Cannabis: From Diagnosis to Treatment

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Faculty Disclosure

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- Funding: National Institutes of Health (NIDA), Food and Drug Administration
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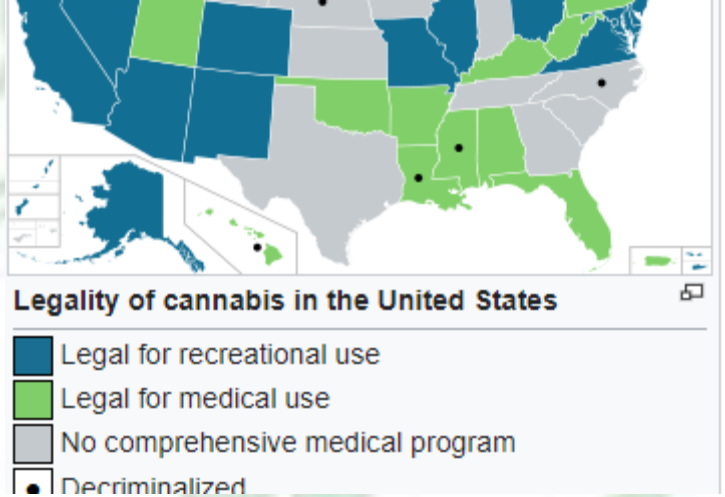
- (Co)Edited Update in ADHD Pharmacotherapy (Elsevier); *Straight Talk About Psychiatric Medications for Kids* (Guilford); *ADHD Across the Lifespan* (Cambridge), *MGH Comprehensive Clinical Psychiatry* (Elsevier), *MGH Psychopharmacology and Neurotherapeutics* (Elsevier); *Pharmacotherapy of ADHD*, Child Adolesc Psych Clin N Am (Elsevier)

Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g., substance use disorders)

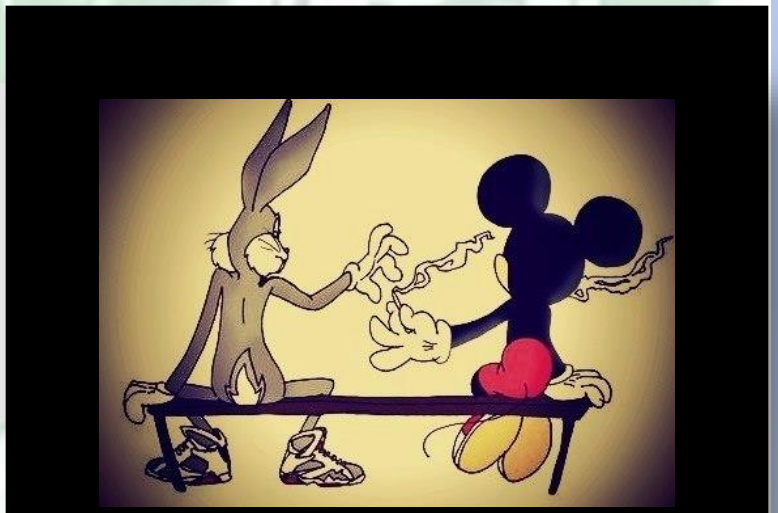


As of September 2024

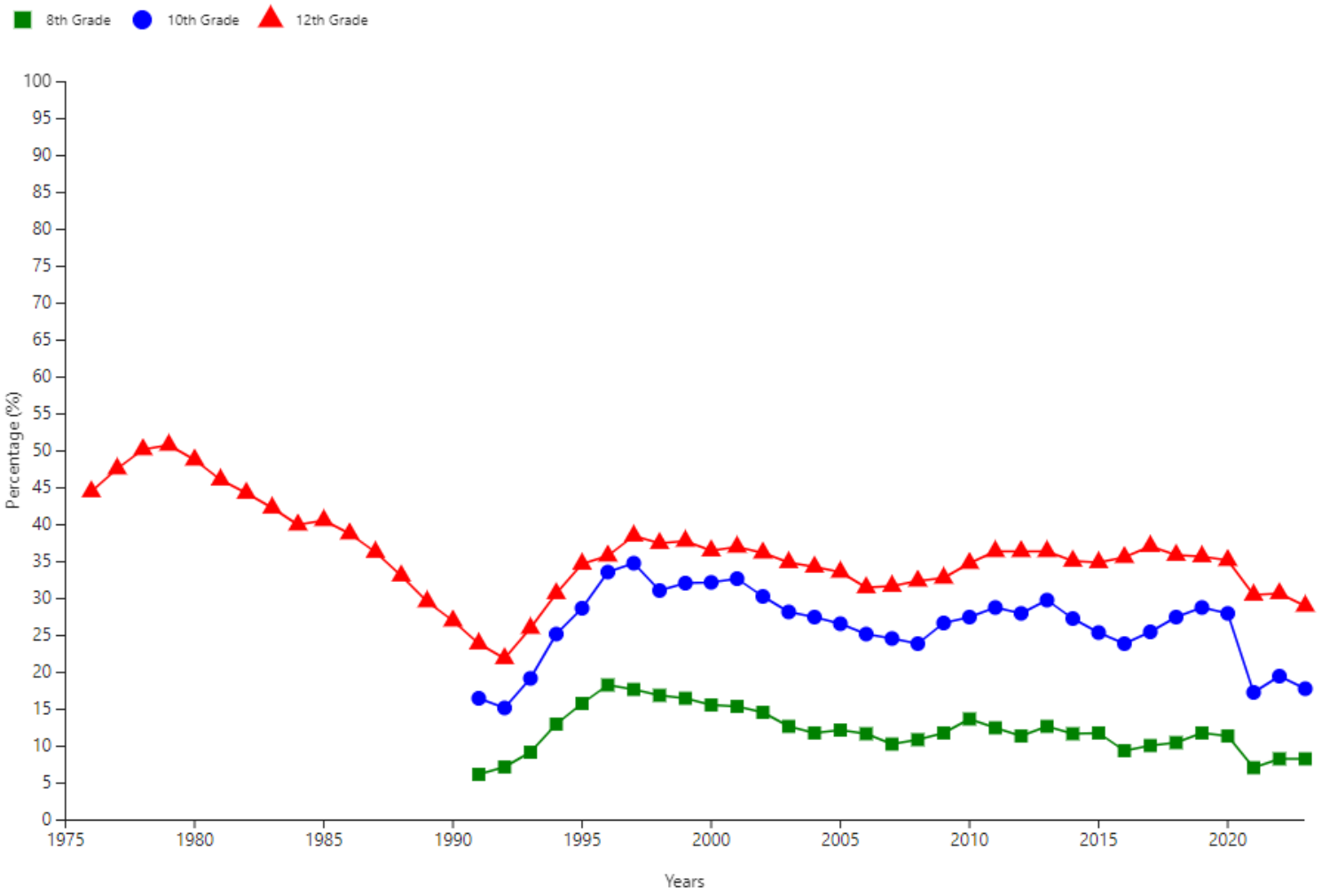
Medical: 39 States+ DC

Recreational: 24 States, 3 territories, DC

None: 4 States



Marijuana (Cannabis): Trends in Last 12 Months Prevalence of Use in 8th, 10th, and 12th Grade



12th Grade

10th Grade

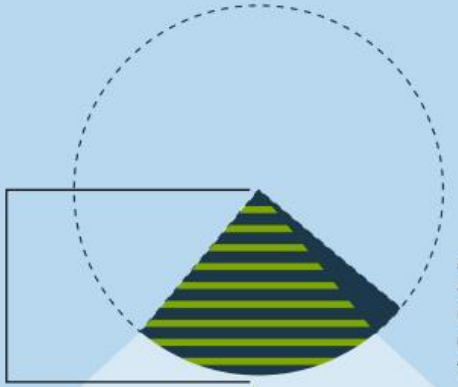
8th Grade

Miech, R. A., Johnston, L. D., Patrick, M. E., O'Malley, P. M., & Bachman, J. G. (2023). Monitoring the Future national survey results on drug use, 1975–2023: Secondary school students. Monitoring the Future Monograph Series. Ann Arbor, MI: Institute for Social Research, University of Michigan. Available at https://monitoringthefuture.org/results/annual-reports/

Illicit Drug Use in the Past Year

NSDUH asked respondents aged 12 or older about their use of drugs in the 12 months before the interview.

70.3 million
1 in 4
(24.9%) used illicit drugs in the past year.



24.7 million
(8.8%) used illicit drugs other than marijuana in the past year.

61.9 million
(22%) used marijuana in the past year.

22.7 million vaped marijuana in the past year.

7.4 million
About 1 in 5
people aged 12 to 20 used marijuana in the past year.

4.3 million
About 1 in 9
people aged 12 to 20 vaped marijuana in the past year.

NSDUH, 2022

Most Popular

The sanctions against Russia went from toothless to devastating overnight as its economy began collapsing. Here's a timeline


Ukraine's President Zelenskyy is calling for urgent EU membership—but is that even possible?


What is a 'no-fly zone' and how could it escalate the Ukraine-Russia conflict?

