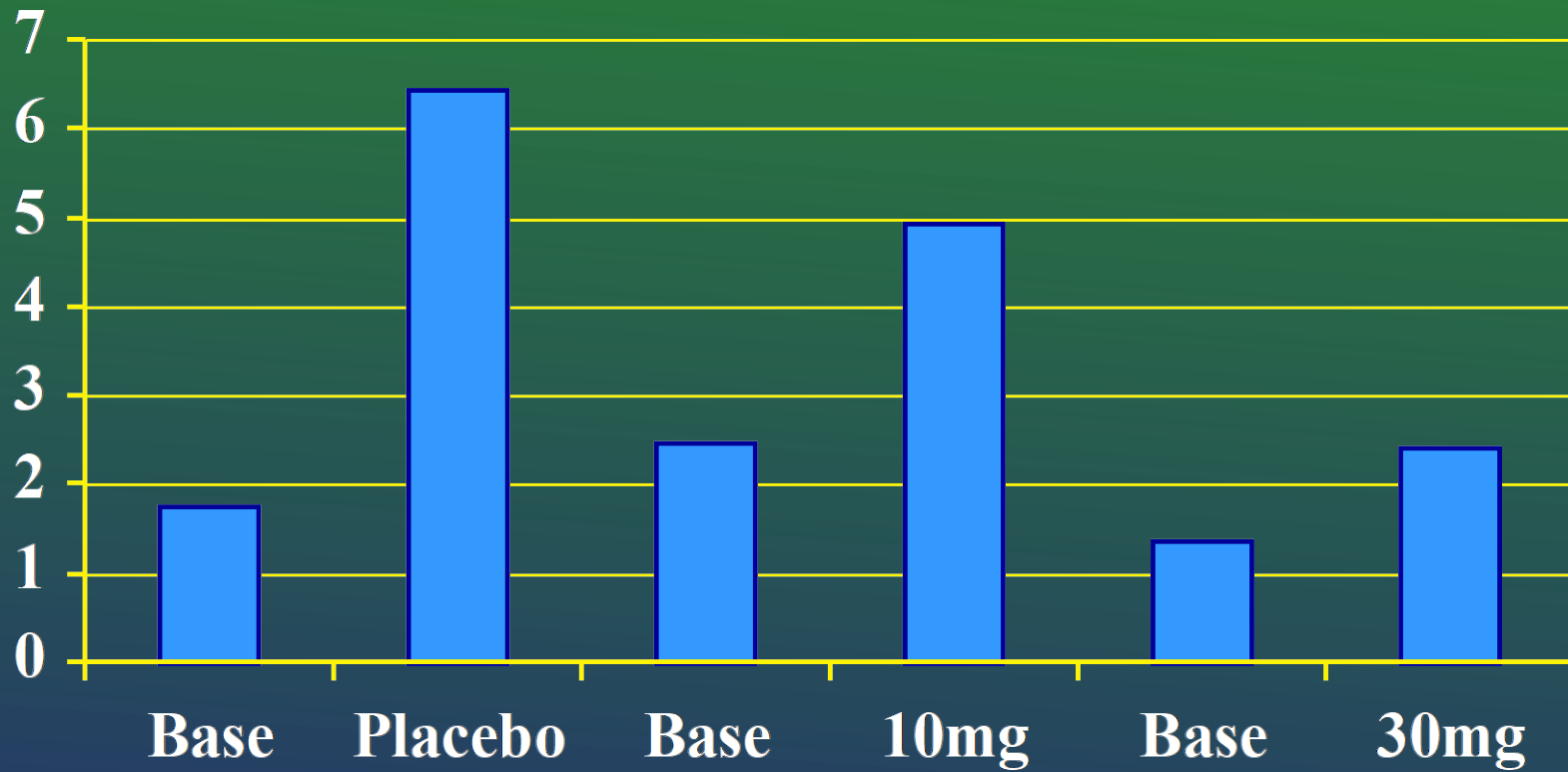


Timecourse: Withdrawal Discomfort Score

(Budney et al., 2003)



