The Changing Landscape of Marijuana (Cannabis): What's Real and What's Not

Alan J. Budney, Ph.D.
Dartmouth College, Geisel School of Medicine
Center for Technology and Behavioral Health
alan.j.budney@dartmouth.edu

APA Division 50
Clinical Forum 11/11/16

Disclosures - Budney

Funded by ***National Institute on Drug Abuse -***

NIH has supported my research and conference attendance for about 25 yrs

Copy of Slides, Articles, or Other:

alan.j.budney@dartmouth.edu

https://www.youtube.com/watch?v=o4W6cS_9xxk

Reefer Madness

Goals / Conclusions

1. Characterize cannabis use, misuse, or addiction
   - substantial abuse potential and consequences
2. Clinical Epidemiology: Prevalence of Problems
   - comparable or greater than other substances; increasing?
3. Treatment Responsivity
   - “efficacious” treatments
   - but, limited efficacy, need more potent methods, extend reach
4. Describe the Changing Landscape
   - more potent products, alternative ways of use – increase risk?
   - therapeutic use / medical marijuana: Data are sorely lacking!!

DO YOU THINK…

- Cannabis has addictive potential?
- Cannabis withdrawal is clinically important?
- Quitting Cannabis is relatively easy?

- Cannabis has benefit for ADHD, PTSD, Anxiety?
- Cannabis has benefit for Epilepsy?
- Cannabis has therapeutic benefit for Pain?
- Cannabis use increases risk of psychosis?

DO YOU THINK …

- Vaping is a safe way to use Cannabis?
- Eating is a safe way to use Cannabis?
- Cannabis is as dangerous as Alcohol?
- We should legalize Cannabis?
  - Medical? Recreational? Just One, Both?

We Know that Cannabis Use Can Develop into an "*Addiction*"

Cannabis Use Disorder (CUD)
is not qualitatively
different from other SUDs

Evidence for Addictive Potential
Biological, Behavioral, Epidemiological

- Endogenous cannabinoid system in the CNS
- Effects of administration and cessation on the reward centers of the brain are similar to that of other drugs with addictive potential
- Functions as a reinforcer in the human laboratory
- People meet use disorder (“dependence”) criteria
- Evidence for a Withdrawal syndrome
- People seek help for CUD
- Difficult to quit; high rates of relapse

How Does Cannabis Compare to Cocaine Dependence?

	Cannabis	Cocaine
# of DSM-III-R criteria	**6.3 (1.8)**	**7.7 (1.2)***
Continued Use	97%	97%
Cut Down	86%	93%
Larger Amounts	80%	100%*
Excessive time	73%	87%*
Withdrawal	75%	81%
Tolerance	63%	97%*
Reduced Activities	41%	87%*

(Budney et al., 1998)

Cannabis Use Disorder (CUD) Compared with other SUDs

Shmulewitz et al. 2015; Hasin et al. 2013; Budney, 2006

Over 30 International Population-based Studies

CUD highly similar to other disorders

- unidimensional construct (IRT analyses)
- full range of criterion are endorsed
- less severe than cocaine, opioid or alcohol
- most prevalent SUD behind alcohol & tobacco

Cannabis Withdrawal

Cannabis Withdrawal demonstrated in:

- Non-human studies (primate, rodent, dog)
- Human inpatient/outpatient laboratory studies
- Clinical survey studies

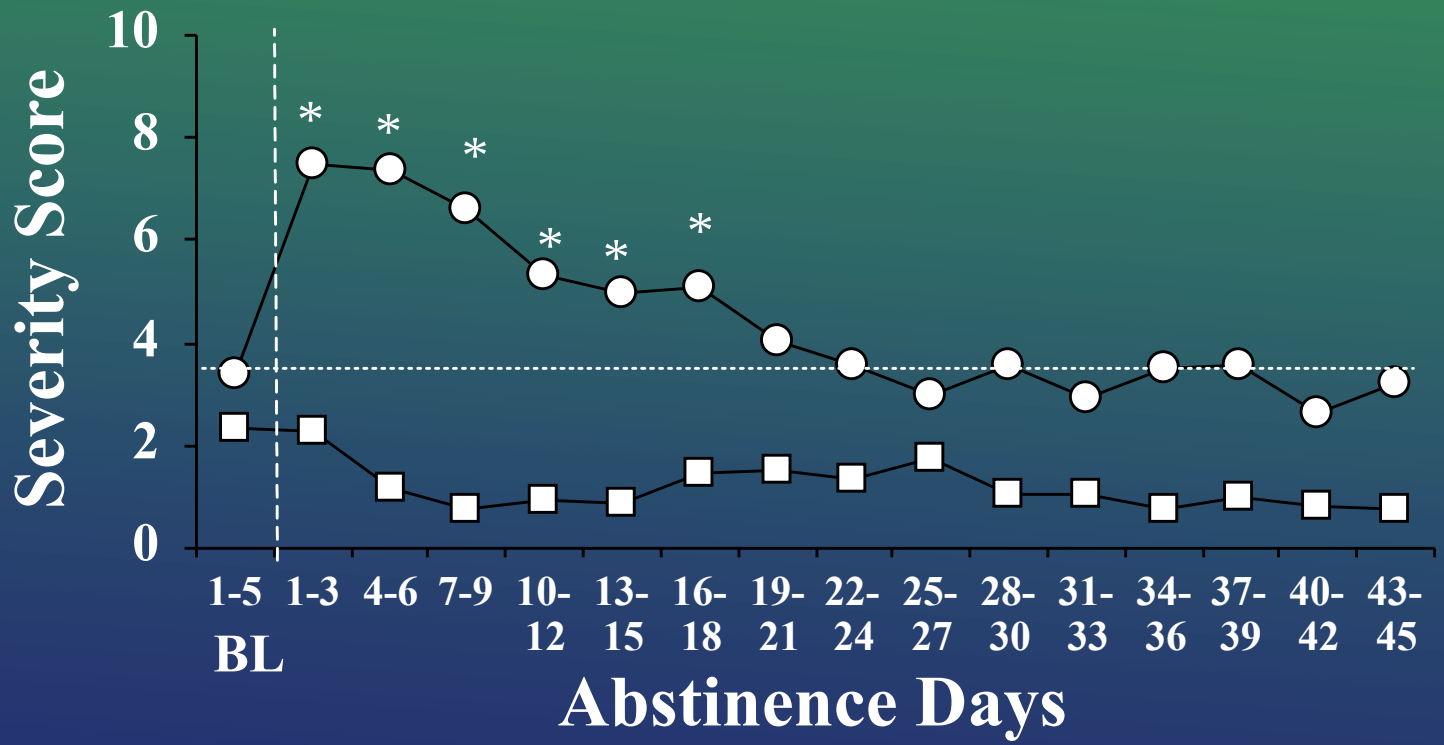
Budney et al. 2004

True Withdrawal Syndrome
(Hughes 1990)