FINANCE • LEGAL MARIJUANA

Marijuana is worth more than alcohol to Massachusetts for the first time ever

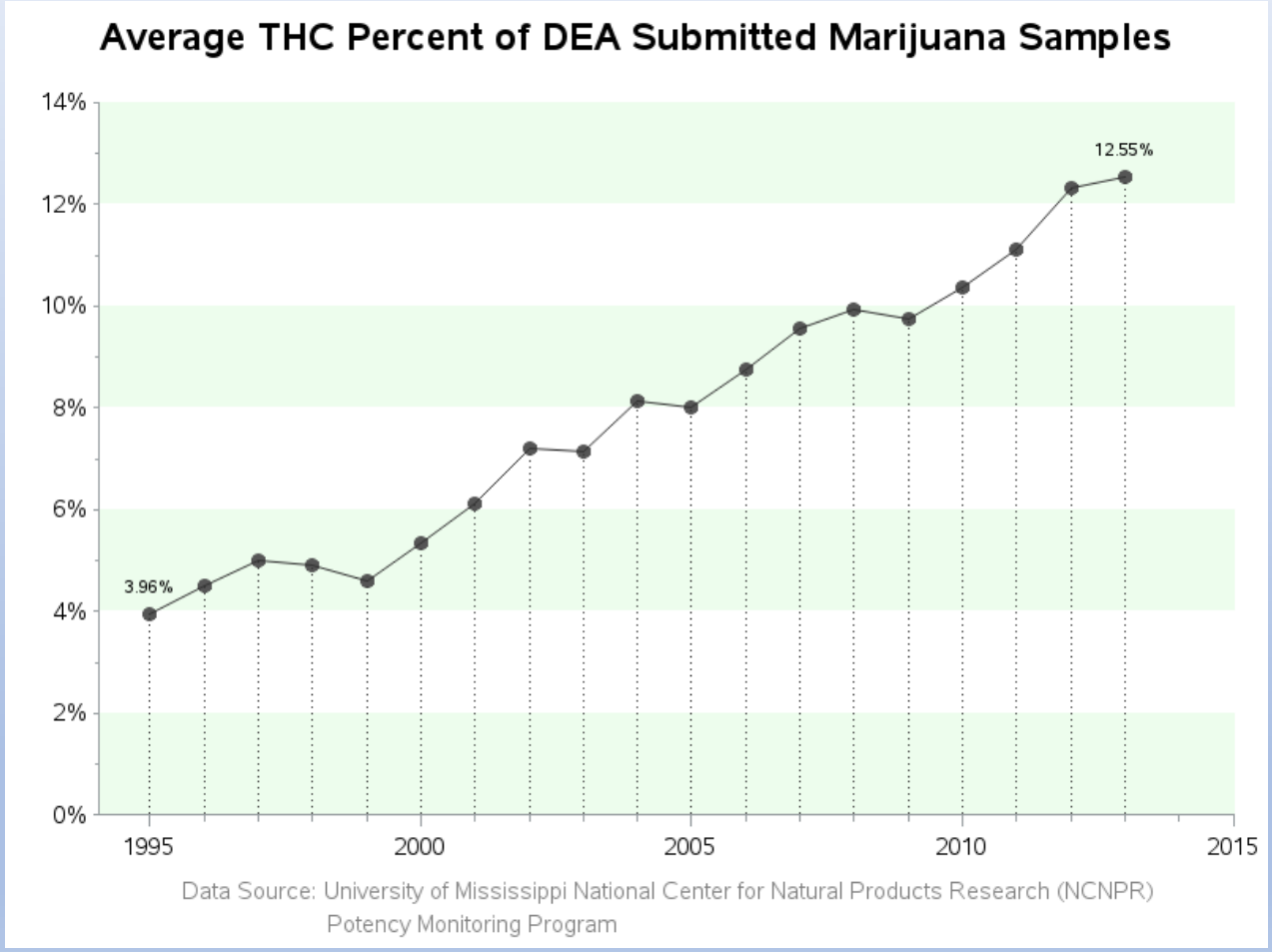
BY **NICOLE GOODKIND**

January 25, 2022 5:51 PM EST


AVERAGE COST OF MARIJUANA
Price For An Ounce Of Medium Quality Marijuana
$197
$187
$345
$244
$322
$330
$335
$248
$331
$287
$308
$297
$273
$300
$271
$287
$235
$311
$270
$227
$233
$302
$283
$255
$281
$299
$265
$283
$551
$234
$244
$200
$284
$272
$277
$233
$228
$266
$340
$250
$170
$229
$235
$243
$258
$305
$267
$227
$266
National Average Price of Medium Quality Marijuana
Source: User-Submitted Global Price Index of Marijuana
oxfordtreatment.com

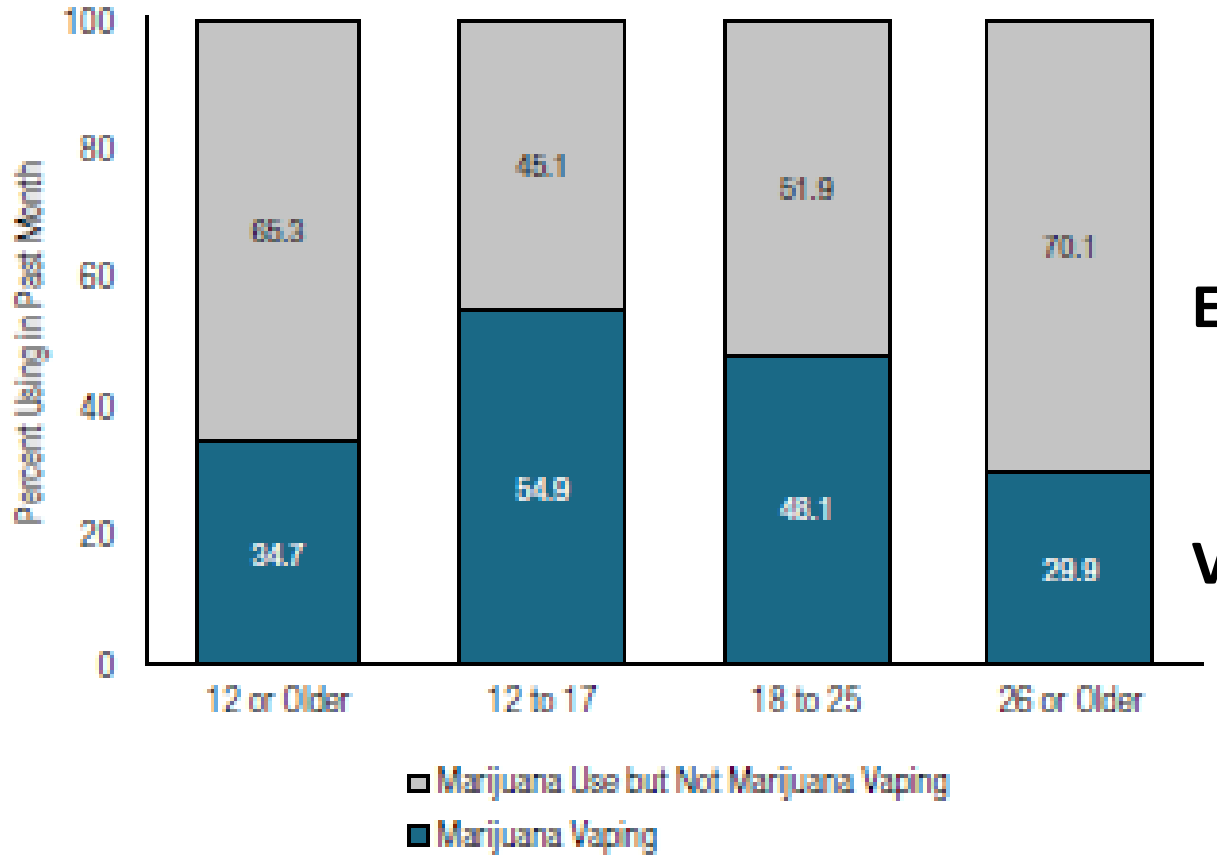
Marijuana Basics

Marijuana Potency Is Increasing Yearly



Current
14-16%

Figure 12. Type of Past Month Marijuana Use: Among Past Month Marijuana Users Aged 12 or Older; 2022



Edible, smoking

Vaping

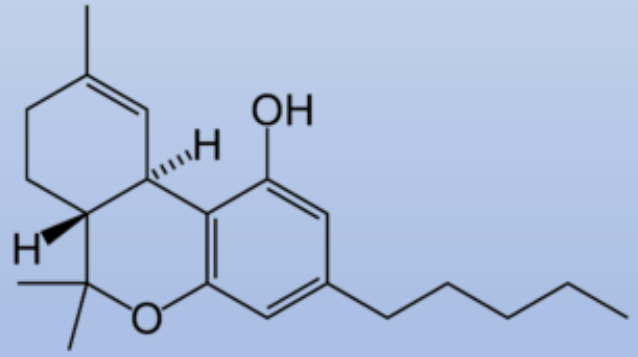
NSDUH 2022; SAMSHA Report 2023

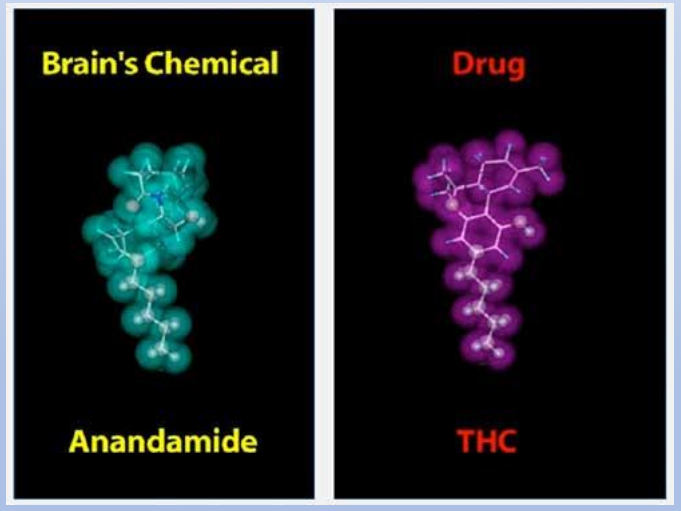
Marijuana Preparations

- **Smoked**
  - **Leaves of *Cannabis indiva (sedative)* vs *sativa (thoughts & feelings)* (much overlap genetically)**
  - **10-16% THC (vs 3-4% in the 70's and 80's)**
- **Hash**
  - **Resin of *cannabis indiva or sativa***
  - **5-40% THC**
  - **Powder referred to as "*Kief*" (trichome resin buds)**
- **Hash "Oil" (Wax)**
  - **Very potent distillate of hash**
  - **30-90% THC**
- **Edibles**
  - **Cannabis leaves, hash, hash oil**
  - **Delayed onset of euphoria, higher overdose rate**
- **Synthetic (K2, Spice)**
  - **Synthetic THC-like compounds**
  - **Very long duration of action, psychotogenic, seizures**
  - **Not picked up on routine toxicology testing**

Biochemistry of Marijuana

- Active Ingredients
  - Delta-9 Tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
- Binds to the cannabinoid receptors (brain, body)
- Similar to naturally occurring Anandamide
  - Sanskrit for “awe inspiring”





Pertwee, R (1997). “Pharmacology of cannabinoid CB1 and CB2 receptors”. *Pharmacology & Therapeutics*. 74(2):129–80; Tanda and Goldberg, *Psychopharm. (Berl).* 2003;169:115-34.