Pharmacological Specificity: Oral THC reduces Withdrawal Discomfort

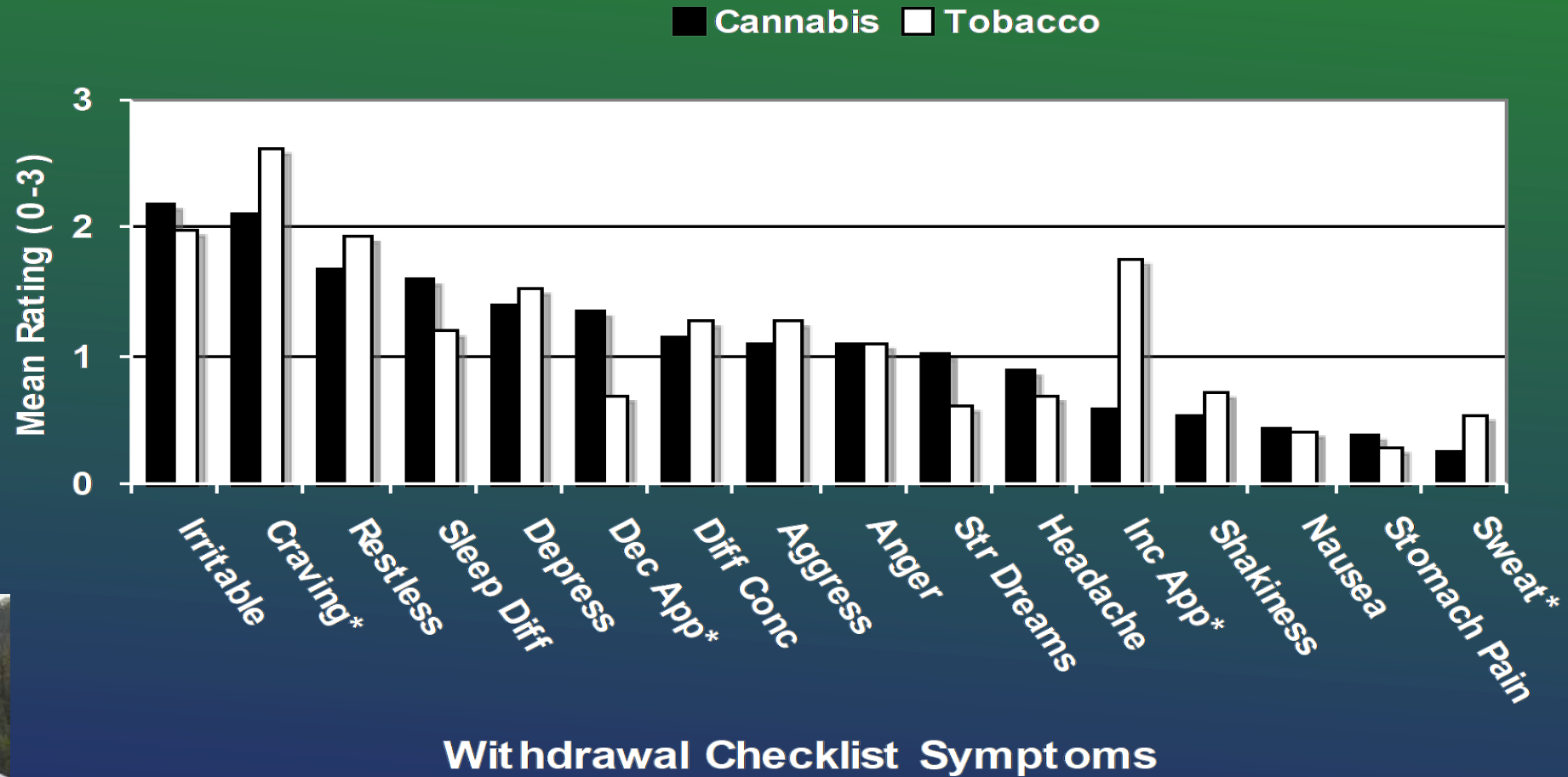


(Budney, Vandrey, Moore, Hughes, 2007)