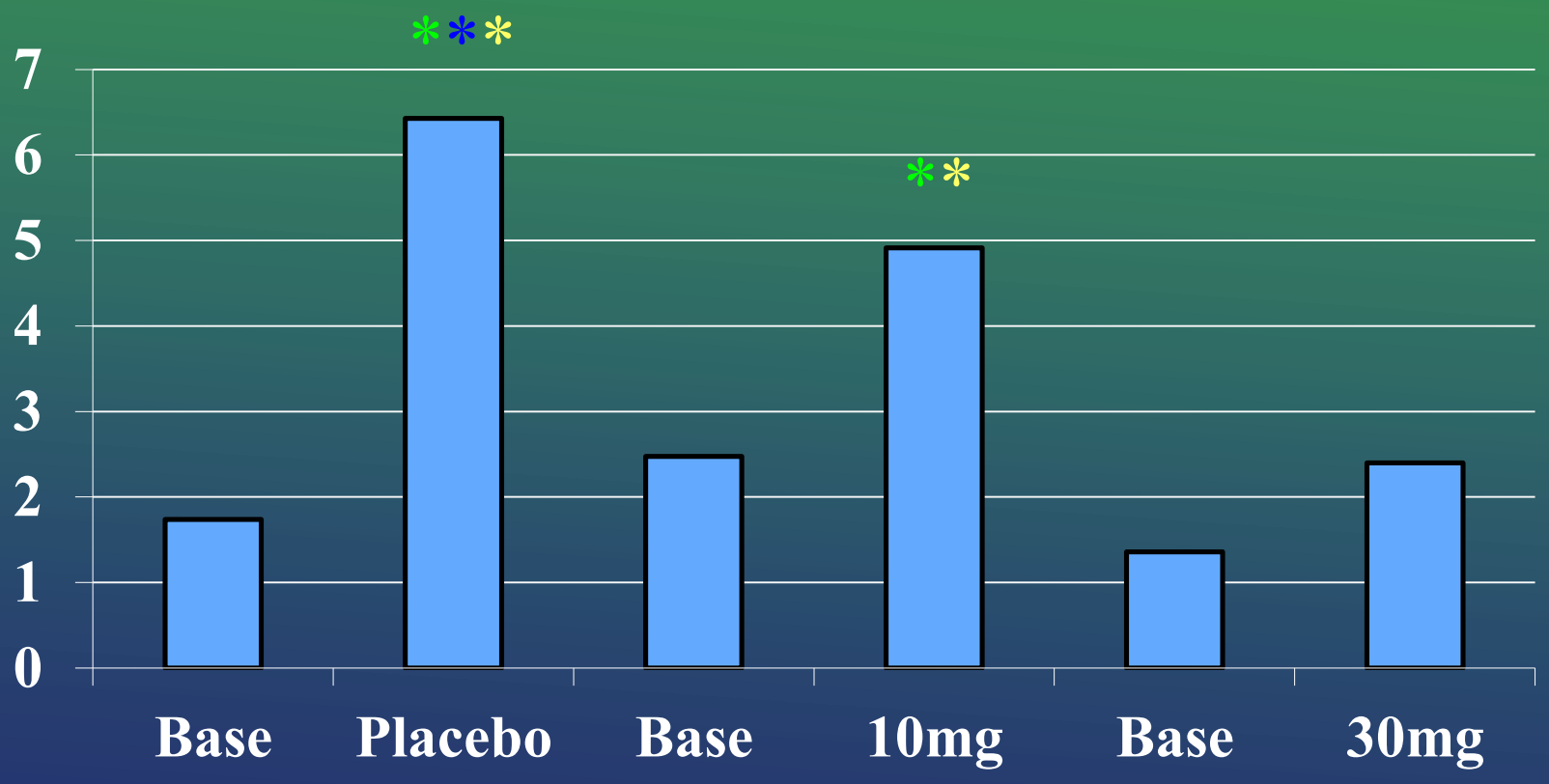
- Reliable abstinence symptoms
- Not Rare
- Onset, with Transient Timecourse
- Pharmacological Specificity
- Clinical Importance

Cannabis Withdrawal Onset and Timecourse

(Budney et al. 2003)



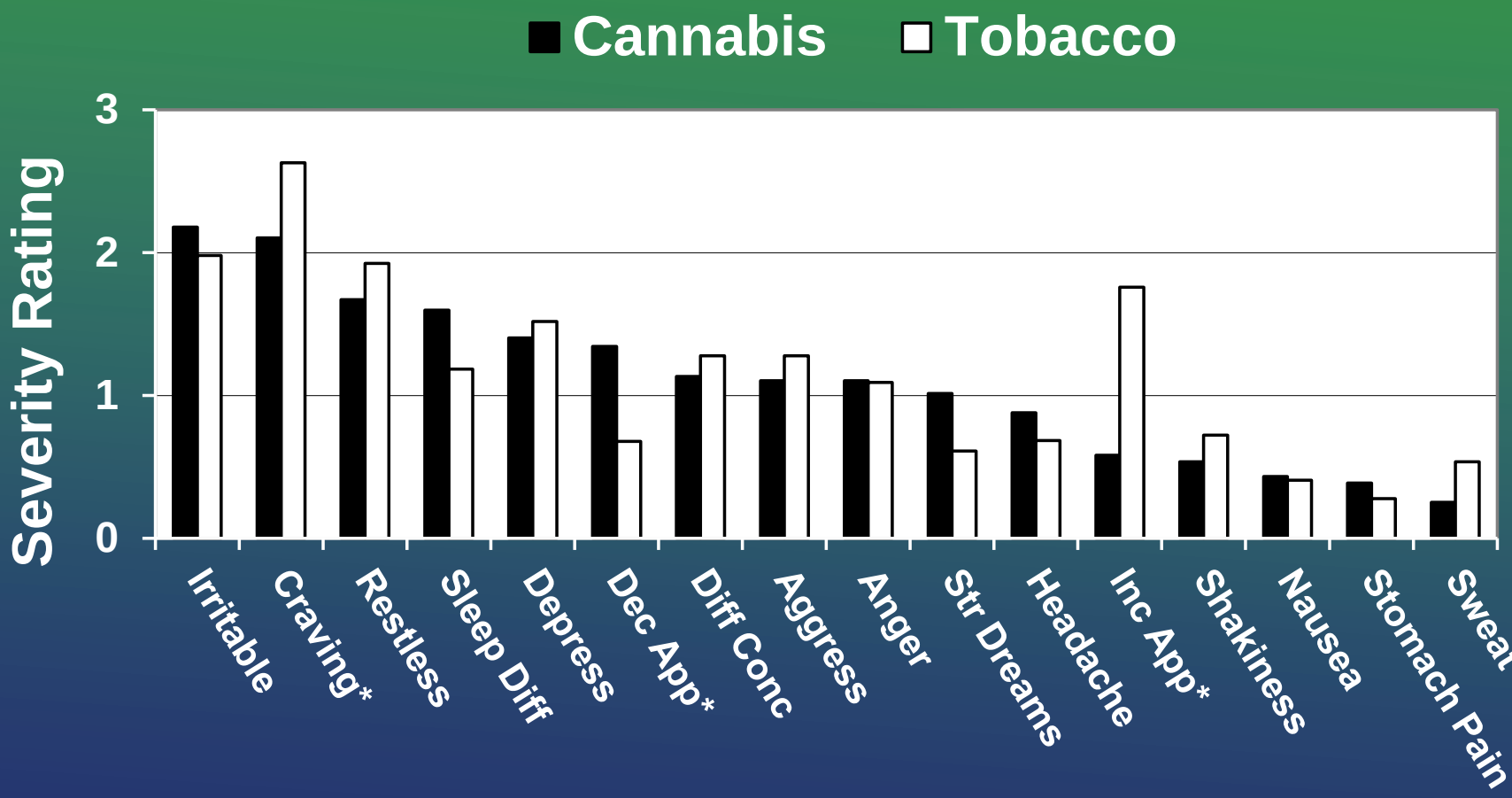
Pharmacological Specificity: Effect of oral THC (dronabinol) on Withdrawal



Budney, Vandrey et al, 2007

Cannabis & Tobacco Withdrawal

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



Clinical Importance of Cannabis WD

Use cannabis (or other substances) to relieve WD

Complain about WD; makes quitting difficult

# of WD symptoms predicts dependence severity

WD severity predicts rapid relapse (adolescents)

(Budney et al., 2006)

Cannabis Withdrawal Symptoms

1) irritability, anger, or increased aggression
2) nervousness or anxiety
3) sleep difficulty (insomnia)
4) decreased appetite or weight loss
5) restlessness
6) depressed mood
7) at least 1 physical symptom causing significant discomfort (stomach pain, shakiness/tremors, sweating, fever, chills, headache)

Cannabis Use Disorder is real.

When it occurs, it manifests much the same as other types of Substance Use Disorders

What is the prevalence of CUD?

How often does CUD occur among users?