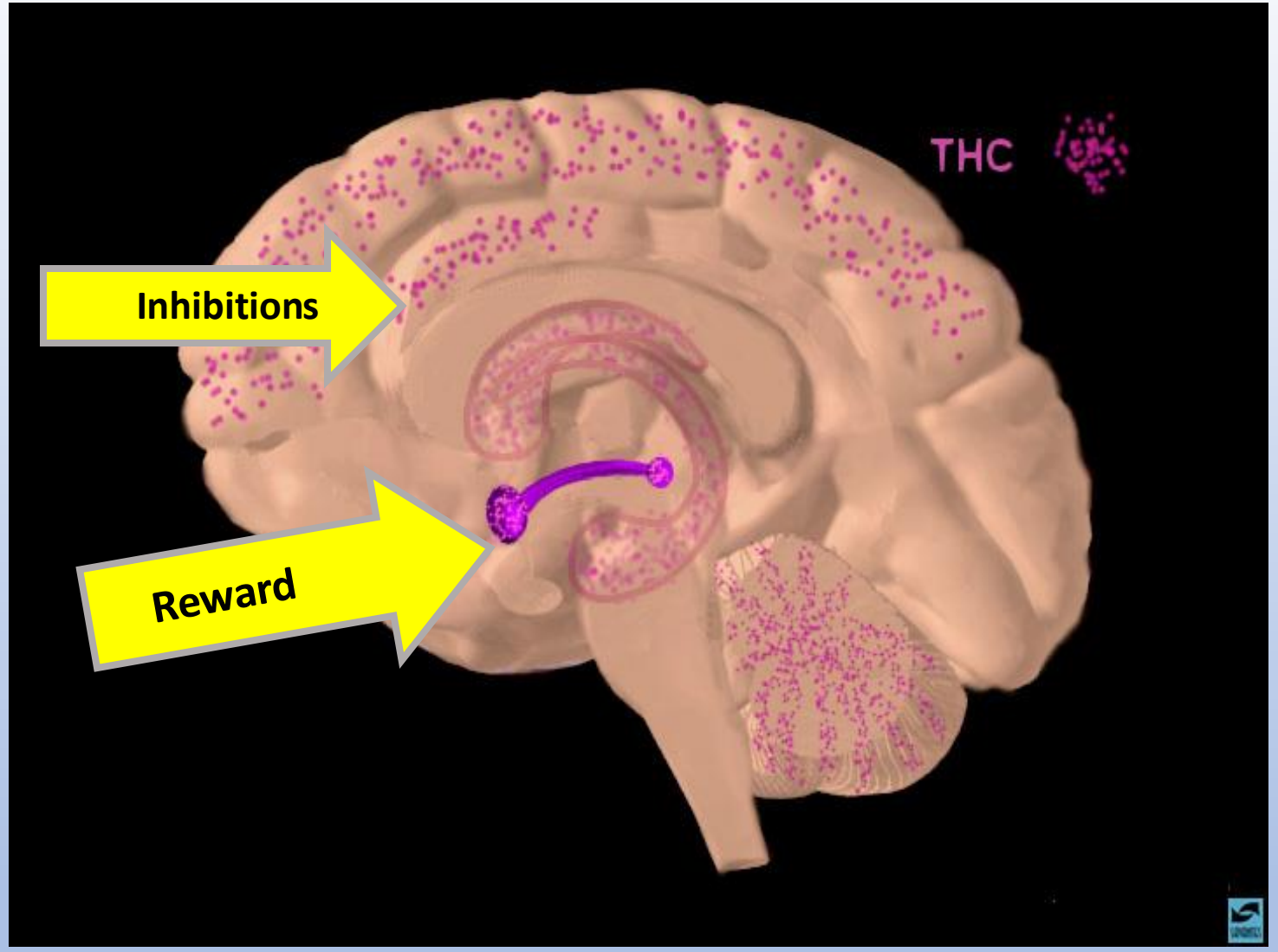
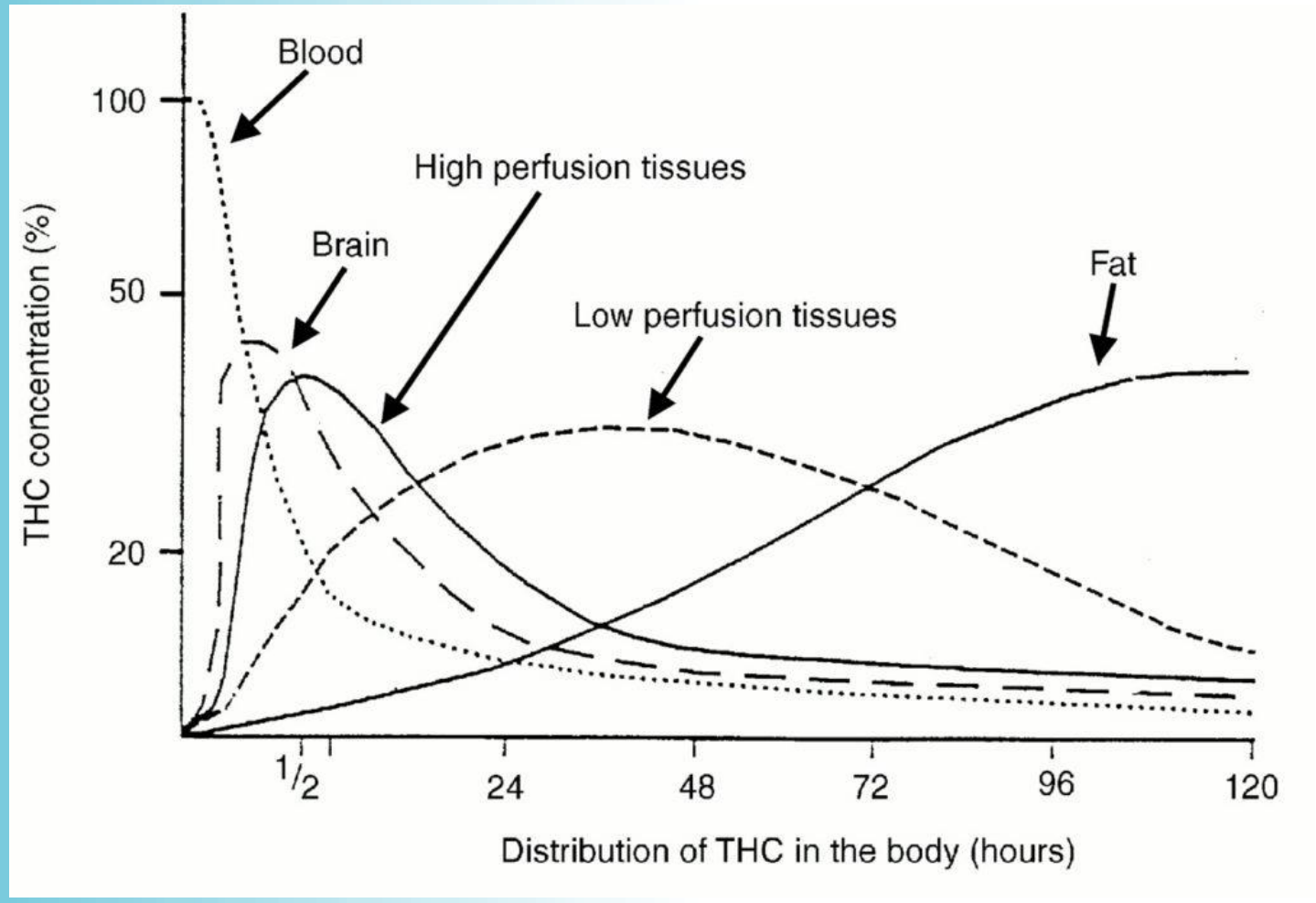


Photo courtesy of the NIDA Web site. From *A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana;* Wilens et al. *Contem Peds.* 2013.

Marijuana Distribution after Smoking

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Marijuana rapidly redistributes from blood to brain and other tissues. Distribution to fat is delayed.

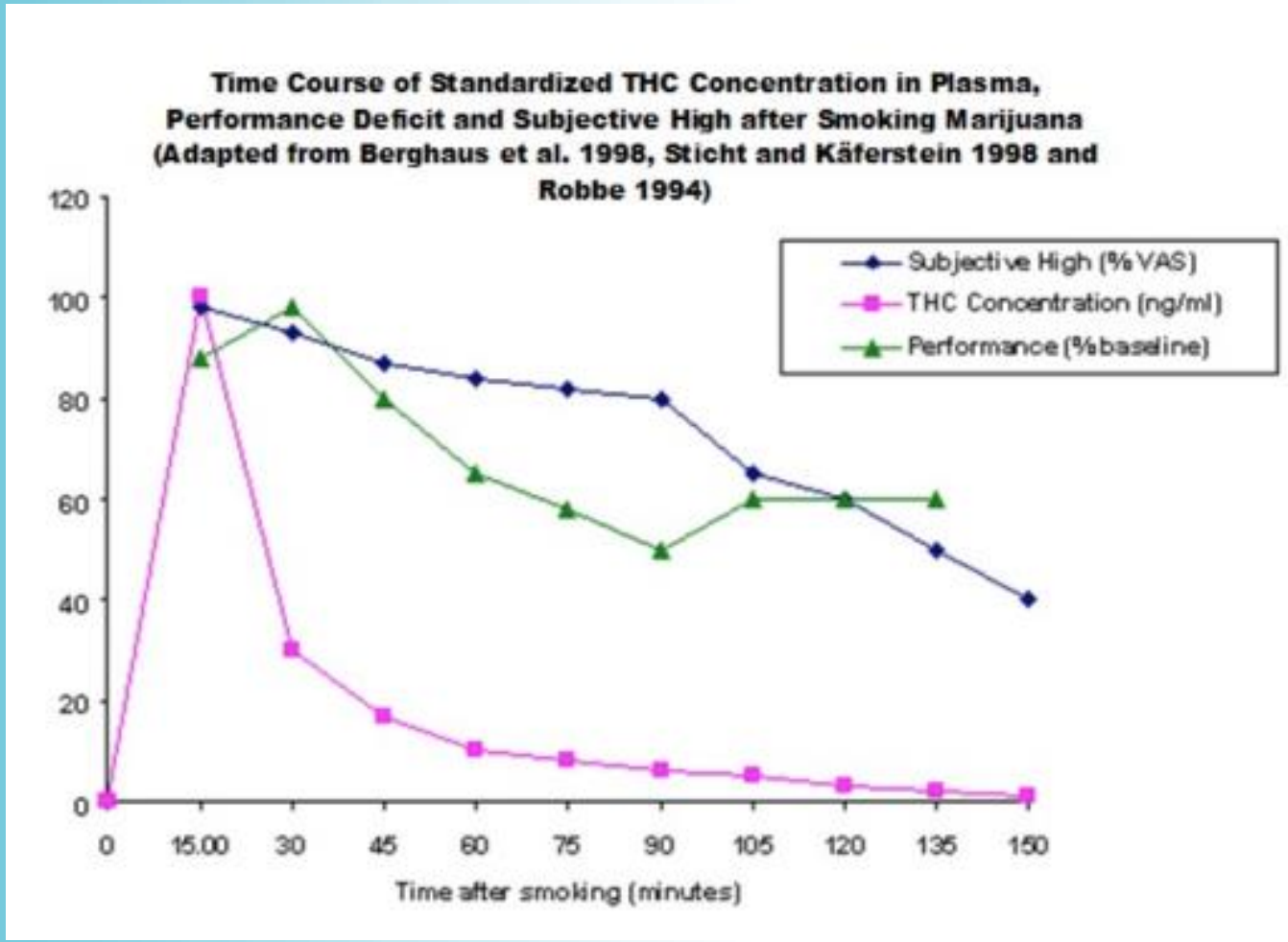


Wadieh E et al. Neuropsychiatric Effects of Marijuana, Addiction Medicine and Therapy. 2017. Vol 3(2): 61-64