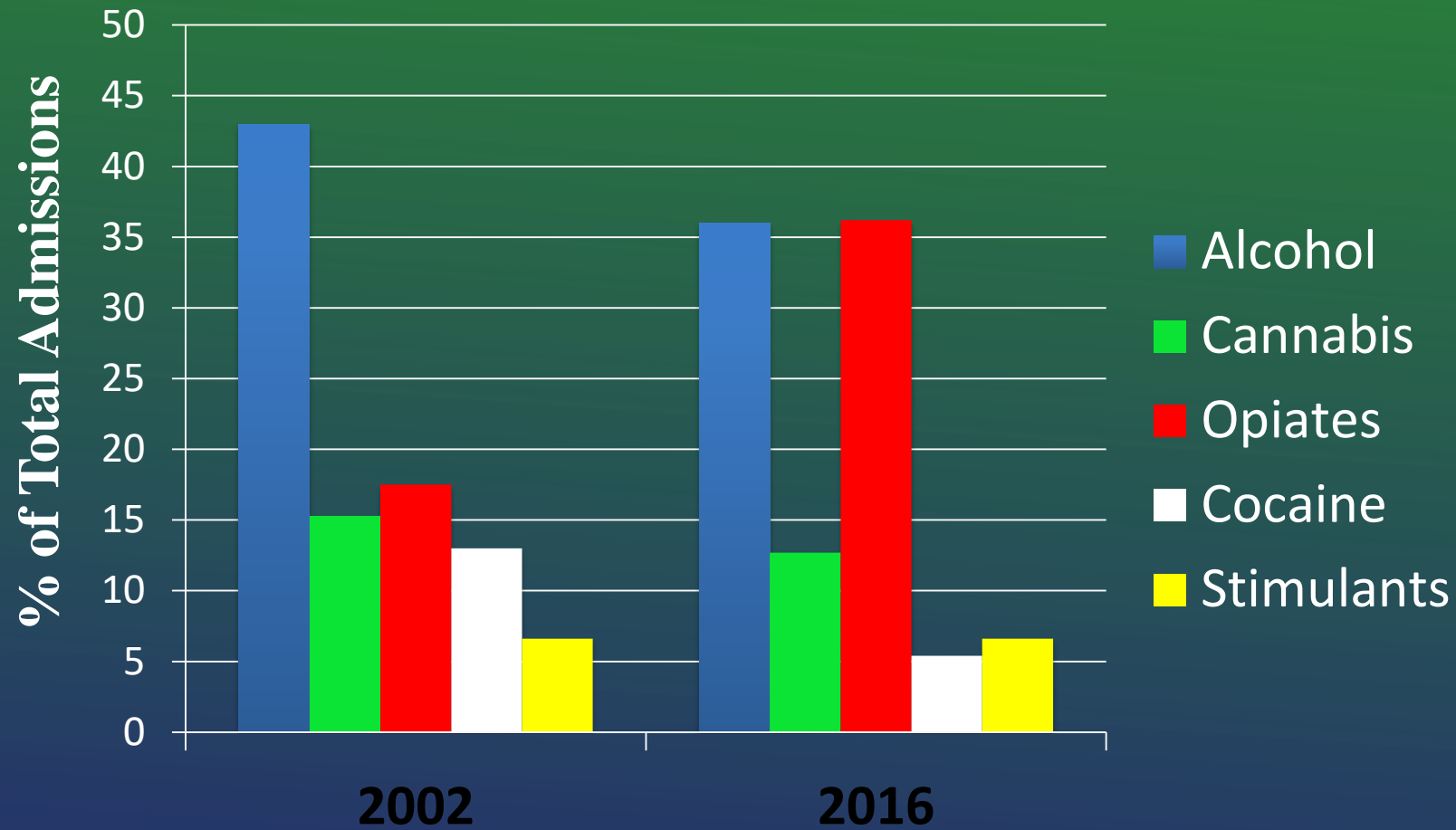
Cannabis and Tobacco Withdrawal are Comparable

(Vandrey et al., 2005; Vandrey et al. 2008, Budney et al., 2009)

Symptom Severity



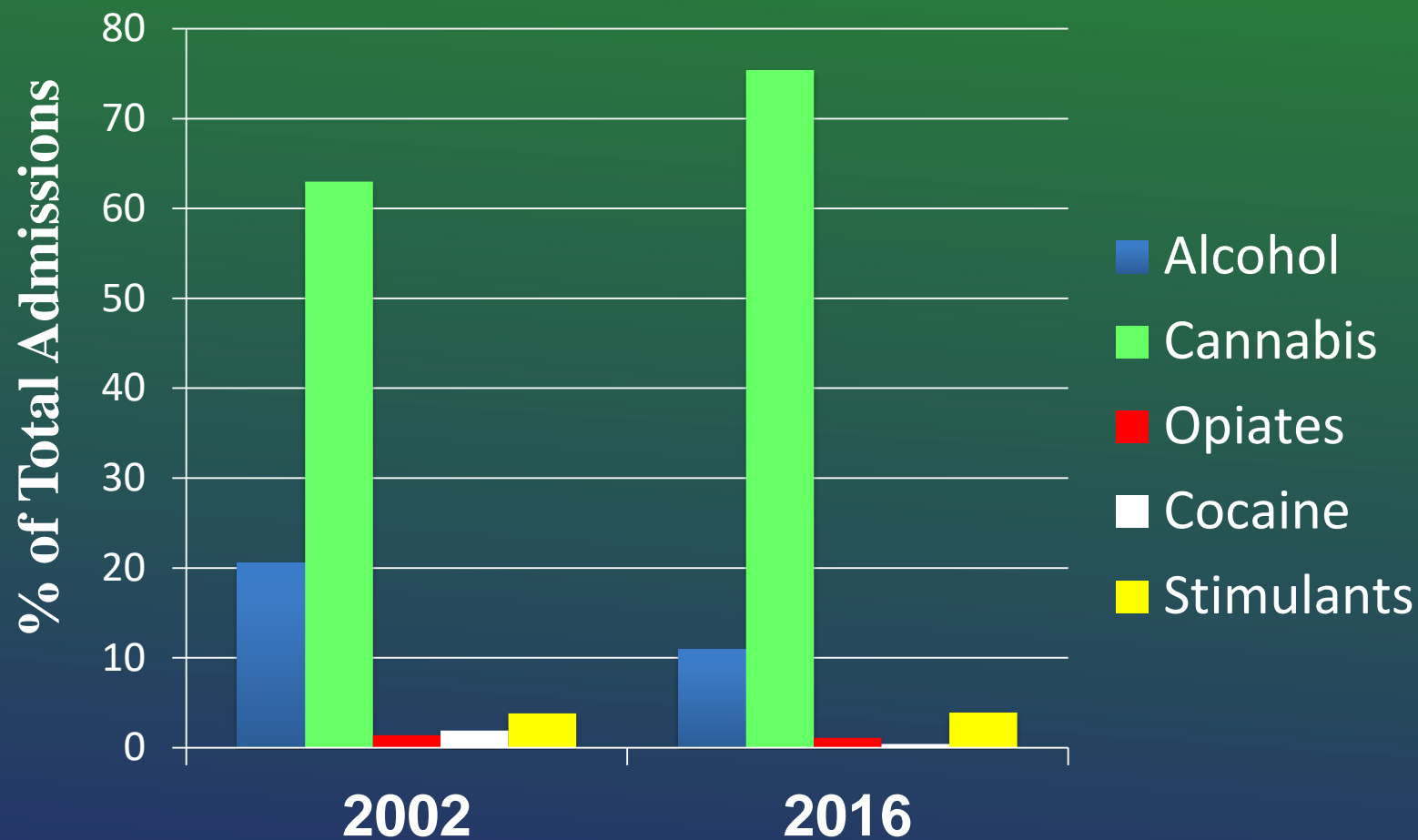
U.S. Treatment Admissions Primary Substance TEDS Data (age 12 and above)