NESARC 2002 vs. 2012

Past Year Marijuana Use

Table 1. Past-Year Prevalence of Marijuana Use by Sociodemographic Characteristics, 2001-2013[a]

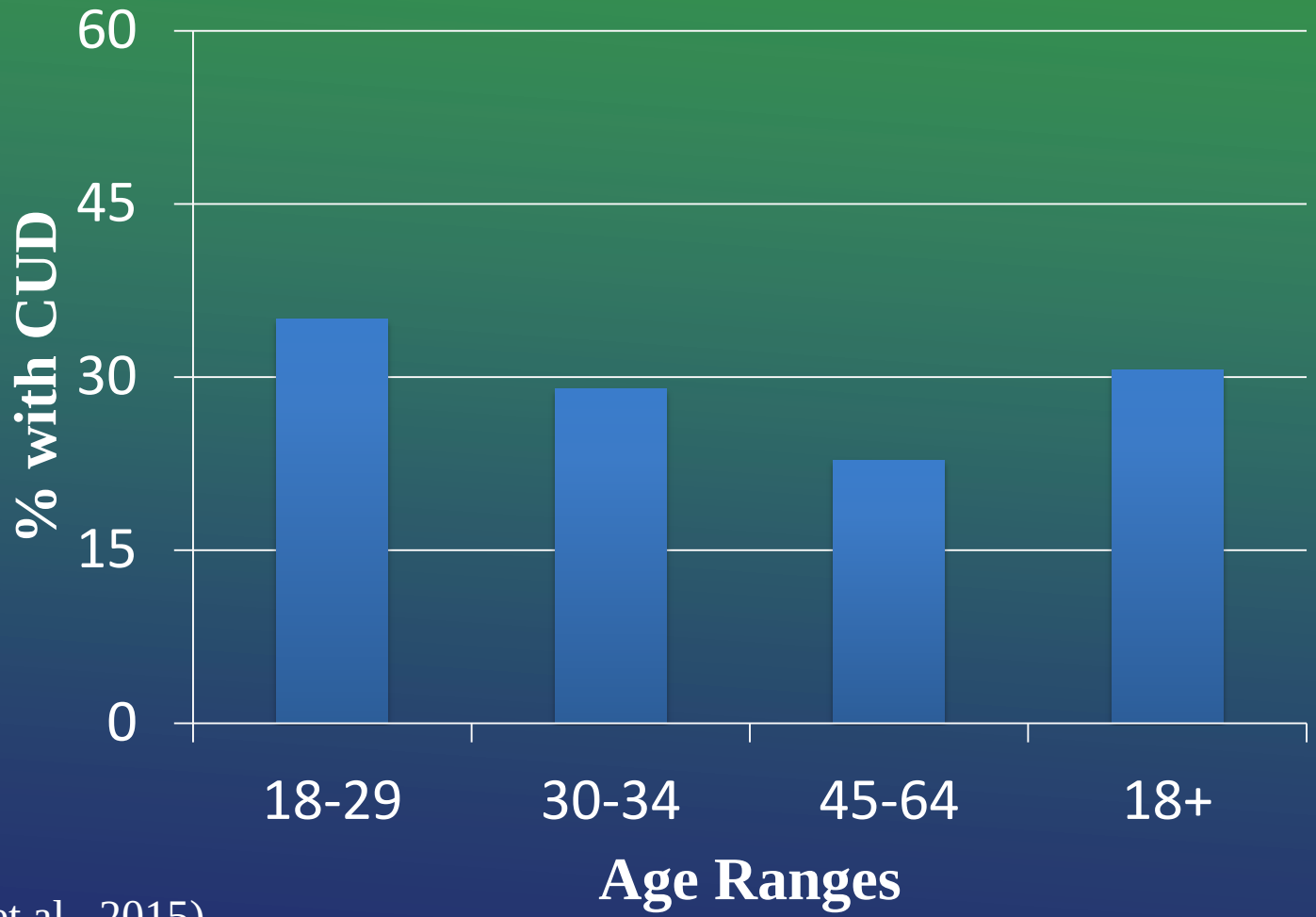
Sociodemographic Characteristics	% (SE)	
	NESARC Wave 1, 2001-2002	NESARC-III, 2012-2013
Total	4.1 (0.15)	9.5 (0.27)
Sex		
Male	5.6 (0.24)	12.3 (0.40)
Female	2.6 (0.15)	6.9 (0.29)
Age, y		
18-29	10.5 (0.47)	21.2 (0.67)
30-34	4.1 (0.24)	10.1 (0.41)
45-64	1.6 (0.15)	5.9 (0.28)
≥65	0.0 (0.02)	1.3 (0.22)
Race/ethnicity		
White	4.1 (0.17)	9.4 (0.34)
Black	4.7 (0.35)	12.7 (0.64)
Native American	7.0 (1.15)	17.1 (2.32)
Asian	3.1 (0.54)	5.0 (0.59)
Hispanic	3.3 (0.31)	8.4 (0.50)

Hasin et al. (2015)

NESARC 2002 - 2012
Rates of Past Year CUD

	2002	2012
18 and older:	1.5%	2.9%
18-29 years:	4.4%	7.5%
30-44 years:	1.2%	2.9%
45-64 years:	0.4%	1.3%

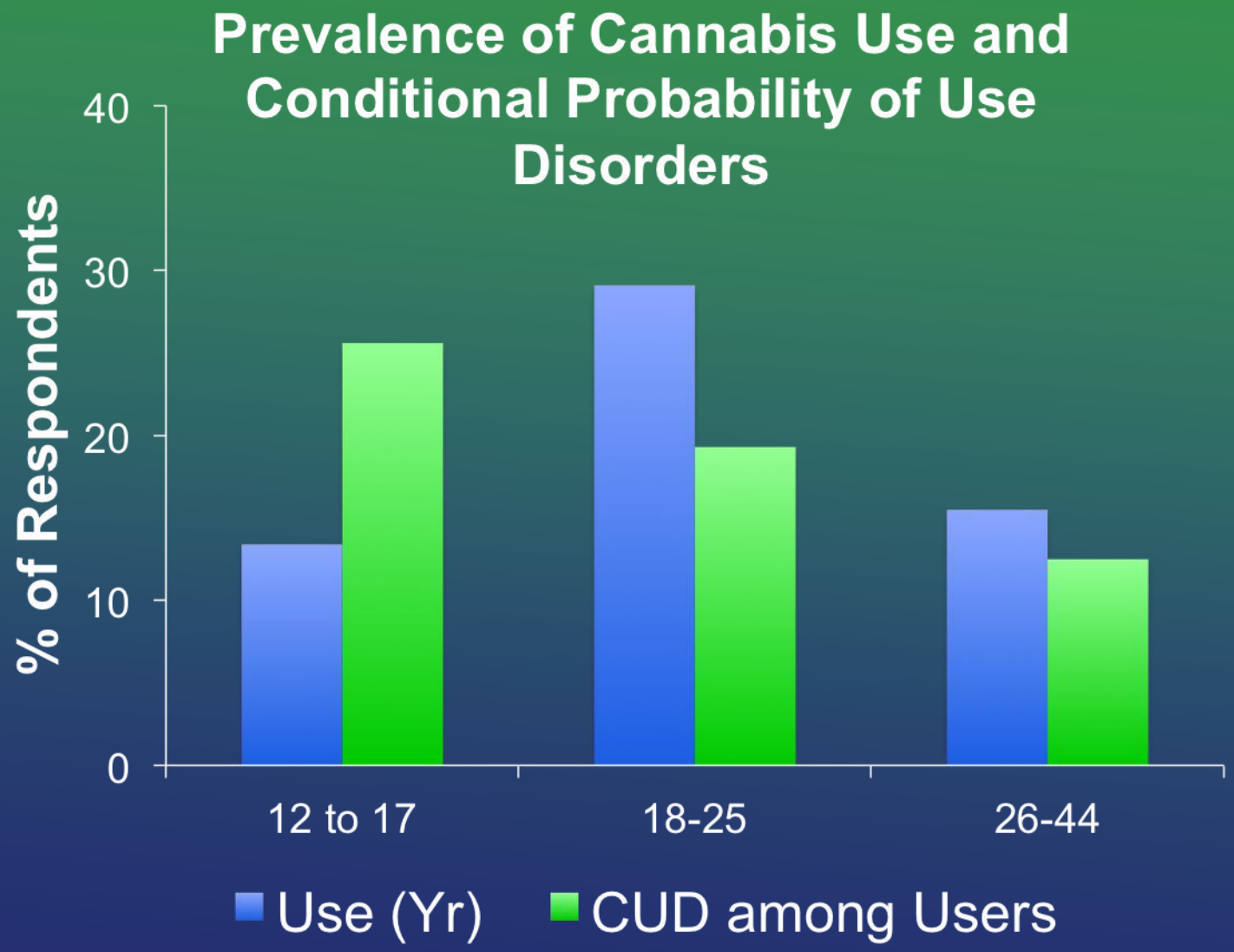
NESARC 2012
Conditional Probability of Past Year CUD