Euphoria, Performance, and THC Levels

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Time course of smoked marijuana compared to performance difficulties and euphoria (VAS)



Robbe HWJ (1994). Influence of Marijuana on Driving. Institute for Human Psychopharmacology, University of Maastricht; Sticht, G. & Käferstein, H. (1995). Pharmacokinetic evaluation of published studies on controlled smoking of marijuana. In N. Kloeden & A. J. McLean (eds.), Alcohol, drugs and traffic safety (Vol.1, pp. 397-402). Adelaide: University of Adelaide, NHMRC Road Accident Research Unit

frontiers in Psychiatry

CLINICAL TRIAL
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Effects of Cannabidiol and Delta-9-Tetrahydrocannabinol on Emotion, Cognition, and Attention: A Double-Blind, Placebo-Controlled, Randomized Experimental Trial in Healthy Volunteers

*Timo Woelfl[1], Cathrin Rohleder[1,2], Juliane K. Mueller[1,3], Bettina Lange[1], Anne Reuter[1], Anna Maria Schmidt[1], Dagmar Koethe[2,4], Martin Hellmich[5] and F. Markus Leweke[1,2]**

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The two main phytocannabinoids—delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)—have been extensively studied, and it has been shown that THC can induce transient psychosis. At the same time, CBD appears to have no psychotomimetic potential. On the contrary, emerging evidence for CBD's antipsychotic properties suggests that it may attenuate effects induced by THC. Thus, we investigated and compared the effects of THC and CBD administration on emotion, cognition, and attention as well as the impact of CBD pre-treatment on THC effects in healthy volunteers. We performed a placebo-controlled, double-blind, experimental trial (GEI-TCP II; ClinicalTrials.gov identifier: NCT02487381) with 60 healthy volunteers randomly allocated to four parallel intervention groups, receiving either placebo, 800 mg CBD, 20 mg THC, or both cannabinoids. Subjects underwent neuropsychological tests assessing working memory (Letter Number Sequencing test), cognitive processing speed (Digit Symbol Coding task), attention (d2 Test of Attention), and emotional state (adjective mood rating scale [EWL]). Administration of CBD alone did not influence the emotional state, cognitive performance, and attention. At the same time, THC affected two of six emotional categories—more precisely, the performance-related activity and extraversion—, reduced the cognitive processing speed and impaired the performance on the d2 Test of Attention. Interestingly, pre-treatment with CBD did not attenuate the effects induced by THC. These findings show that the acute intake of CBD itself has no effect *per se* in healthy volunteers and that a single dose of CBD prior to THC administration was insufficient to mitigate the detrimental impact of THC in the given setting. This is in support of a complex interaction between CBD and THC whose effects are not counterbalanced by CBD under all circumstances.

Keywords: cannabinoids, cannabis, tetrahydrocannabinol, cannabidiol, healthy subjects, model psychosis, rct

CBD -> No Effects

THC -> reduced cognitive processing speed and impaired performance on the d2 Test of Attention

Medical Marijuana

FDA Approved Marijuana-Based Medications

TABLE 1 Cannabis Products

Products Generic (Brand)	Cannabinoid Content	Administration Formulation and Dosage	FDA Approval	Indications	Approved Countries
Dronabinol (Marinol and Syndros)	Synthetic δ-9-THC	Oral capsule or solution 5–15 mg/m^2 per dose, up to 6 doses daily	Approved in 1985, Schedule III controlled substance	CINV (pediatric and adult), anorexia associated with weight loss in AIDS (adult)	United States, Australia, Germany, New Zealand, and South Africa
Nabilone (Cesamet)	Synthetic δ-9-THC	Oral capsule 1 or 2 mg twice a day, up to 6 mg daily (adult)	Approved in 1985, Schedule II controlled substance	CINV	United States, Canada, Ireland, Mexico, and United Kingdom
Nabiximols (Sativex)	Ratio of 2.7 δ-9-THC to 2.5 CBD, plant derived	Oromucosal spray 1 spray daily, up to 12 sprays daily with at least 15 min between sprays (adult)	Phase III trials Schedule V	Neuropathic pain, cancer pain, multiple sclerosis spasticity	Canada, Czech Republic, United Kingdom, Denmark, Germany, Poland, Spain, and Sweden
CBD (Epidiolex)	CBD, plant derived	Oral solution 2 up to 50 mg/kg per d (research trials)	**Approved in 2018, Controlled V**	Epilepsy	None
Cannabis plant products (eg, marijuana and oral cannabis extracts)	Varying concentration of plant-derived THC to CBD	Includes smoking (marijuana) and oral (cannabis extracts)	None, Schedule I controlled substance	None approved	Medically and recreationally legal in certain states via physician certification

Wong SS, Wilens TE. Medical Cannabinoids in Children and Adolescents: A Systematic Review. *Pediatrics.* 2017 Nov;140(5).

Pediatric Epilepsy Studies of Medical Cannabinoids

Study by Indication Authors, y	Sample Size	Diagnoses (Inclusion Criteria)	Mean Age (Range)	Design	Medication	Measures	Findings
Epilepsy							
Devinsky et al,[12] 2017	61	Treatment-refractory epilepsy in Dravet syndrome	9.8 y (2.3–18.4)	RCT	CBD	Convulsive-seizure frequency	Reduced convulsive seizures compared with a placebo
Gofshteyn et al,[13] 2017	7	FIRES[a]	7.1 (3.9–8.5)	Open-label trial	CBD	Seizure frequency and duration, EEG	Reduced seizures in 86% of patients
Kaplan et al,[14] 2017	5	Treatment-refractory epilepsy in SWS	8.8 (2–19)	Open-label trial	CBD	Seizure frequency	Seizures improved in 60% of patients
Treat et al,[15] 2017	119	Epilepsy	7.5 (0.1–18)	Retrospective chart review	OCE	Seizure frequency	Seizures improved in 49% of patients, with 24% responders (>50% reduction)
Devinsky et al,[16] 2016	137	Treatment-refractory epilepsy	10.5 (1–22.2)	Open-label trial	CBD	No. of seizures, LAEP, PESQ	37% decrease in monthly motor seizures
Tzadok et al,[17] 2016	74	Treatment-refractory epilepsy	1–18	Retrospective chart review	CBD-enriched OCE	Seizure frequency	Reduced seizures in 89% of patients
Hussain et al,[18] 2015	117	Treatment-refractory epilepsy	6 (3–10)	Parent survey	CBD-enriched OCE	Seizure frequency	Reduced seizures in 85% of patients
Press et al,[19] 2015	75	Treatment-refractory epilepsy	7.3 (0.5–18.3)	Retrospective chart review	OCE	Seizure frequency	Reduced seizures in 57% of patients
Saade and Joshi,[20] 2015	1	MMPSI[a]	10 mo	Case report	CBD	Seizure frequency, EEG	Reduced seizure frequency
Porter and Jacobson,[21] 2013	19	Treatment-refractory epilepsy	9.1 (2–16)	Parent survey	CBD-enriched OCE	Seizure frequency	Reduced seizures in 84% of patients
Lorenz,[22] 2004	6	Neurodegenerative disease, mitochondriopathy, posthypoxic state, epilepsy	12.3 (8.8–14)	Case series	Dronabinol	Seizures	Reduced seizures in 2 of the patients

Wong SS, Wilens TE. Medical Cannabinoids in Children and Adolescents: A Systematic Review. *Pediatrics.* 2017 Nov;140(5).

TW_Published Article_A Scoping Review Cannabidiol in Psych_12 2021.pdf - Adobe Acrobat Reader DC (32-bit)

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Review article

A scoping review of the use of cannabidiol in psychiatric disorders

Anna E. Kirkland [a,*], Matthew C. Fadus [b], Staci A. Gruber [c,d], Kevin M. Gray [a], Timothy E. Wilens [b,e], Lindsay M. Squeglia [a]

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ARTICLE INFO

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Anxiety
Psychosis
Treatment
CBD
Clinicians

ABSTRACT

Cannabidiol (CBD) has become a fast-growing avenue for research in psychiatry, and clinicians are challenged with understanding the implications of CBD for treating mental health disorders. The goal of this review is to serve as a guide for mental health professionals by providing an overview of CBD and a synthesis the current evidence within major psychiatric disorders. PubMed and PsycINFO were searched for articles containing the terms "cannabidiol" in addition to major psychiatric disorders and symptoms, yielding 2952 articles. Only randomized controlled trials or within-subject studies investigating CBD as a treatment option for psychiatric disorders ($N = 16$) were included in the review. Studies were reviewed for psychotic disorders ($n = 6$), anxiety disorders ($n = 3$), substance use disorders (tobacco $n = 3$, cannabis $n = 2$, opioid $n = 1$), and insomnia ($n = 1$). There were no published studies that met inclusion criteria for alcohol or stimulant use disorder, PTSD, ADHD, autism spectrum disorder, or mood disorders. Synthesis of the CBD literature indicates it is generally safe and well tolerated. The most promising preliminary findings are related to the use of CBD in psychotic symptoms and anxiety. There is currently not enough high-quality evidence to suggest the clinical use of CBD for any psychiatric disorder.