US Treatment Admissions

Primary Substance

TEDS Data (12-17 years)



Most Vulnerable Populations

Highest Rates of CUD / Experience Consequences

- Poverty --- Disadvantaged minorities, low SES
 - Reduction/Deprivation of Prosocial Reward
 - Increased Stress
- Psychiatric Disorders
 - perceived benefits, symptom relief
- Physical Disorders
 - perceived benefits, symptom relief

TAKE HOME

- (1) Cannabis (THC-laden) is more similar than dissimilar to other substances that are considered “substances of abuse”
- (2) Cannabis Use Disorder is Real
- (3) CUD manifests much the same as other types of Substance Use Disorders

Aim 2

Operationalize “Medical” Marijuana / Cannabis

Cannabis Products: Smoking / Vaping



High Potency Products - Concentrates



Edibles



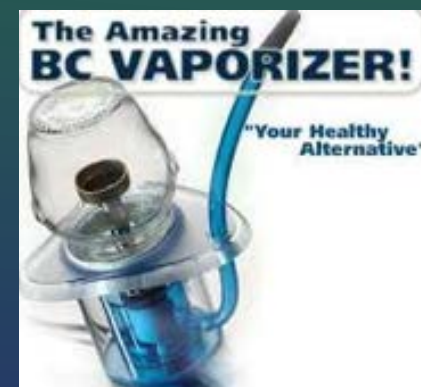


Lotions / Creames / Salves / Patches



510 x 288

Vaping Delivery Devices



Aim 2

Operationalize “Medical” Marijuana / Cannabis

There is no such thing as “*Medical Marijuana*”!

Same plant and compounds as Recreational Marijuana

We do have FDA approved cannabinoid medicines:

- Marinol, Dronabinol (THC pills)
- Epidiolex (CBD oral solution)

Other countries have: Sativex (CBD/THC oramucosal spray)

Cannabis / Marijuana / Cannabinoids

What are we talking about?

- Is cannabis the same thing as marijuana?
- THC, CBD THC/CBD ratio?
- What else in the plant/product is important?
- What are their effects? Interactions?
- What can cause harm? is safe? is therapeutic?
- How much of what ...?

What is “active” in the Cannabis Plant?

- CBGA (Cannabigerolic acid)
- **THCA (Δ^9 -tetrahydrocannabinolic acid)**
- **CBDa (Cannabidiolic acid)**
- CBCA (Cannabichromenenic acid)
- CBGVA (Cannabigerovarinic acid)
- THCVA (Tetrahydrocannabivarinic acid)
- CBDVA (Cannabidivarinic acid)
- CBCVA (Cannabichromevarinic acid)
- **Terpenes: essential oils, smells, flavor**

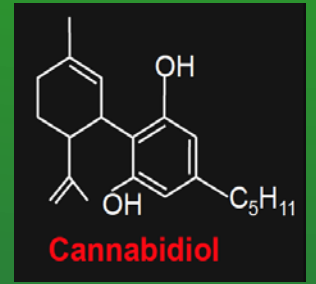
Delta-9 THC

**** Primary psychoactive constituent**

Dose related effects:

- High, euphoria
- Cognitive impairment (memory, learning, attention, time perspective, impaired judgment)
- Anxiety, Panic, Hallucinations, Psychosis?
- Analgesic, appetite stimulant, anti-nausea

Cannabidiol (CBD)



Cannabis plants have varying amounts of CBD

****** *May moderate the adverse effects of THC*
(anxiety, psychosis, and cognitive deficits)

****** *Demonstrated efficacy* as an anti-epileptic

- *“Potential”* as an antipsychotic?

- *“Potential”* as an anxiolytic, anti-depressant, stress reduction,
pain relief, anti-inflammatory, anti-cancer agent, Type 1
diabetes, etc., etc.

Entourage Effect: Mixture or Ratio of Compounds

Cannabis plants / products have varying amounts of all of these compounds.

How important are these?

Logically, combinations should have some effect, but these have not been studied well clinically

Why Is Defining the “Product” so
Important?

Example: “Marijuana and Breastfeeding...”