(Hasin et al., 2015)

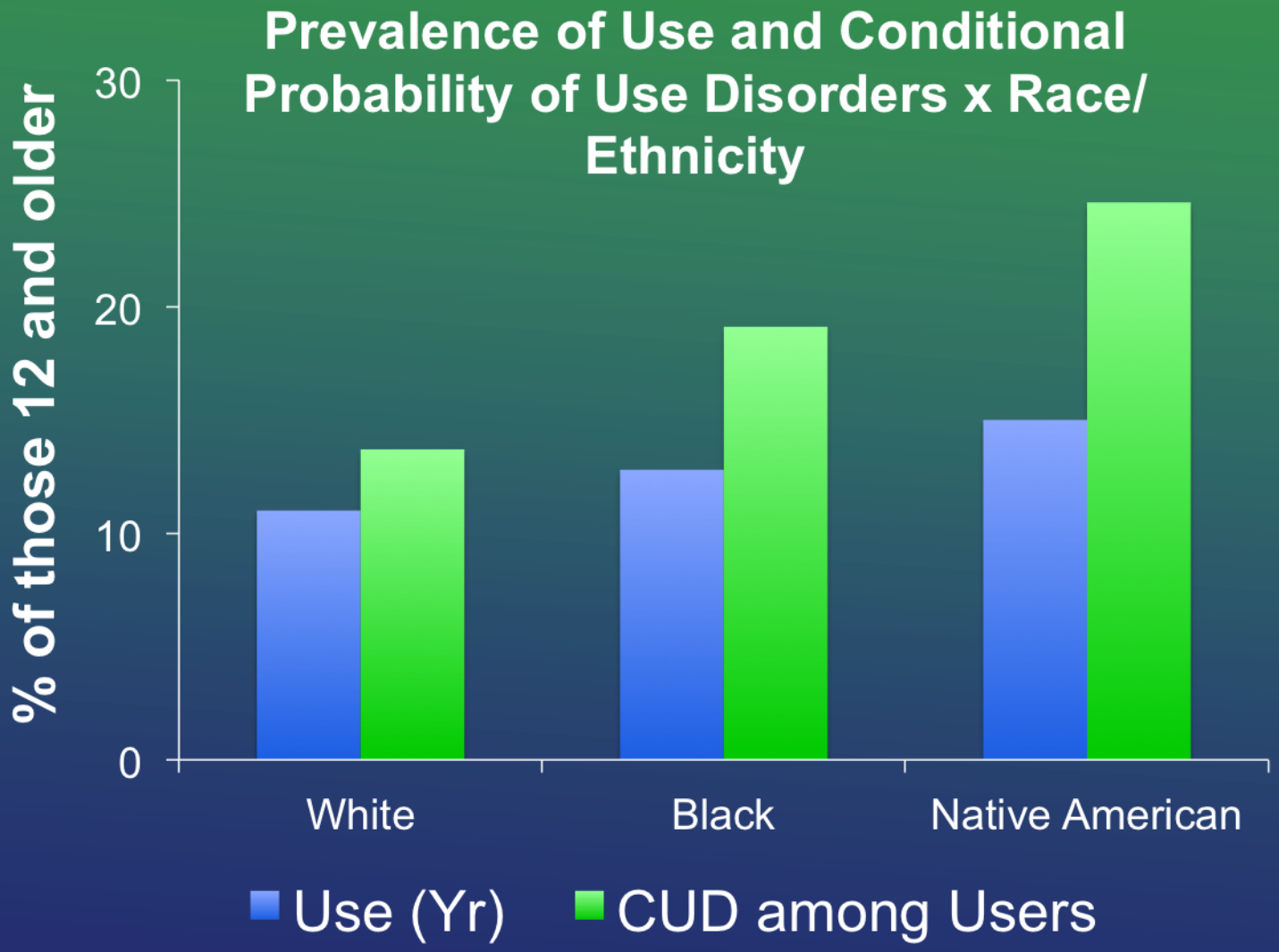
NSDUH 2011

(Wu et al., 2013)



NSDUH 2011

(Wu et al., 2013)



Summary

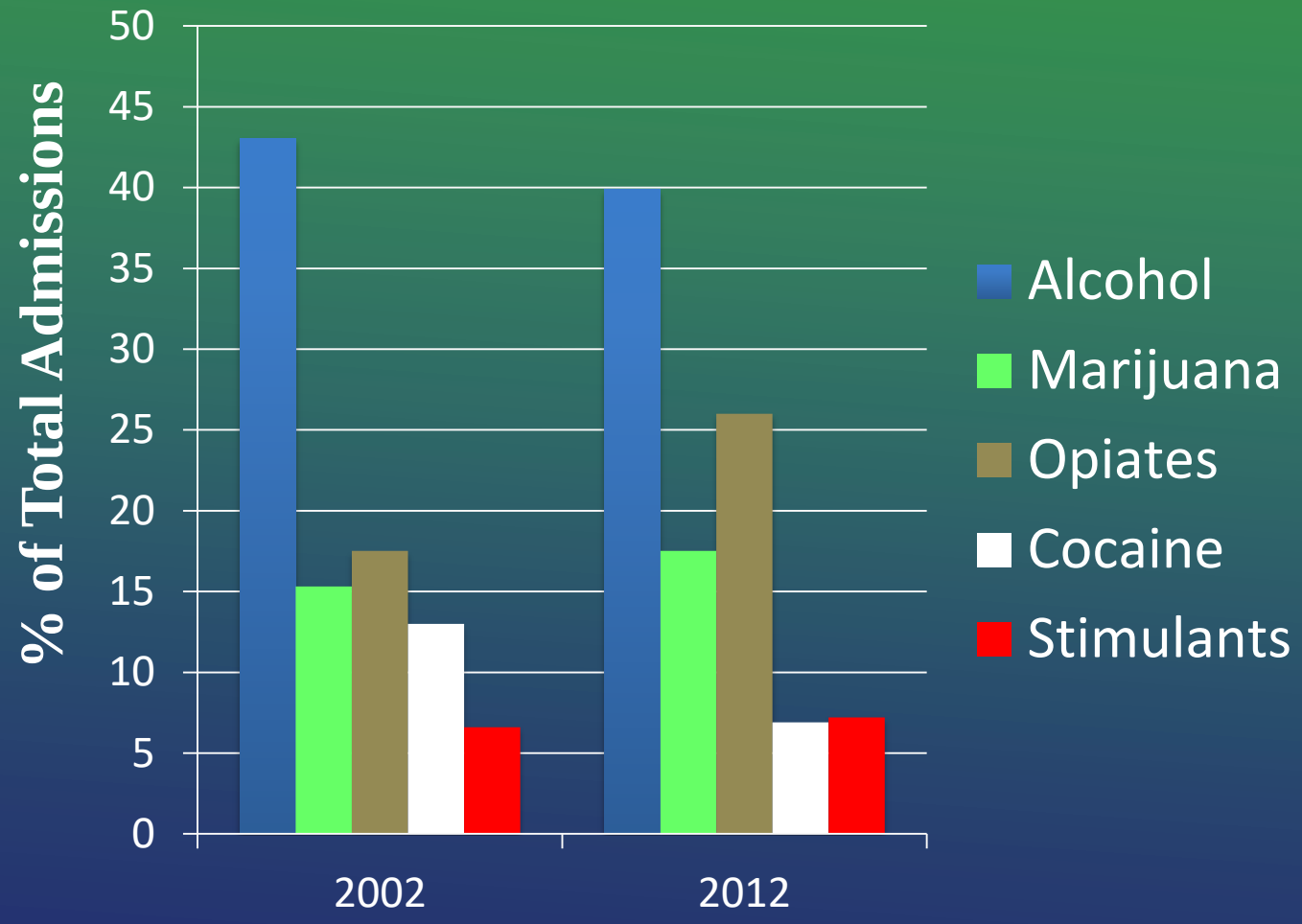
- 50% increase in cannabis users over last decade
- Almost 50% increase in Cannabis Use Disorders
- Increase in CUD related to increased # of users?