The most promising preliminary findings are related to the use of CBD in psychotic symptoms and anxiety (adults)

Medical CBD May Be Effective in Dysregulated Young People with Autism Spectrum Disorders (ASD)

Retrospective chart review (Aran et al. J AutDevDis 2019)

-Mean age 11.8 years, 77% low functioning, 83% male

-Findings: CGI indicates 61% of youth improved

-Side Effects: sleep, irritability, loss of appetite

Retrospective study (Barchel et al., Front Pharm 2019)

-CBD:THC 20:1 oil; dose titrated to response in ASD youth

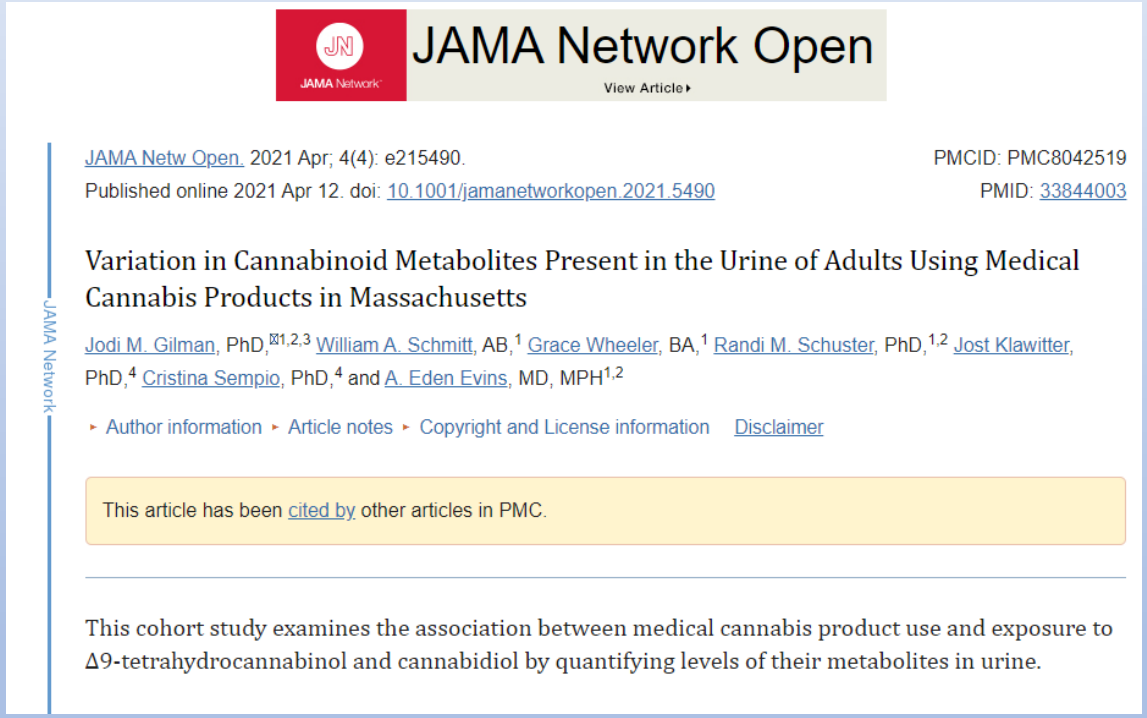
-N=53, Median age 11 year, treated for mean of 66 days

-Improvements in self-injury, rage-attacks, hyperactivity in two-thirds

-Sleep (N=23) improved in 75%, worsened in 7%

Anxiety (N=17) improved in 47%, worsened in 24%

Medical Marijuana May Not Contain CBD or THC



JAMA Network Open

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PMID: 33844003

Variation in Cannabinoid Metabolites Present in the Urine of Adults Using Medical Cannabis Products in Massachusetts

Jodi M. Gilman, PhD,[✉1,2,3] William A. Schmitt, AB,[1] Grace Wheeler, BA,[1] Randi M. Schuster, PhD,[1,2] Jost Klawitter, PhD,[4] Cristina Sempio, PhD,[4] and A. Eden Evins, MD, MPH[1,2]

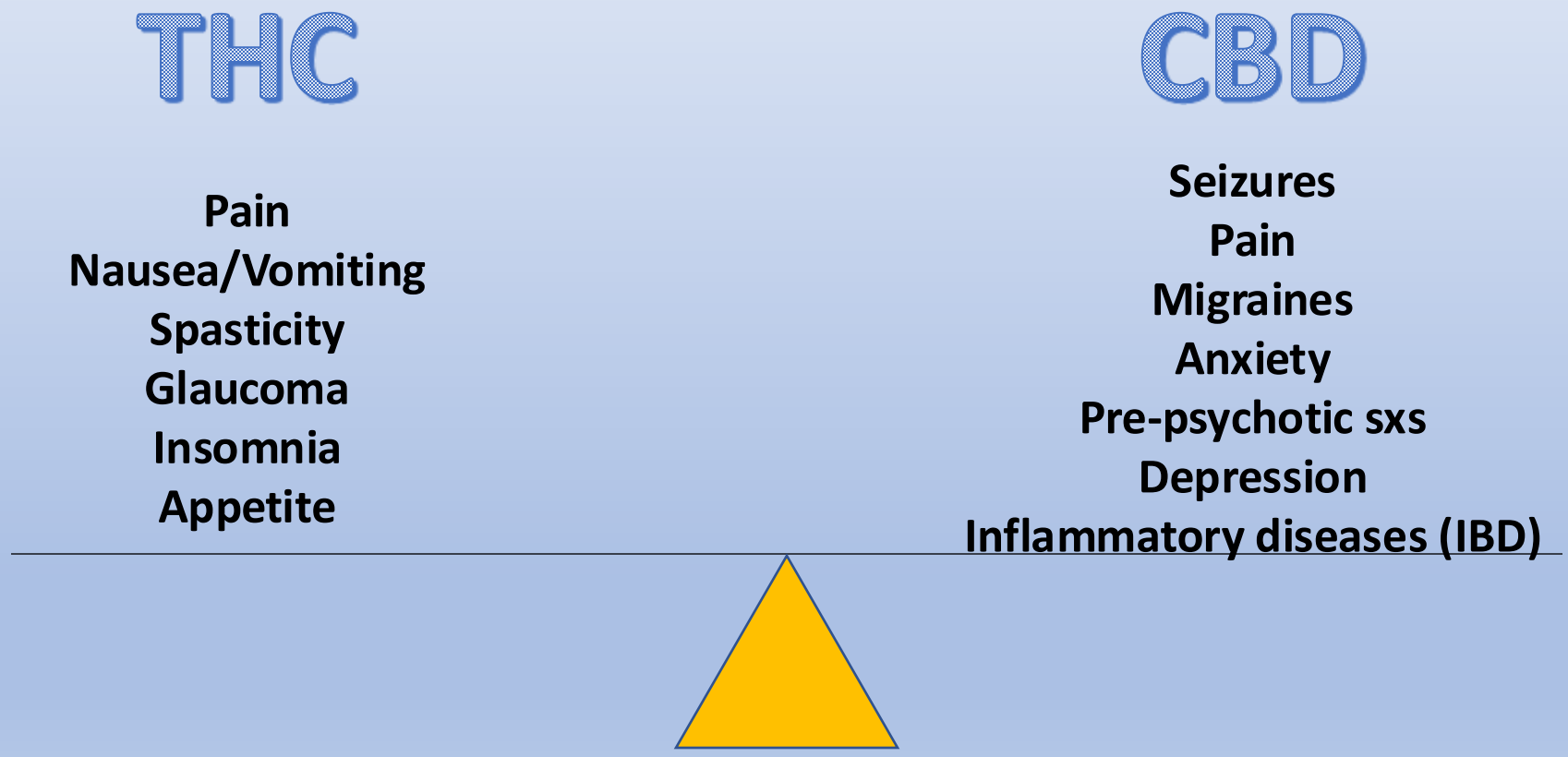
This cohort study examines the association between medical cannabis product use and exposure to Δ9-tetrahydrocannabinol and cannabidiol by quantifying levels of their metabolites in urine.

Study of Medical MJ
N = 97 (220 samples)
<u>Findings</u>:
Among CBD or CBD+THC products:
30% and 37% w/o CBD

In predominate CBD:
78% with THC

Among THC or THC+CBD products:
11% and 35% w/o THC

Putative Medical Uses of Major Constituents of Marijuana: THC & CBD



Prevention of Marijuana Misuse

MEDPAGE TODAY®

Pediatrics

AAP: Parents, Don't Smoke Pot in Front of the Kids

— Advice for families and their physicians

by Ryan Basen
Staff Writer, MedPage Today

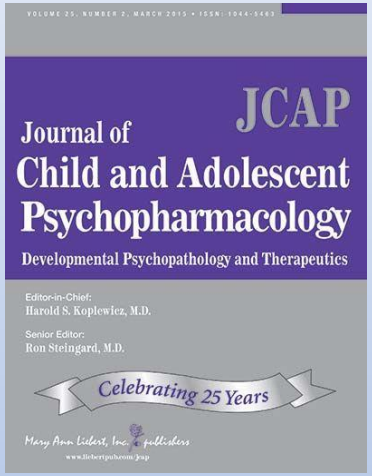
February 27, 2017

How Clinicians Can Help Prevent Marijuana Use

- Encourage non- judgmental discussion
- Parental monitoring of kids
  - Children's activities
  - Friends
  - Personal space
- Parental marijuana use ➔ children's use
- Advocate for sensible public laws around marijuana
  - Legalization issues
  - "0" tolerance policies
- Screen & Treat Mental Health issues

Longer Term Treatment of Childhood Psychopathology Reduces the Risk for Subsequent SUD

RESULTS



- PRISMA based search of the literature examining the long-term impact of treating psychopathology with pharmacotherapy in childhood
- N= 21 studies in ADHD, 2 studies on Major Depression, and 3 studies on psychotic disorders
- Majority reported reductions in SUD (N=14) followed by no effects (N=10) and enhanced rates of SUD (N=2)
- Earlier-onset and longer-duration treatment was associated with the largest SUD risk reduction

(Wilens et al., J Child Adolesc Psychopharm. November, 2022)

META-ANALYSIS SUBSTANCE USE

Systematic Review and Meta-Analysis: Medical and Recreational Cannabis Legalization and Cannabis Use Among Youth in the United States

Aditya K.S. Pawar, MD, Elizabeth S. Firmin, BA, Timothy E. Wilens, MD, Christopher J. Hammond, MD, PhD

Objective: Dramatic changes in state-level cannabis laws (CL) over the past 25 years have shifted societal beliefs throughout the United States, with unknown implications for youth. In the present study, we conducted an updated systematic review and meta-analysis examining estimated effects of medical cannabis legalization (MCL) and recreational cannabis legalization (RCL) on past-month cannabis use among US youth.

Method: A systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, followed by a subsequent meta-analysis investigating the associations between state-level cannabis laws (ie, MCL vs non-MCL, and RCL vs non-RCL) and past-month cannabis use prevalence among US adolescents and young adults. Supplemental analyses examined age-group effects and design-related factors.