Mrouh et al., 2017

Human and animal data will be analyzed from 4 perspectives:

- (1) the effects of **THC** on the mother in relation to lactation and care of the offspring,
- (2) transfer of the chemical into breast milk,
- (3) transfer to the offspring, and
- (4) the indirect and direct effects of **THC** on the offspring.

What do we know about the compounds?

- 1) THC \neq CBD \neq CBG \neq Cannabis/Marijuana
- 2) THC gets you high; CBD does not
- 3) CBG, CBV, CBC, CBD, --- ???
- 4) Dose matters, Route of Administration matters

TAKE HOME

When you are trying to understand/summarize the effects of cannabis/marijuana - positive or negative, **you need to first define what you or the other person or the scientific article is talking about.**

What was tested in that study or what did you take?

THC

CBD

THC/CBD

Other Cannabinoids

Extracted / synthesized

Smoked, Oral

Dose

Aim 3: **Data** on Therapeutic Cannabis Products?

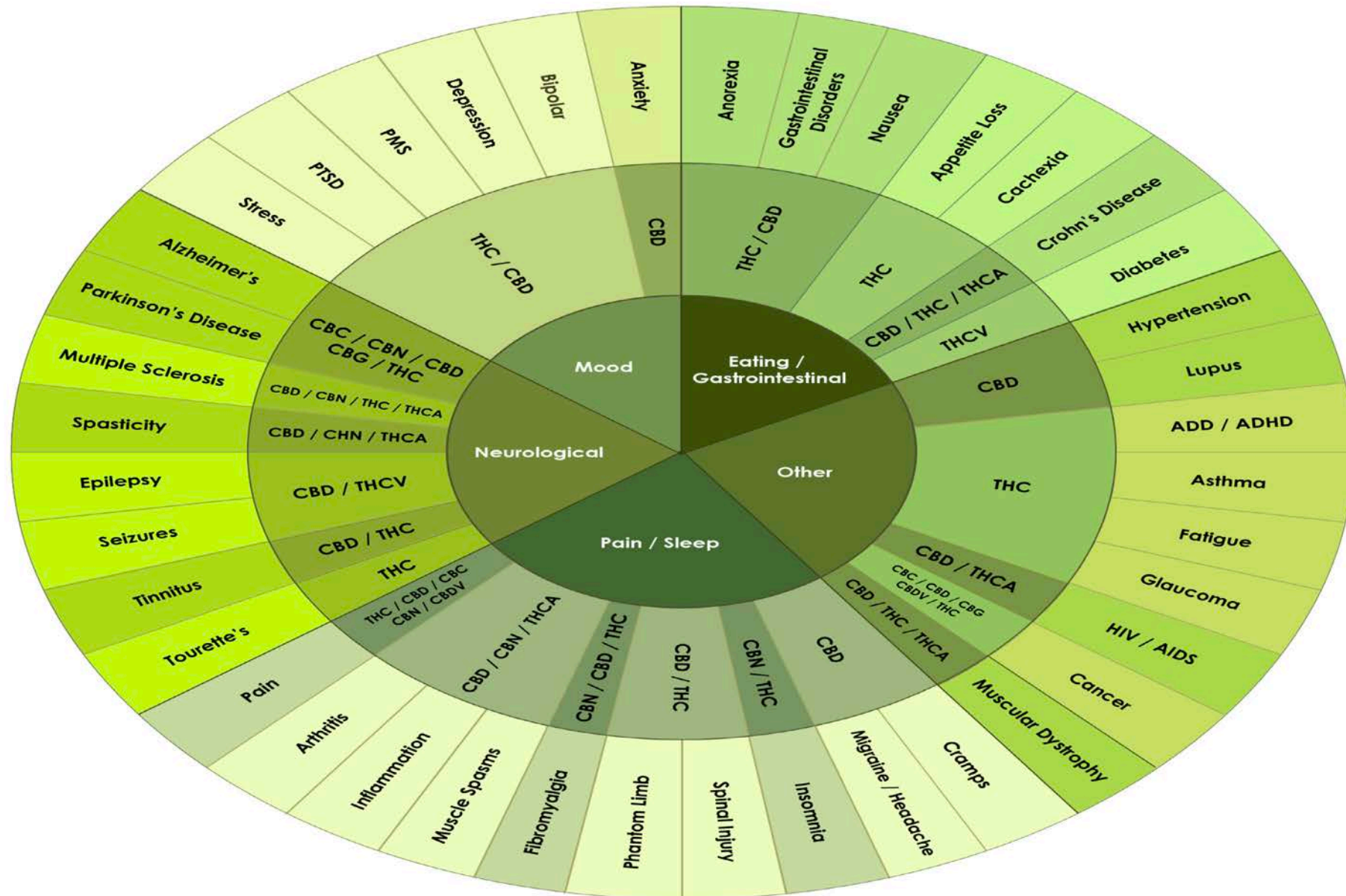
What has your state government told the public and you about these products / compounds?

What do those “dispensing” / selling / promoting these products act like they know?

What do they tell consumers / customers?