<u>However</u>:

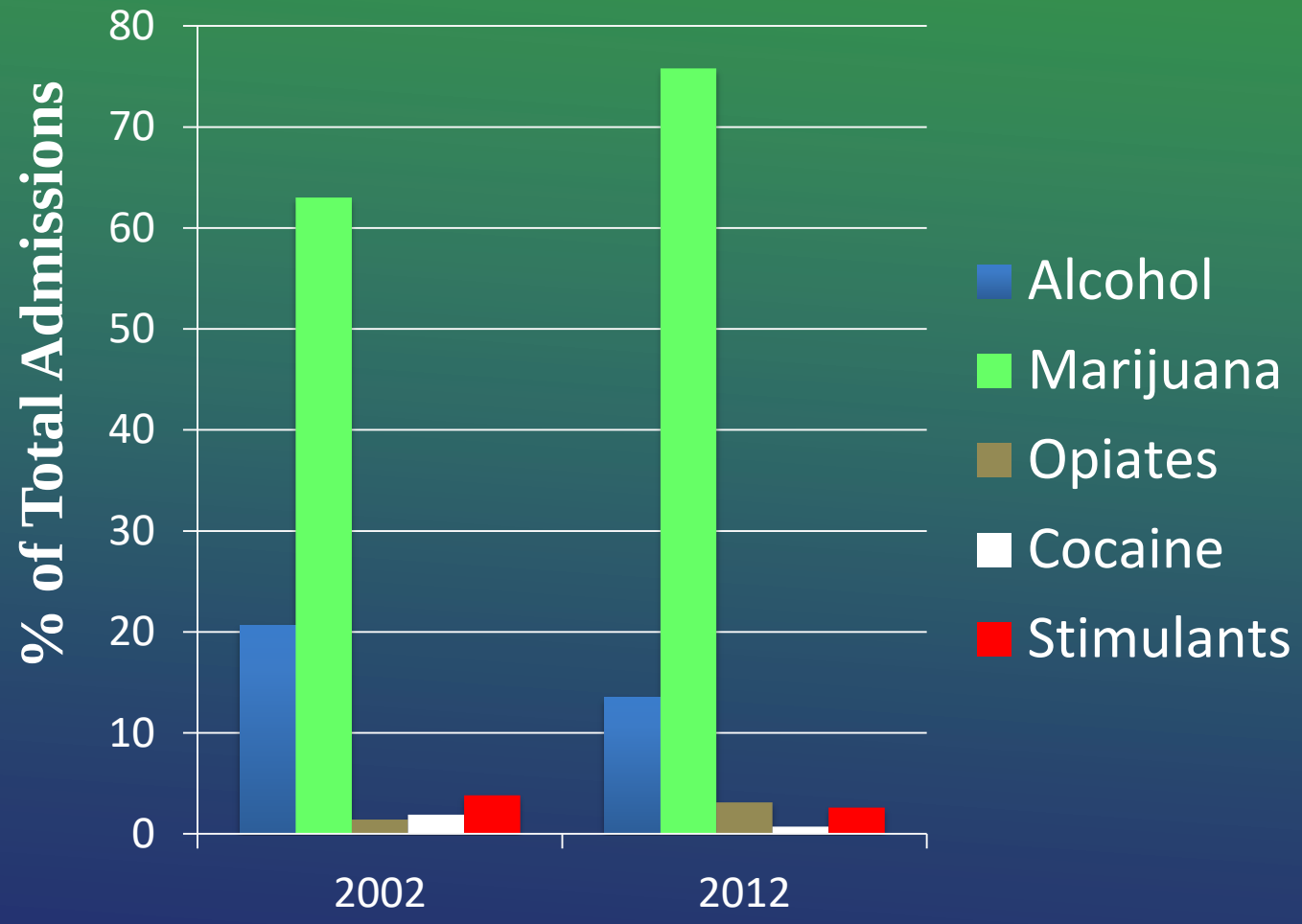
- NHSDU: only shows 12% increase
- MTF (youth): similarly lower rate of increase

What do we know about the prevalence of treatment seeking for CUD?

Treatment Admissions Primary Substance 2012 TEDS Data (12 and older)



Treatment Admissions Primary Substance 2012 TEDS Data (12 – 17 years)



Persons with CUD make up a substantial proportion of treatment admissions!

What do we know about how effective treatment is for CUD?

Pharmacotherapy / Medications

Potential Targets:

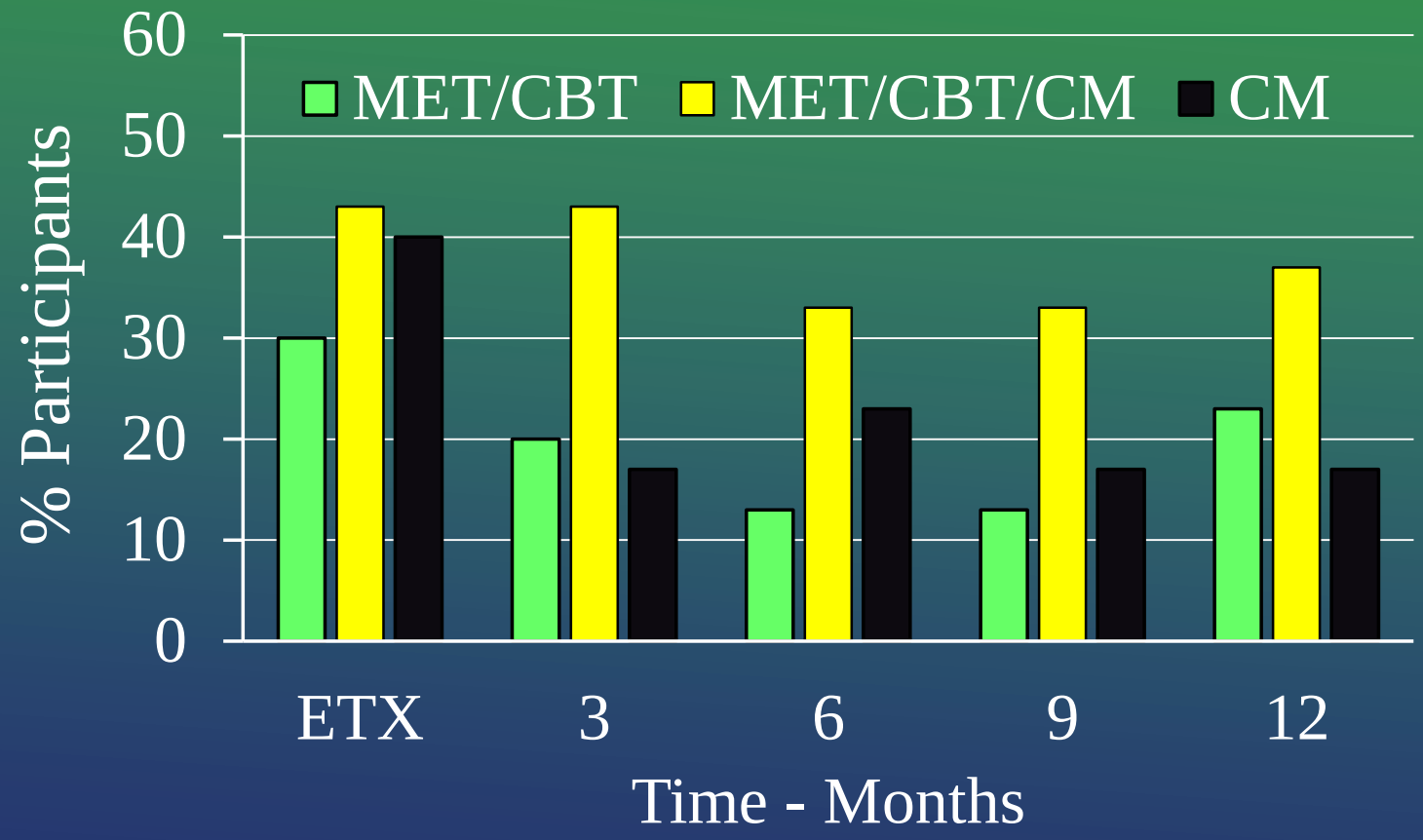
- Withdrawal symptoms: mood, sleep, anxiety
- CB1 receptor agonist substitution
- CB1 antagonists
- Opioid antagonists
- GABA and Glutamate (Gabapentin, NaC)
- Enzymatic targets (FAAH)