Results: Our search identified 4,604 citations, 34 and 30 of which were included in qualitative and quantitative analyses, respectively. Meta-analysis of MCL studies identified no significant association between MCL and change in past-month youth cannabis use (odds ratio [OR] = 0.981, 95% CI = 0.960, 1.003). Meta-analysis of RCL studies showed significantly increased odds of past-month cannabis use (OR = 1.134, 95% CI = 1.116-1.153). Meta-analysis of more recent studies, however, showed a significantly increased odds of past-month cannabis use among both adolescents and young adults (OR = 1.089, 95% CI = 1.015,1.169, and OR = 1.221, 95% CI = 1.188,1.255, respectively).

Conclusion: Cannabis legalization has complex and heterogenous effects on youth use that may differ across law types. Our meta-analytic results showed modest positive effects of RCL on past-month cannabis use (more so in young adults than in adolescents) and minimal effects of MCL on these outcomes in US youth. Given the shift toward recreational legalization, additional focus on RCL effects is warranted.

Key words: recreational cannabis laws; medical cannabis laws; adolescents; cannabis use; meta-analysis

J Am Acad Child Adolesc Psychiatry 2024;■(■):■-■.

- Study of influence of Medical or Recreational Cannabis Laws on Use in Teens
- N=34 studies (med legal) and 30 (recreational legal)

Findings:

- No impact of medically legal on use
- Recreationally legal increased odds of past month cannabis in young adults > adolescents

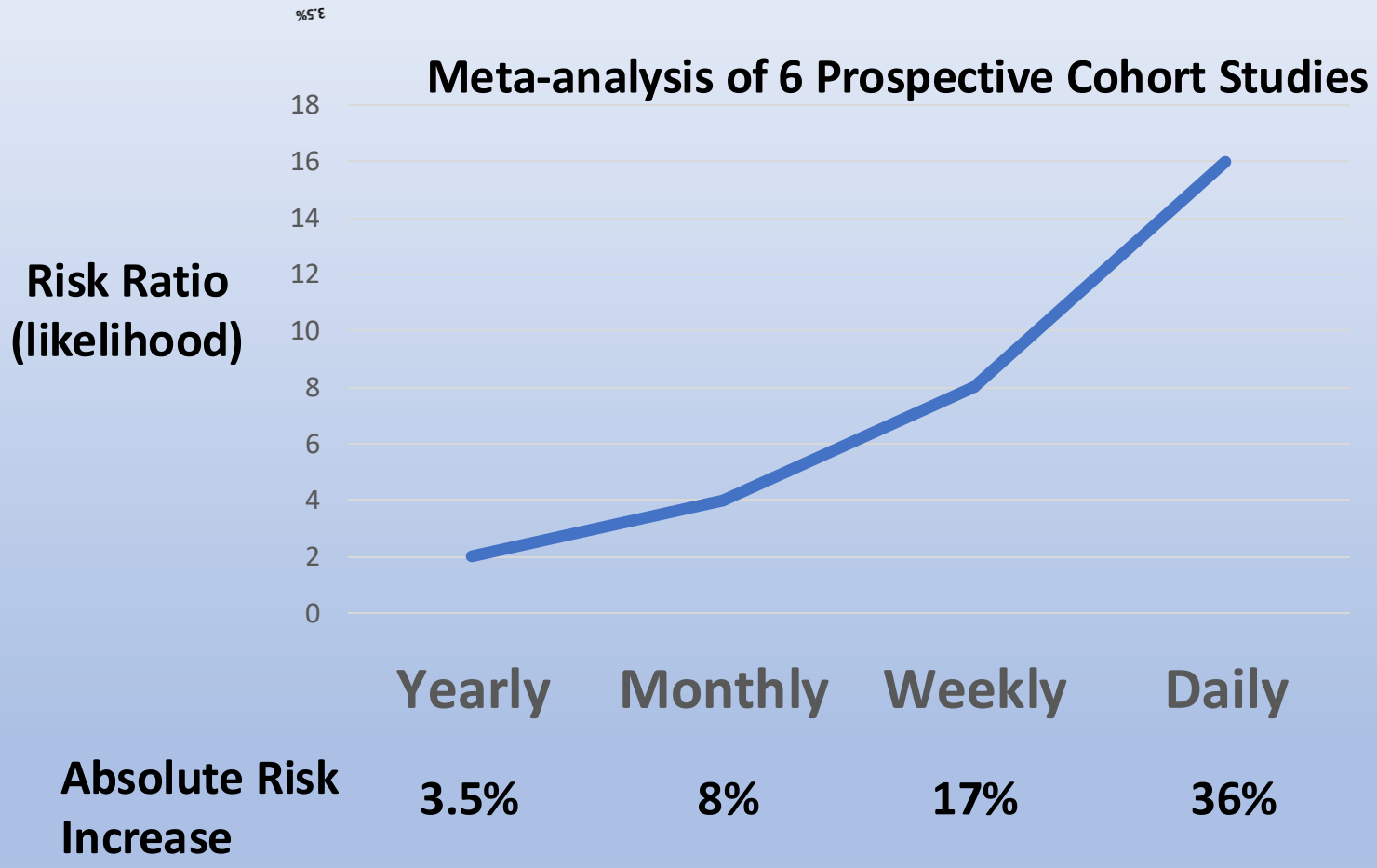
Recreational Marijuana Initiative
Position of the MGH/MGHfC

- We endorse allowing academic medical centers to study the effects of marijuana and its active constituents and metabolites on medical or psychiatric conditions and/or physical, emotional, behavioral, and cognitive safety in children.
- We do not endorse the recreational use of marijuana at any age because of the potential downstream effects on children:
  - The increase in the availability of marijuana and the change in the perception of harm may lead to an earlier-onset and increased rate of marijuana use in children
  - There are known structural and functional brain changes associated with early-onset marijuana use in children with potential persistent effects into adulthood
  - Similarly, there are transient and persistent neuropsychological effects of marijuana use in children with persistent effects into adulthood
  - The addictive potential of marijuana may drive marijuana and other substance use disorders in children. This is of particular concern in that one-half of substance use disorders onset in adolescence; and adolescent-onset substance use disorders predict a more pernicious and longer course of these disorders in adults.
  - There are well known deleterious effects of marijuana on driving performance, morbidity, and mortality—with specific concerns on the impact on adolescents. Motor vehicle accidents are the second leading cause of death in young people.
  - An increased availability of marijuana products (e.g., edibles such as candied marijuana derivatives) appears to be fueling marijuana poisonings in children. “All cause” drug related poisonings (including overdoses) are the leading cause of death in young people.
  - Marijuana concentrates with higher tetrahydrocannibinol levels have been associated with increased risk for short-term anxiety, paranoia, and psychosis; as well as the onset of long term psychotic illness (e.g. schizophrenia) in vulnerable individuals.

Marijuana Risks

- **Lung-based (adults)**
  - Wheezing
  - Exacerbation in COPD/Asthma
  - Less irritation compared to cigarettes
- **Cancer risk (adults)**
  - No increased risk of lung or other cancers
  - Trend to decreased prostate cancer
- **Motor vehicle accidents (adolescents/adults)->**
  - About two-fold increased risk while intoxicated
  - Increased in fatal accidents in states with legalization

Likelihood to Develop CUD Increases with Frequency of Use

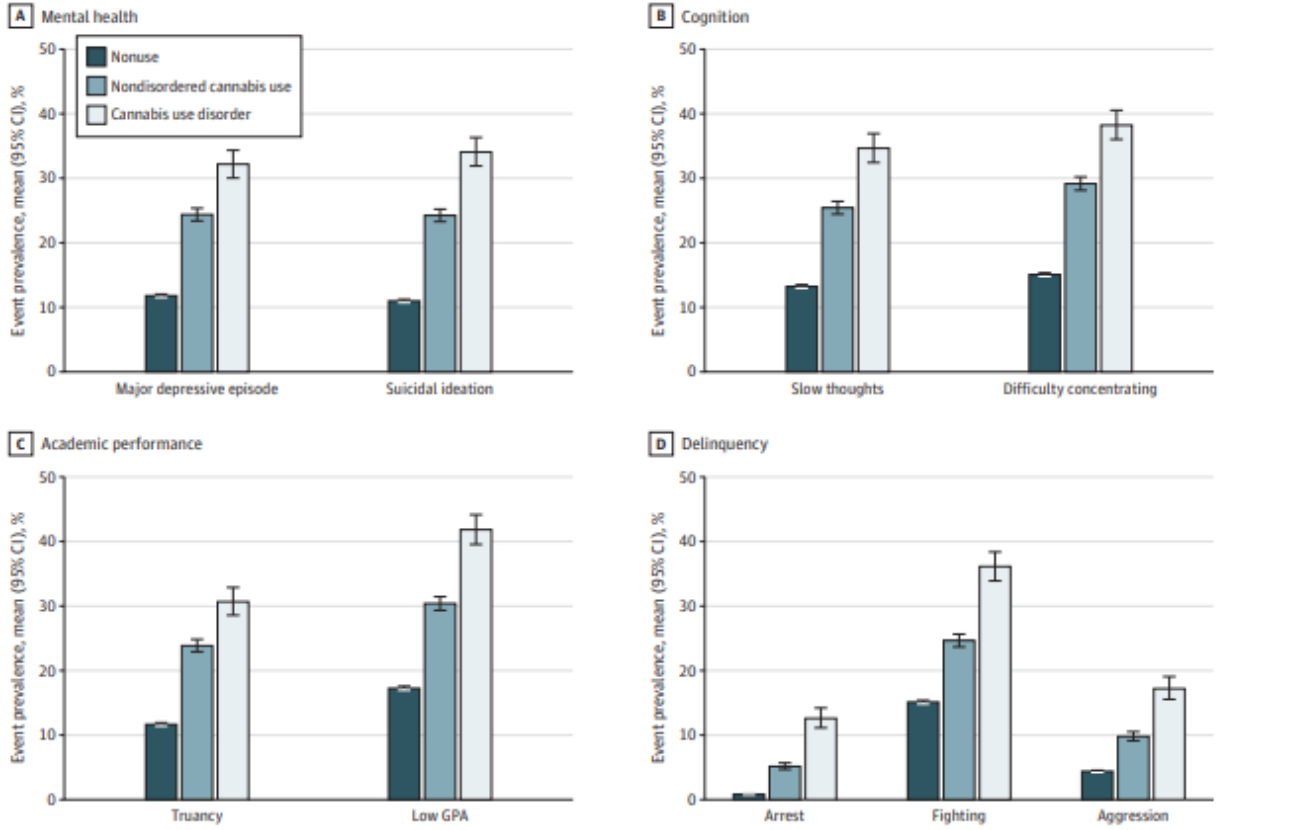


	Yearly	Monthly	Weekly	Daily
Absolute Risk Increase	**3.5%**	**8%**	**17%**	**36%**

Robinson T, et al. *Drug Alc Dep*. 2022. https://doi.org/10.1016/j.drugalcdep.2022.109582

Nondisordered Cannabis Use is Associated with Adverse Psychosocial Outcomes

Figure 1. Prevalence of Adverse Adolescent Psychosocial Events Among Nonuse, Nondisordered Cannabis Use, and Cannabis Use Disorder Groups



Data are from the 2015 to 2019 National Surveys on Drug Use and Health. GPA indicates grade point average.