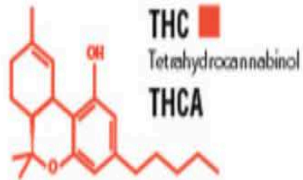
“While there are over 80 different cannabinoids in marijuana, only a handful have been researched **and are known to provide positive effects on the human body.**”

Health Effects of Marijuana	THC	THC-A	THC-V	CBN	CBD	CBD-A	CBC	CBC-A	CBG	CBG-A	Benefits
Pain relief											Analgesis
Reduces inflammation											Anti-inflammatory
Supresses appetite											Anorectic
Stimulates appetite											Appetite stimulant
Reduces vomiting and nausea											Antimetic
Reduces contractions of small intestine											Intestinal antiprokinetic
Relieves anxiety											Anxiolytic
Tranquilizing / psychosis management											Antipsychotic
Reduces seizures and convulsions											Antiepileptic
Suppresses muscle spasms											Antispasmodic
Aides sleep											Anti-insomnia
Reduces efficacy of immune system											Immunosuppressive
Reduces blood sugar levels											Anti-diabetic
Prevents nervous system degeneration											Neuroprotective
Treats psoriasis											Antipsioratic
Reduces risk of artery blockage											Anti-ischemic
Kills or slows bacteria growth											Anti-bacterial
Treats fungal infection											Anti-fungal
Inhibits cell growth in tumours / cancer											Anti-proliferative
Promotes bone growth											Bone-stimulant



NH Dispensary: Educate Yourself and Your Physician

CANNABINOID



BENEFIT

Psychotropic, painkiller,
anti-inflammatory,
anti-microbial

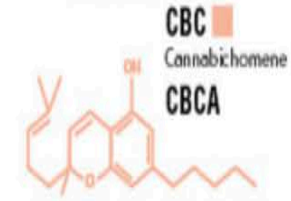
CANNABINOID



BENEFIT

Relieve anxiety,
convulsions, depression,
inflammation and nausea
sedative, sleep aid and
muscle relaxant

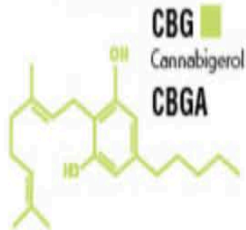
CANNABINOID



BENEFIT

Anti-inflammatory, painkiller,
treats acid reflux,
anti-anxiety, antidepressant

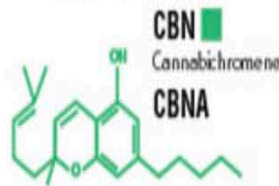
CANNABINOID



BENEFIT

Painkiller, muscle relaxant,
anti-erythemic analgesic,
digestive aid, stomachic
(stomach function)

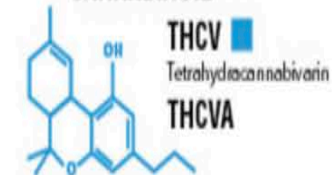
CANNABINOID



BENEFIT

Mild psychotropic, may
stimulate bone growth,
anesthetic, anti-convulsive,
analgesic, anti-anxiety

CANNABINOID



BENEFIT

Anti-obesity, aids memory,
calming aid, antibacterial,
antiviral, immune system

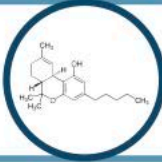
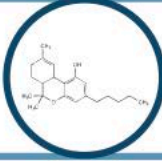
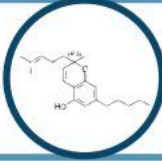
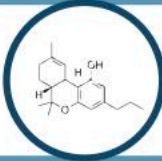
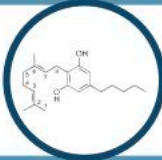
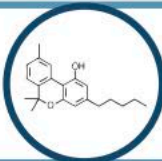
CANNABINOID



BENEFIT

Anti-inflammatory, analgesic,
protects cells lining
digestive tract

NH Dispensary: Educate Yourself and Your Physician

★	THC Tetrahydrocannabinol		THC is a psychoactive cannabinoid that may provide relief for patients with severe pain, nausea, poor appetite, and muscle spasms.
★	CBD Cannabidiol		CBD is a non-psychoactive cannabinoid that may provide relief for patients with severe, persistent muscle spasms, severe pain, and agitation of Alzheimer's Disease.
	CBC Cannabichromene		CBC is a non-psychoactive cannabinoid that may help relieve severe pain, inhibit cell growth in tumors, promote bone growth, and reduce inflammation.
	THCV Tetrahydrocannabivarin		THCV is a psychoactive cannabinoid that may help suppress appetite, reduce seizures, and may promote bone growth.
	CBG Cannabigerol		CBG is a non-psychoactive cannabinoid that may help slow bacteria growth, inhibit cell growth in tumors, promote bone growth, and reduce inflammation.
	CBN Cannabinol		CBN is a non-psychoactive cannabinoid that may provide relief for patients with agitation of Alzheimer's Disease, severe pain, and muscle spasms.