**** No robust findings to date!**

Published Randomized Trials
Behavioral Treatments (Adults)

Stephens, et al. (1994)	SS, CBT
Stephens, et al. (2000)	MET, CBT
Budney et al. (2000)	MET, MET/CBT, MET/CBT/CM
Copeland et al. (2001)	MET/CBT
MTPG (2004)	MET, MET/CBT
Budney et al. (2006)	MET/CBT, CM, MET/CBT/CM
Carroll et al. (2006)	MET/CBT, DC, MET/CBT/CM, DC/CM
Kadden et al. (2007)	MET/CBT, CM, MET/CBT/CM
Kay-Lambkin (2009, 2011)	MET/CBT (computerized)
Budney et al (2011, 2015)	MET/CBT/CM (computerized)
Carroll et al (2012, 2013)	CBT, CM, CBT/CMabst, CBT/CMhmk
Litt et al. (2013)	CaseM, CBT/CMabst, CBT/CMhmk
Hoch et al (2014)	CANDIS (MET/CBT/Problem Solving)

Motivational Incentives Enhance Point PrevalenceAbstinence



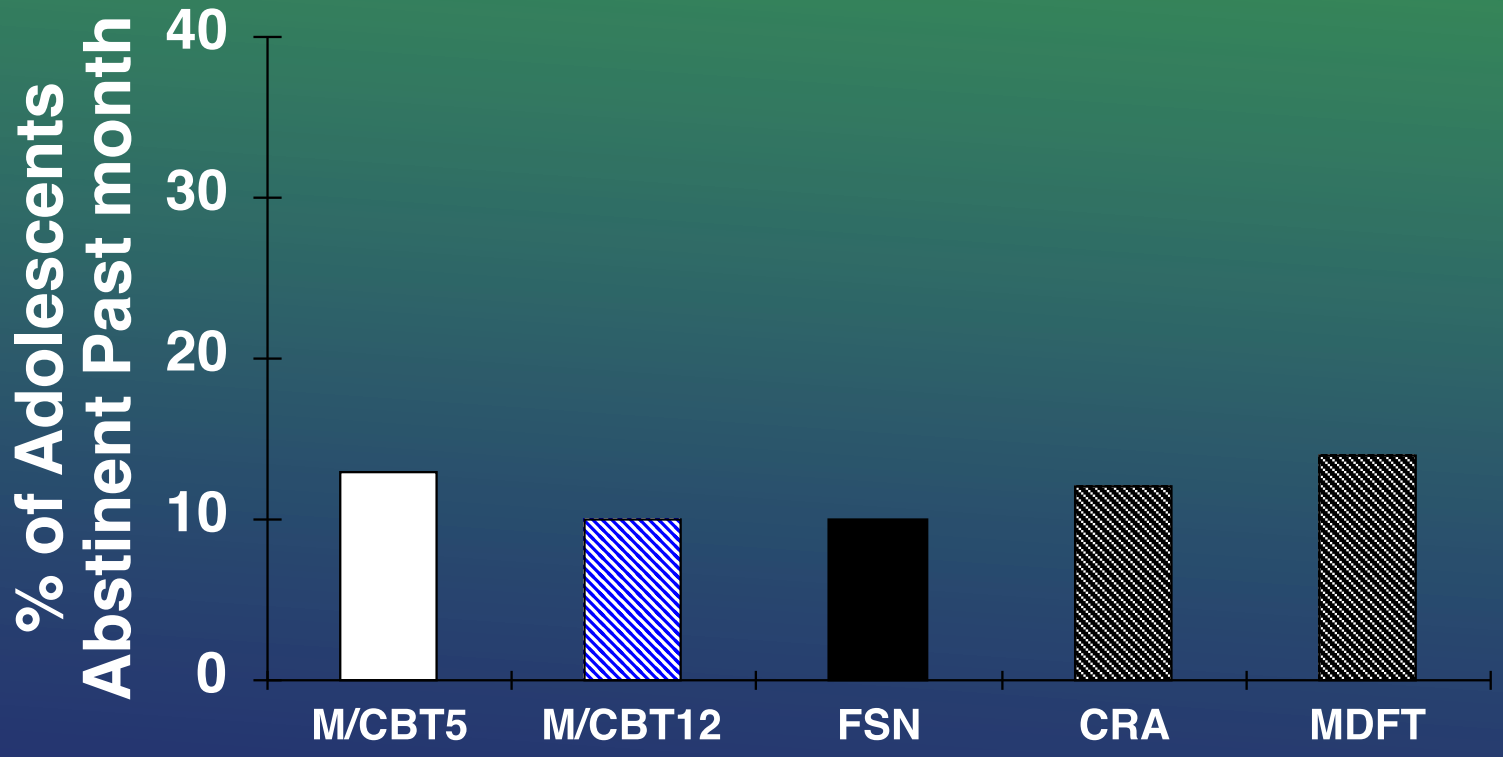
(Budney et al. 2006); replicated in Carroll et al, 2006 and Kadden et al., 2007

Adolescent Treatment Literature

Family-based and group/individual behavioral interventions (Waldron 2008: review)

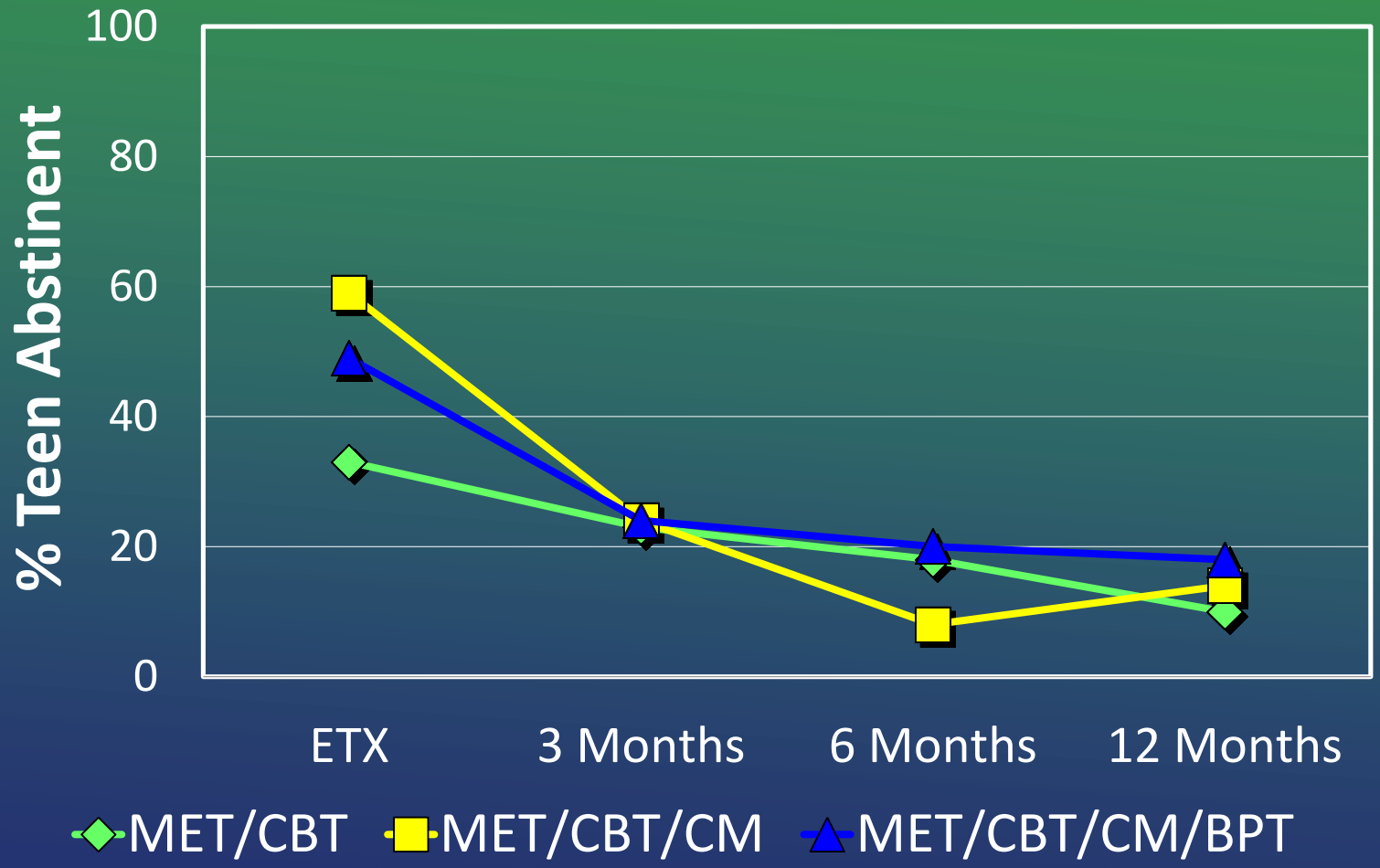
Waldron et al.	FFT, CBT, combo
Liddle et al.	MDFT
Henggeler et al.	MST
Dennis et al./Godley et al.	MET/CBT, ACRA, FSN
Kaminer et al.	MET/CBT
Szapocznik et al.	BSFT
Stanger, Budney et al.	CM