Design

Xsection study of 12 to 17 yo 2015 to 2019 NSDUH
No cannabis use (N=59,617)
-No use
-Use > 12 mo
Nondisordered cannabis(N=6971;10%)
-Within 1 year
-No CUD
Cannabis use disorder (N=1675; 2.5%)
- **CUD by DSM V**

Sultan et al., JAMA Open Network, 2023; JAMA Network Open. 2023;6(5):e2311294. doi:10.1001/jamanetworkopen.2023.11294

J Stud Alcohol Drugs. 2022 Jul;83(4):494-501. doi: 10.15288/jsad.2022.83.494.

Changes in Traffic Crash Rates After Legalization of Marijuana: Results by Crash Severity

Charles M Farmer [1], Samuel S Monfort [1], Amber N Woods [1]

Affiliations + expand

PMID: 35838426 PMCID: PMC9318699 DOI: 10.15288/jsad.2022.83.494

Free PMC article

Abstract

Objective: The objective of this study was to estimate the effects of marijuana legalization and the subsequent onset of retail sales on injury and fatal traffic crash rates in the United States during the period 2009-2019.

Method: State-by-state quarterly crash rates per mile of travel were modeled as a function of time, unemployment rate, maximum posted speed limit, seat belt use rate, alcohol use rate, percent of miles driven on rural roads, and indicators of legalized recreational marijuana use and sales.

Results: Legalization of the recreational use of marijuana was associated with a 6.5% increase in injury crash rates and a 2.3% increase in fatal crash rates, but the subsequent onset of retail marijuana sales did not elicit additional substantial changes. Thus, the combined effect of legalization and retail sales was a 5.8% increase in injury crash rates and a 4.1% increase in fatal crash rates. Across states, the effects on injury crash rates ranged from a 7% decrease to an 18% increase. The effects on fatal crash rates ranged from a 10% decrease to a 4% increase.

Conclusions: The estimated increases in injury and fatal crash rates after recreational marijuana legalization are consistent with earlier studies, but the effects varied across states. Because this is an early look at the time trends, researchers and policymakers need to continue monitoring the data.

Study of impact of

- **MJ legalization**
- **MJ retail sales.**

Examination of injury-crash and fatal crash data 2009-2019. Compared to non-legal MJ states

Overall, MJ legal+sales:

- **5.8% increase in injury crash rates**
- **4.1% increase in fatal crash rates**

JAMA Psychiatry | Original Investigation

Association of Cannabis Use During Adolescence With Neurodevelopment

Matthew D. Albaugh, PhD; Jonatan Ottino-Gonzalez, PhD; Amanda Sidwell, BS; Claude Lepage, PhD; Anthony Juliano, PsyD; Max M. Owens, PhD; Bader Chaarani, PhD; Philip Spechler, PhD; Nicholas Fontaine, BS; Pierre Rioux, MSc; Lindsay Lewis, PhD; Seun Jeon, PhD; Alan Evans, PhD; Deepak D'Souza, MD; Rajiv Radhakrishnan, MD; Tobias Banaschewski, MD, PhD; Arun L. W. Bokde, PhD; Erin Burke Quinlan, PhD; Patricia Conrod, PhD; Sylvane Desrivières, PhD; Herta Flor, PhD; Antoine Grigis, PhD; Penny Gowland, PhD; Andreas Heinz, MD, PhD; Bernd Ittermann, PhD; Jean-Luc Martinot, MD, PhD; Marie-Laure Paillère Martinot, MD, PhD; Frauke Nees, PhD; Dimitri Papadopoulos Orfanos, PhD; Tomáš Paus, MD, PhD; Luise Poustka, MD; Sabina Millenet, PhD; Juliane H. Fröhner, MSc; Michael N. Smolka, MD; Henrik Walter, MD, PhD; Robert Whelan, PhD; Gunter Schumann, MD; Alexandra Potter, PhD; Hugh Garavan, PhD; for the IMAGEN Consortium

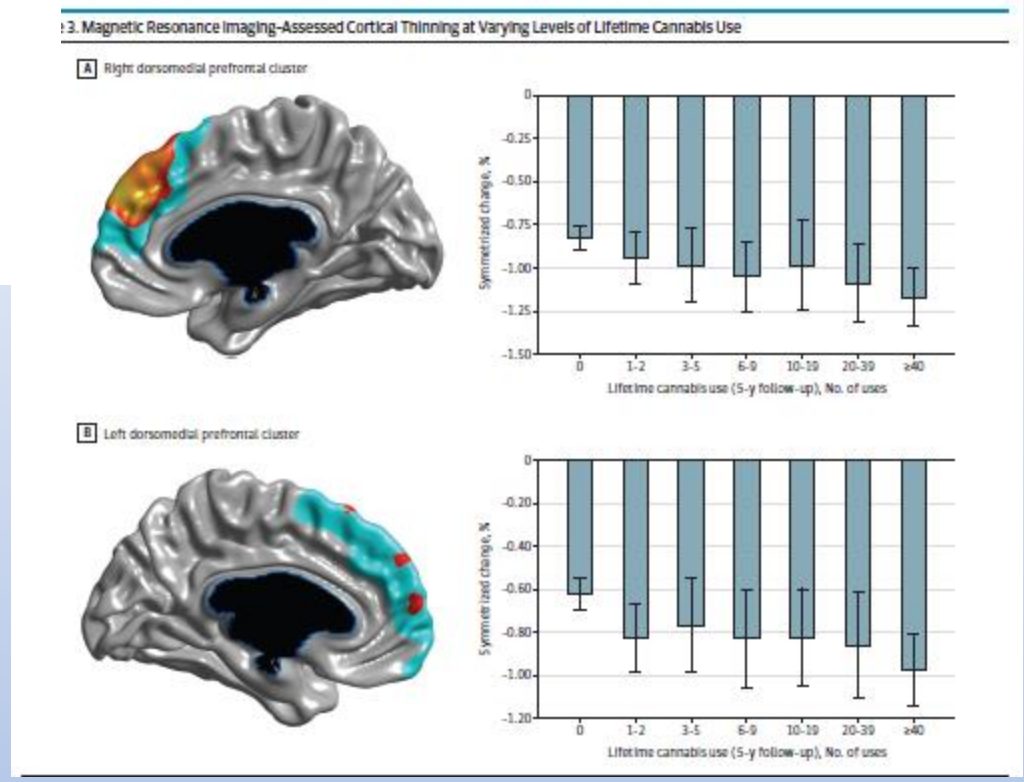


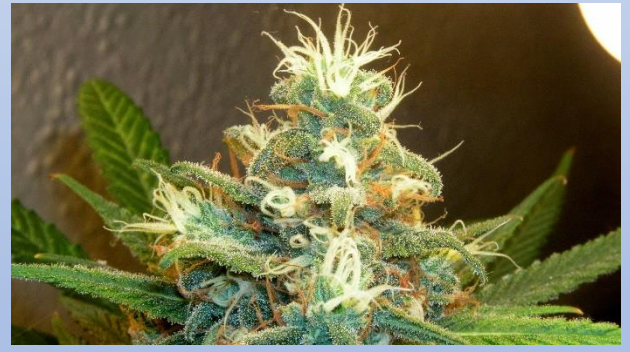
IMAGEN Multisite Study (8 sites)
N=799 children with scans and 5 year f/u
Mean age 14.4 yo (base) and 19 yo at f/u
MRI imaging for cortical thickness development
Main findings
-No differences at baseline between cannabis users
-Age related thinning in cannabis use –dose response relationship
-Overlay in cortical thinning linked to CB1 receptor density (from other PET study)

JAMA Psychiatry. 2021;78(9):1031-1040. doi:10.1001/jamapsychiatry.2021.1258
Published online June 16, 2021.

MGH Study: Cannabis Use Disorder (CUD) Is Linked to Anger in Young Adults (N=163)

- **Findings**
  - **Higher trait anger scores (irritability) in CUD vs other SUD**
  - (CUD TAS 20.8 versus No CUD TAS 17.5, t (161) = -2.923, p=0.004)
  - **More severe CUD → Higher trait anger**
  - (correlational pattern p=0.002; last use p=0.009; number of days p=0.001; THC level p=0.3)
  - **Early-onset CUD (<16 years) → higher trait anger scale**
  - (20.8 versus 18.0, t (154) 2.42, p=0.01)
- **Conclusion**
  - **CUD is linked to early-onset and more severe irritability and anger in young people**
  - **Normalized TAS: Low – 15; High =21**

McKowen JW, Lowman KL, Watt L, Yule AM, Burke C, Kaminiski T, Wilens T, Kelly J. The Relationship Between Cannabis Use and Self-Reported Trait Anger in Treatment-Seeking Young People. *Cannabis Cannabinoid Res*. 2022 Jul 12. doi: 10.1089/can.2021.0239.