NH Approved Conditions for Therapeutic Use of Cannabis

AIDS or / HIV+

Alzheimer's Disease

Amyotrophic Lateral Sclerosis (ALS)

Cachexia

Cancer

Chronic Pancreatitis

Crohn's Disease

Epilepsy

Glaucoma

Hepatitis C Lupus

Multiple Sclerosis (MS)

Muscular Dystrophy

Parkinson's Disease

Spinal Cord Injury or Disease

Traumatic Brain Injury (TBI)

Ulcerative Colitis

Moderate to Severe Pain

Moderate to Severe PTSD

>1 injuries that interferes with daily activities as documented by the patient's provider

UNDER CONSIDERATION:

Insomnia

Anxiety

Opioid Use Disorder

Tick-Bourne Illnesses

Content of Active Compounds (THC/CBD) in Cannabis Products

e.g.: One Dispensary in New Hampshire

Plant Material / Flowers *

THC: 0.6% - 30.6% *

CBD: 0.04% - 14.6% *

Concentrates (Oils, Tinctures, Wax, Patches)

THC: 35.3% - 87.5% **

CBD: 0.01% - 40.3% **

Edibles

THC: 20mg – 100mg **

CBD: 20mg

Capsules

THC 5-50mg

CBD 5-25mg

Content of Active Compounds (THC/CBD/CBG)

One Dispensary in New Hampshire

FLOWER

\$20 (1G), \$55 (1/8 OZ), \$100 (1/4 OZ), \$190 (1/2 OZ), \$360 (OZ)

CBD-RICH

KNOWN FOR ITS NON-PSYCHOACTIVE QUALITIES, CBD HAS BEEN REPORTED TO BE BENEFICIAL FOR ITS ANALGESIC, ANTI-INFLAMMATORY PROPERTIES

AC CBD-Rich

Cannabinoid Profile: 0.60% THC | 13.90% CBD | <0.12% CBG

SS1:1: 1:1 CBD:THC

Cannabinoid Profile: 5.8% THC | 7.5% CBD | 0.14% CBG

- FLOWER
- THC-RICH
- C99: Sativa: *22.60% THC | <0.12% CBD | 0.13% CBG*
- BbK: Indica. *23.2% THC | <0.12% CBD | 0.8% CBG*
- PN: Sativa: *25.70% THC | <0.12% CBD | <0.12% CBG*
- BV: Hybrid *16.5% THC | <0.12% | 2.7% CBG*
- GG#4: Hybrid *24.7% THC | <0.12% CBD | 0.30% CBG*
- *20% off all week!!!*
- PRE-ROLLS (0.5 GRAM PRJS) **AVAILABLE IN 10 PACKS
- *1 PRE-ROLL.....\$8 7 PRE-ROLLS.....\$46 **10 PACK (SINGLE STRAIN).....\$65*

CONCENTRATES

ROSIN

A SOLVENT FREE EXTRACT, ROSIN IS CREATED BY HEAT AND PRESSURE. KNOWN FOR POTENCY, IT'S BEST TO START LOW AND SLOW WITH THIS WAXY CONCENTRATE.

PN: ***62.9% THC / <0.1% CBD / 3.19% CBG***

COLD BREW CONCENTRATE PREMIUM

C99: ***84% THC / <0.1% CBD / 0.4% CBG***

BbK: ***82.6% THC / <0.1% CBD / 2.2% CBG***

GG#4: ***81.4% THC / <0.1% CBD / 1.27% CBG***

PN: ***65.7% THC / <0.1% CBD / 1.44% CBG***

Which of these products is good for each of the approved medical conditions?

*** Your State does not provide that information

How much **THC**, CBD, ratio of each, CBG

How much should you take of each?

How often should you take it? For how long?

Should you smoke it? Vape it? Eat it? Drop it on your tongue?

Or rub it on?

What Do We Know from Scientific Studies?

National Academy of Sciences

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research (2017)

<https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state>

National Academy of Sciences

Current data and summaries are confusing

“Potential” is clear:	biological plausibility -	yes
	laboratory models -	yes
	pre-clinical demonstrations -	yes
	case reports /open label -	sometimes
	controlled clinical data -	almost never

Evidence Modifiers

(NAS 2017)

There is conclusive evidence...

There is moderate evidence...

There is limited evidence...

There is no or insufficient evidence to support or refute ...

There is substantial evidence of a statistical association between cannabis use and...

e.g., Social Anxiety and CBD

Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder.

Regular cannabis use is likely to increase the risk for developing social anxiety disorder.

** There is **limited evidence** that cannabis or cannabinoids are effective for: improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol)

LIMITED Evidence for Therapeutic Effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest. For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

This review identified **one randomized trial** with a high risk of bias that compared **a single 600 mg dose** of cannabidiol to a placebo **in 24 participants (undergraduate students) with generalized social anxiety disorder**

e.g., Social Anxiety and CBD

This review identified **one randomized trial** with a high risk of bias that compared **a single 600 mg dose** of cannabidiol to a placebo **in 24 participants** (undergraduate students) with generalized social anxiety disorder.