Cannabis Youth Treatment Study
Abstinence at Discharge



(Dennis et al. 2004)

Incentives Enhance Abstinence Outcomes During but not Post Treatment



Stanger et al. 2015

CUD Treatment for Youth and Adults

Not yet identified effective Pharmacotherapy

Behavioral treatments are efficacious

Access to efficacious treatments is poor

Many people do not respond

Youth response appears lower than with adults?

Success in disadvantaged populations is low?

**** Much room for Improvement**

How Do We Improve?

Behavioral Science and Neuroscience Provide Targets

- Enhance Delivery Systems / Improve Access
- Endogenous Cannabinoid System; Withdrawal Syndrome
- Genetics
- Improve Brain Function / Impulsivity / Decision Making
- Innovative Incentive Programs
- Target Concurrent Tobacco Use
- Target Non-responders
- Innovative Use of Technology
- Extend Reach to Intervene with More Problem Users

What We Know About the Impact of the **Changing Landscape of Cannabis Laws and Regulations**

Potential for Positive and Negative Impact

- Higher Potency / New Products / New Delivery Systems
- Impact on Use, Attitudes, Perceived Risk
- Impact on Health, Public Safety
- Addiction / Problematic Use
- Science: Understanding of Cannabis

Legalization: "Medical" / "Recreational"

(20-30 minutes)

- Why is this important to Psychologists?
  - Unregulated Medicine? Populous Medicine?
  - Data-based; Empiricism
- Approvals/Conditions
- Nature of the Supportive Science
- What's real / what's not?
- Adverse Effects? What is tolerable?

A Changing Landscape of Cannabis Laws

- Medical marijuana legal in 28 states and DC
- Recreational marijuana legal in 8 states plus DC
- Both medical and recreational laws vary greatly by state
  - Approved medical conditions (in medically legal states)
  - Dispensaries allowed
  - Possession limits
  - Type of marijuana regulated (i.e. plant, edibles, concentrates)
- Legalization increases access to novel and potent forms of cannabis with little knowledge of consequences to public health

Reefer Madness
High Potency Cannabis Products

Reefer Madness Edibles

Reefer Madness Devices

The “Farmacy” and the Market

EXPOs

KUSH EXPO
WINNER
BEST VAPE PEN
WINNER
BEST EDIBLE
LIQUID GOLD
LIQUID GOLD
BARS
GFarmaLabs

Medical Cannabis Landscape:

What “should” you know before approving / prescribing cannabis for a medical or psychiatric condition?

Approved Medical Conditions across States

- Cachexia, cancer, chronic pain, epilepsy and other disorders characterized by seizures, glaucoma, HIV or AIDS, multiple sclerosis and other disorders characterized by muscle spasticity, and nausea, Hepatitis C, ALS, Crohn's disease, Alzheimer's disease, anorexia, arthritis, migraine, Parkinson's disease, posttraumatic stress disorder, decompensated cirrhosis, muscular dystrophy, severe fibromyalgia, spinal cord disease (including but not limited to arachnoiditis), Tarlov cysts, hydromyelia syringomyelia, Rheumatoid arthritis, fibrous dysplasia, spinal cord injury, traumatic brain injury and post concussion syndrome, Arnold-Chiari malformation and Syringomelia, Spinocerebellar Ataxia (SCA), Parkinson's Disease, Tourette Syndrome, Myoclonus, Dystonia, Reflex Sympathetic Dystrophy, RSD (Complex Regional Pain Syndromes Type I), Causalgia, CRPS (Complex Regional Pain Syndrome Type II), Neurofibromatosis, Chronic inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyneuropathy, Sjogren's Syndrome, Lupus, Interstitial Cystitis, Myasthenia Gravis, Hydrocephalus, nail-patella syndrome or residual limb pain; terminal illness with a life expectancy of under one year, one or more injuries that significantly interferes with daily activities as documented by the patient's provider, Huntington's disease

Product / Medication / Drug / Herb

- What the medication is and its availability
- How much is needed (dose); schedule of dosing; course of treatment; tolerance?
- Its relative efficacy to safety profile; specific to the patient
- Available alternatives

REVIEW Open Access

Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders

Katherine A Belendiuk[1], Lisa L Baldini[2] and Marcel O Bonn-Miller[3,4,5*]

Addiction Science & Clinical Practice (2015)
www.ncbi.nlm.nih.gov/pubmed/25896576

Belendiuk et al., 2015

Common conditions shared by > 80% of MML states:

- Alzheimer’ s disease
- Cachexia/wasting synd.
- Crohn’ s disease
- Glaucoma,
- HIV/AIDS,
- Severe & chronic pain- severe nausea.
- amyotrophic lateral sclerosis
- cancer
- epilepsy and seizures
- Hepatitis C
- MS / muscle spasticity
- Post-traumatic stress disorder (PTSD)

*… for the majority of these conditions, there is insufficient evidence to support the recommendation of medical marijuana at this time

Additional Suggested Reading:

Medical Marijuana: Review of the Science and Implications for Developmental-Behavioral Pediatric Practice

Hadland, SE, Knight, JR, Harris, SK. J Dev Behav Pediatr 36:115–123, (2015)

Does Cannabis Cause, Exacerbate or Ameliorate Psychiatric Disorders? An Over-simplified Debate Discussed. M. Haney, A.E. Evins *Neuropsychopharmacology*, August 2015

Suggested Reading:

Does Cannabis Cause, Exacerbate or Ameliorate Psychiatric Disorders? An Over-simplified Debate Discussed. M. Haney, A.E. Evins *Neuropsychopharmacology*, August 2015

www.nature.com/npp/journal/vaop/naam/abs/npp2015251a.html

Medicinal Cannabis: Challenges and Needs

Cannabis studied in context of illicit not medical use

Cannabinoids more so than cannabis studied

Highly variable plant(s) over 100 “active” compounds

Education needed for clinicians and patients

Data needed to determine effects, side-effects & risks

Product? Potency? Dose? Route of Administration?

Basic Behavioral and Clinical Pharmacology

With Cannabis it's all about THC dose …or is it?

- Cannabidiol?
- Over 100 compounds; over 70 phytocannabinoids

Potency / Dose Matter!

THC Potency

Lab studies have not gone **above 8% THC**, and only one study has gone that high.

- confiscated cannabis **averaged 12.8%** in 2012

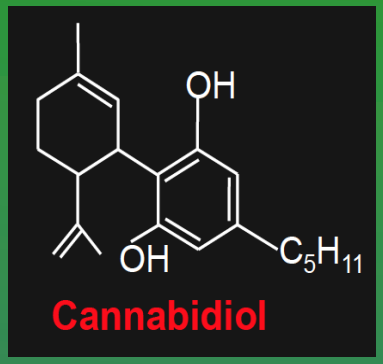
Existing data on lab and epidemiological studies capture results from use of much lower THC levels than now used

Need to learn more about higher % THC products!

Unlike alcohol, we do not have current norms on a standard dose (drink) and how much you can use before becoming "intoxicated", or in medical danger

Unlike alcohol – different methods of administration

Cannabidiol (CBD)



Cannabis plants have varying amounts of CBD

Suggestive data that it may *moderates effects of THC*

- Potential as an anxiolytic?
- Potential as an antipsychotic?
- Marketed (like marijuana) as a medication for multiple problems: e.g., epilepsy, SUDs!
- 1:1 ratio with THC in Sativex (approved medication)

Recent lab study suggests effects are not so clear?