Cannabidiol was associated with a **greater improvement on the anxiety factor of a 100-point visual analogue mood scale** (mean difference from baseline -16.52 , $p = 0.01$) compared with a placebo during a simulated public speaking test. (Bergamaschi et al., 2011)

DOSE: single 600mg CBD

What is being sold:

25mg CBD Capsules. \$80 pack of 10

CBD-Rich Tincture 400mg (10ml). \$90 400mg per bottle *1 drop = 1mg

CBD Dosing

Social Anxiety Study. single dose: 600mg CBD

Epidiolex Trial: 10-20mg/kg

100lbs (45kg): 450 to 900mg CBD day

Hurd et al. lab testing 400-600mg doses

What is being sold:

25mg CBD Capsules. \$80 pack of 10

CBD-Rich Tincture 400mg per bottle *1 drop=1mg \$90

THC Dosing and Pain

Ware et al. (2010) RCT Chronic Neuropathic Pain

9.4% THC (25mg) 3-5x per day with is equivalent to 2.5mg dose or 7.5-12mg per day

Result: Lowered pain score (0-10 scale) by 0.7 pts (6.1 to 5.4 compared to placebo)

What is being sold:

By Prescription: 2.5-5 mg tablets of dronabinol or marinol (prescription)

Cannabis Dispensary:

Plant Material	THC: 0.6% - 30.6%
Concentrates	THC: 35.3% - 87.5%
Edibles	THC: 20mg – 100mg
Capsules	THC 5-50mg

Therapeutic Effects and the Evidence?

Standards of Evidence?

Terminology for Communicating about Evidence?

Potential for Adverse Effects?

Specificity: Compound, Dose, Route of Administration

Recommendations?

“Potential” “Promising”

Communicating about (and researching) the **Benefits** requires a major shift in how we discuss effects and report scientific findings

How Do You Communicate?

Lack of Evidence?

Specificity of Findings?

Potential for Placebo Effects?

Magnitude of Effects (efficacy)?

Symptom Relief vs. “Cure” vs. Treatment

*** DHMC worksgroup lead by Cynthia Reuter:
Therapeutic Cannabis Guidance Statement

Aim 4: Cannabis Industry Impact

Cannabis Business and Industry

Forbes

Spending on legal cannabis worldwide is expected to hit \$57 billion by 2027

North America, going from \$9.2 billion in 2017 to \$47.3 billion a decade later

**Marijuana
Business Daily**[®]

Select your Edition:

U.S. | International | Hemp Industry

Marijuana executives offer strategies and insights on salaries and recruitment

Weekly Deal Watch: Cultivation and retail continues to dominate M&A cannabis activity

Published May 23, 2019

The cannabis cultivation and retail sector has become increasingly crowded and competitive, but successful operators can still make themselves attractive acquisition targets. [READ MORE >](#)

The Cannabis Lobby

The Cannabis Trade Federation (CTF) has hired 15 lobbyists to push the Strengthening the Tenth Amendment Through Entrusting States Act



Joint effort: cannabis lobby heads to Washington to woo US lawmakers

Industry leaders descended on the capital this week amid hopes the country at large is slowly embracing legalization





The Market







How to Recommend Sexual Cannabis Products to an Inquisitive Customer

LEAFLY STAFF
June 18, 2016



Cannabis Industry: “Big Pharma”?

Internet Headline:

“Infusing marijuana with data: Cannabis industry vets aim to clear the haze in a booming industry”

...as they plotted their next endeavor, one word kept coming up in almost every conversation: **data**

...yet hardly anyone knew, at least when it came to numbers,

what do consumers liked most

Cannabis Industry: “Big Pharma”?

Headset is part of a wave of new firms trying to bring the kinds of **consumer metrics** enjoyed by big brands such as Coca-Cola, Toyota and Nestle to cannabis.

The legal recreational pot business in the U.S. is expected to reach \$7 billion this year, a 28 percent increase over 2018

...pumping money into an industry that is attracting tech workers from the likes of Microsoft, Apple and Amazon who are leaping into the trade and bringing their **data-based marketing skills**

The public is being lead to believe cannabis/marijuana is good for everything that ails you, and that it is relatively harmless.

Many of the conditions/disorders that have been approved as appropriate for use of “medical” cannabis include conditions that make one vulnerable to developing a substance use disorder

Perceived Risks and Benefits?

College Freshman and Sophomores (n > 1000)

(2018)

Cannabis has therapeutic benefit for:

Depression	Yes	71-86%
Anxiety	Yes	68-94%
ADHD	Yes	31-54%
PTSD	Yes	51-80%
Pain	Yes	80-95%

- Politicians / Legislatures have decided to inform the public that Marijuana/Cannabis is a medicine that can help with just about everything –
- They have let the Industry (sales people) inform the consumer (patient / vulnerable population) what product / dose / route is best for them.
- Cannabis Industry is booming!!!!

Cannabis Regulatory Science and Policy

- Mitigate harm, maximize benefit
- Keep Industry impact under control
- Protect the public and those most vulnerable

**Science
and
Common Sense**

Thanks for Listening!