- appeared almost inert when studied carefully in experienced cannabis users

Schubart et al. (2013); Neisink et al. (2013) Haney et al., (2015)

KanaVape is legal, natural and tasty

Developing a legal hemp vaporizer meant pushing the edge of science. True to the original plant while avoiding the combustion and smell, KanaVape brings you a premium CBD rich hemp e-liquid in a stylish vaporizer pen. Keep a clear mind and an active lifestyle with KanaVape – anytime, anywhere.

Summary: Potency / Product

- Cannabis is not just THC
- Cannabidiol ≠ Cannabis or Marijuana
- Need data on higher % THC
- Need data on Cannabidiol and THC/Cannabidiol
- Know little about how dose interacts with method of use

Are the Products What They Appear?

Vandrey et al. (2015)

- Edible cannabis products (N=75) purchased from medical dispensaries
- 3 quasi-randomly selected stores in San Francisco, Los Angeles, and Seattle
- State-approved patients given budget of $400 to purchase variety of products

	Accurate	Under	Over
#, % Products	12 (17%)	17(23%)	45 (60%)
THC, mg			
- label	15 - 200	20 - 1000	2 - 325
- actual	15 - 183	34 - 1246	<1 - 267
Discrepancy (Mean, SD) (Max)	 -3 (4) 9	 28 (13) 55	 - 47 (29) -99

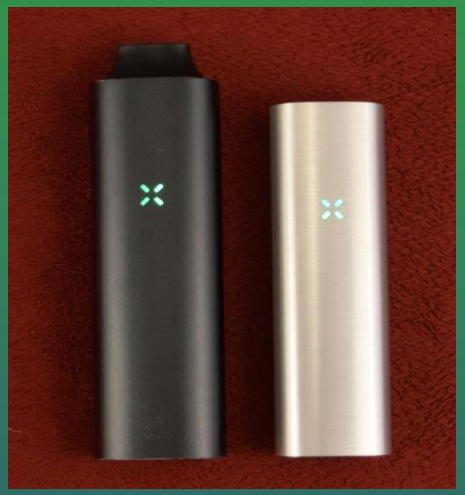
Route of Administration

Smoking vs. Vaping vs. Eating

- onset, timecourse, euphoric effects, adverse effects

Vaping Devices

Desktop



Portable

Pens

Differences between devices:

- Cost
- Temperature control
- Type of cannabis (i.e. plant vs. concentrate)
- Discretion

Other Vaping Devices

Dabbing

Water pipe (generally made of glass)

Uses blowtorch/nail to vape product

Concentrates/oils/extracts

Many different custom devices (called dabs or oil rigs)

Vaping

“Vaping” is the slang term for the vaporization of substances (e.g., flavors, nicotine, or cannabis products) whereby liquid, oil, or plant material is heated to a temperature that releases an aerosolized mixture of water vapor and active ingredients (e.g., nicotine in e-cigs and THC in cannabis), which is then inhaled.

Avoids combustion of the substance and the inhaling of smoke, which contains carbon monoxide and other by-products of combustion.

Vaping: Knowns and Unknowns

Benefits

- Clear harm reduction impact with respect to respiratory / lungs / carcinogenic factors.
- Facilitate use of cannabis for medical purposes (titrate, no combustible smoke, etc.).

Concerns

- long-term effects of frequent vaping are unknown.
- may have a positive impact on cannabis initiation, problem development and maintenance?
  - better tasting, more efficient high, more discreet use, combined with flavors or nicotine, attractive packaging, part of an evolving vaping culture, **perceived as safe**

(Budney et al., 2015 *Addiction)*

Youth Concerns: Vaping Culture

- FLAVORS, NICOTINE, CANNABIS, CAFFEINE
  - Earlier Initiation? Combine Products
  - Initiation by Youth at Lower Risk?
  - More frequent use?
  - More problematic use?
  - Health Concerns?

DIXIE

GREEN HORNET

MEDICAL
CANNABIS
DARK CHOCOLATE
PURE INDICA
Minimum Cannabinoid Content 60 mg
NET WT. 1.6 oz / 45 g
The Marijuana Report.com

DARK
CHOCOLATE
+SEA SALT
& 4.20 GRAMS OF
MEDICAL CANNABIS
THE
4.20
BAR
EH
EVERGREEN

Edi-Pure
Sweet 'n Sour
25 X 10mg Value Pack
250mg Active THC
450mg Trichome Oil Extract
For Medical Use Only
Keep From Children
Edi-Pure
Peach Tarts
10 X 25mg Value Pack
250mg Active THC
450mg Trichome Oil Extract
For Medical Use Only
Keep From Children
Edi-Pure
Peanut Butter
Sandwich
125mg THC 5 x 25mg
Keep Out of Reach of Children

105mg THC
PATTY'S
PEPPERMINT

Edi-Pure
Fried Apple
Pie
Edi-Pure
Crème Filled
Cupcake
125mg THC Infusion
Edi-Pure
Crème Filled
Cupcake
125mg THC Infusion
Keep Out of Reach of Children

Edibles

- Onset much slower, eventually similar effects
    - “overdose” concerns
- Increase access and ease of use
- Discreet
- Reinforcing taste in addition to drug effect

Edibles: Concerns

Labels related to dose and onset of effects?

- Why are all these cannabis products needed?
  - alcohol lollipops, alcohol in chocolate?
  - caffeine???
- What is their purpose.... Marketing to youth, easier to ingest, sell as much as possible?
- Child protective packaging?
- Overdosing / Toxic Accidents

IMPACT ON PROBLEM DEVELOPMENT

Medical and Recreational Laws:

- Perceived Risk, Availability, New Products

Cannabis Products:

- Potency, Attraction, Reinforcing Efficacy

Delivery Devices:

- Safety, Efficiency

Advertising / Competition / Sales:

- Cost, Attraction, Nudging

Product Packaging / Labeling:

- Attraction, perception of risk or benefit

What We Know:

1. Cannabis has substantial addictive potential
2. CUD is common, resembles other SUDs, and may be increasing
3. Interventions for CUD have efficacy, but there is much room for improvement
4. Factors that influence the probability of CUD are similar to other SUDs
5. Changing Laws and Regulations will impact the development and prevalence of CUD

What We Still Need to Know:

1. How to translate knowledge into more effective CUD prevention and treatment – efficacy and dissemination
2. How to best communicate accurate information about cannabis use and its associated risks to the public
3. How to address the changing legal and regulatory systems to minimize impact on rates and consequences of CUD

The emerging legislation on cannabis in the US and elsewhere strongly indicates an urgent need for a major push for Cannabis Regulatory Science

How Science Works

Silver Lining

- stimulating thoughtful and important science and discourse related to cannabis and drug policy

- more objective, thoughtful contemplation of pros and cons

- Perhaps More Effective Prevention Messaging?

- maybe develop some potent therapeutic compounds

In the end, more rational policy and regulation…

Take Home Messages

Science and Common Sense Policy is Needed Now More than Ever

Educate yourself through traditional means: read the scientific literature!

Also get on the Internet!

Funding and Support

NIDA research and training awards
NIAAA research awards

University of Vermont
University of Arkansas for Medical Sciences
Dartmouth College, Geisel School of Medicine

THANKS!!!!

Faculty/Trainees	Staff / Therapists
Cathy Stanger	Patty Costello
Stephanie Fearer	Eliza Wessinger
Brent Moore	Gray Norton
Ryan Vandrey	Leanna Delhey
John Hughes	Lee Whetstone
Steve Higgins	Doris Ogden
Warren Bickel	Jonathan Young
Denise Walker	Heath Rocha
Roger Roffman	Andrea Meier
Bob Stephens	Merrie Vannucci
Pam Brown, Jen VanScoyoc	Marlo Lowe
Stacy Ryan	Bobby Ward
Amanda Elton / Clint Kilts	Sarah Clark
Jody Kamon	Nancy Culbertson
Dustin Lee, Jacob Borodovsky	Stanley See, Hao Yang
Ben Crosier	Nick Tacke, Samantha Auty
James Sargent	Jennifer Darsie