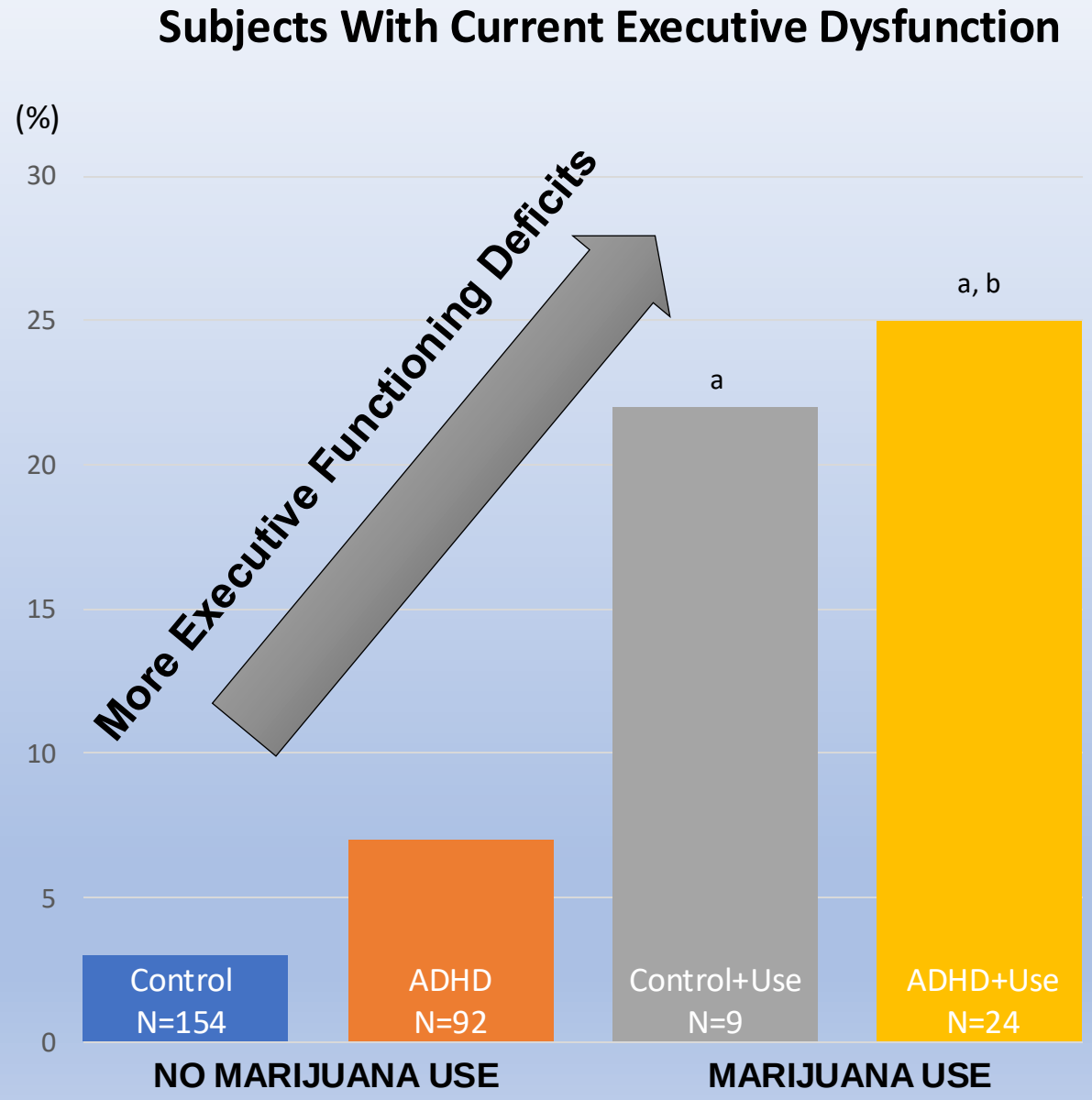


Characteristics of Cannabinoid Hyperemesis Syndrome (CHS)

- **Regular cannabis use**
- **Cyclical nausea and vomiting**
- **Resolution of symptoms after stopping cannabis**
- **Compulsive hot baths/showers with symptomatic relief**
- **Abdominal pain**
- **Male predominance**
- **Often young people**

Pattatahan M, et al. Pharmaceuticals (Basel). 2012 Jul; 5(7): 719–72; Venkatesan T, et al. *Neurogastroenterol Motil*. 2019 Jun; 31(Suppl 2): e13606.

Marijuana Use in Adolescents Causes Executive Functioning Deficits



Pairwise Comparisons:

[a] $p < 0.05$ vs. Controls;

[b] $p < 0.05$ vs. ADHD

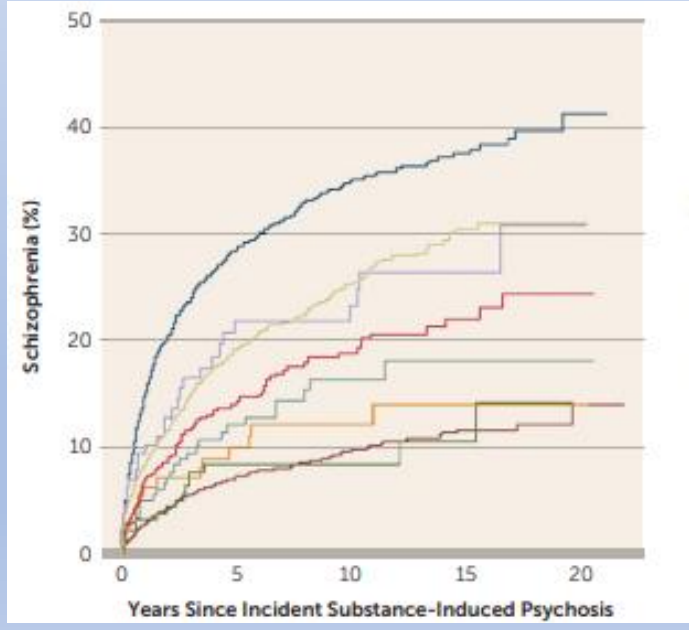
Wilens et al J Am Acad Child Adolesc Psych: 2011.

Marijuana Use & Psychotic Symptoms

- **Marijuana use during adolescence is related to subclinical or full acute psychotic episodes and future psychotic disorders**
  Casadio et al. 2011. Semple et al. 2005; Wilkinson et al. 2014; Moore et al. 2007; Kuepper et al. 2011 Starzer *Am J Psych*. 2018.

- **Synthetic marijuana (K2/Spice) bidirectionally linked with serious mental illness/psychosis, prolonged psychosis**

- ***Almost one-half of individuals who experience psychosis with marijuana develop schizophrenia***
  Starzer et al. 2018.



Bechtold J, et al. *Am J Psychiatry.* Aug 01 2016;173(8):781-789. Starzer, et al. *Am J Psychiatry* 175:4, April 2018.

Quantify use through toxicology

- Substances of misuse metabolites can be detected in saliva, serum, urine, hair
- Commonly assessed with urine or oral fluid toxicology screens
- Careful: Oral fluids do not assess for marijuana reliably

Courtesy A. Yule

Quantify use through toxicology

- Quantitative levels, “THC Level”
  - Urine test
  - THC level: THC/urine Cr
    - >500—Heavy use (multiple times per day)
    - 200 to 500—Regular use (3 to 6 times per week)
    - <100 to 200—Some use (1 to 3 times per week)
    - ↑THC concentration of product used--↑THC Level

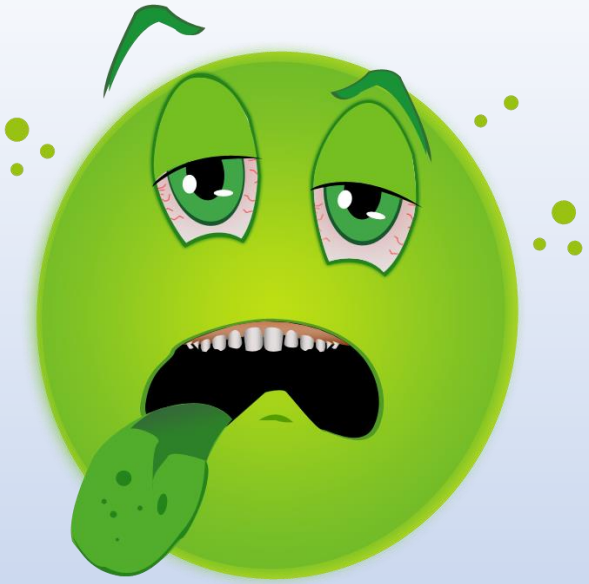
Courtesy A. Yule

Cannabis Diagnosis

- **Continuing to use cannabis despite physical or psychological problems**
- **Continuing to use cannabis despite social or relationship problems**
- **Craving cannabis**
- **Difficulty controlling or cutting down cannabis use**
- **Giving up or reducing other activities in favor of cannabis use**
- **Problems at work, school, and home as a result of cannabis use**
- **Spending a lot of time on cannabis use**
- **Taking cannabis in high-risk situations**
- **Taking more cannabis than was intended**
- **Tolerance to cannabis**
- **Withdrawal when discontinuing cannabis (see next)**

- **Mild**: 2-3 symptoms
- **Moderate**: 4-5 symptoms
- **Severe**: $\geq$ 6 symptoms

Cannabis Withdrawal



- **3 or more symptoms that develop within one week of stopping heavy cannabis use**
  - **Irritability, anger, or aggression**
  - **Nervousness or anxiety**
  - **Sleep difficulty (insomnia, disturbing dreams)**
  - **Decreased appetite or weight loss**
  - **Restlessness**
  - **Depressed mood**
  - **One or more physical symptoms causing significant discomfort: abdominal pain, shakiness/tremor, sweating, fever, chills, or headaches**

Budney AJ[1], Hughes JR.; Curr Opin Psychiatry. 2006 May;19(3):233-8.

Substance Use Disorder: Treatment

- **Motivational interviewing**
  - **Engage/collaborative connection with patient**
  - **Discuss issues that are problematic (don't focus only on SUD)**
  - **Set goals**
  - **Follow up related to progress**

Wilens, McKowen & Kane. Contemp Peds 2013.

Substance Use Disorder: Treatment

- **Cognitive Behavioral Therapies**
  - **Identification of high-risk situations**
  - **Reduction in impairing behaviors**
  - **Reduce SUD “cues”**
  - **Enhancing coping skills (e.g., anger, anxiety, boredom)**

Wilens, McKowen & Kane. Contemp Peds 2013.

Substance Use Disorder: Treatment

- **Contingency management**
  - **e.g., pay for improvement; use of “items” such as cell phones, car use to ‘trade’ for negative use**
- **Groups: for youth and parents (support, coaching)**
- **Address behavioral health issues**
  - **e.g., ADHD, mood disorders**

Wilens, McKowen & Kane. Contemp Peds 2013.

Pharmacotherapy for Marijuana Use Disorders

- **N-Acetyl Cysteine (NAC)-nutraceutical-dosing 1200 mg BID**
  RCT; Grey et al. Am J Psych 2012; 2017 (in young adults only)
- **Topirimate**
  (RCTs: Roten et al., Add Beh 38(3) 2013; Miranda et al. Addiction Biol, 2016; Emery et al., Psychopharm, 2021 V 238)
- **Buspirone**
  Pilot RCT; McRae-Clark et al., 2009
- **Gabapentin**
  Pilot RCT; Mason et al., 2012
- **Rimonabant- experimental (CB-1 receptor blocker; EU approval and withdrawal: mood/SI)**
  Huestis MA, et al. Psychopharm 2007

Cannabis Use Disorders: Summary

- **Marijuana is the most common non-alcohol substance of use, misuse, and addiction**
- **Marijuana has substantial addiction potential**
- **Cannabis use (and disorders) onset typically in adolescence**
- **Use in adolescents ≤16 years of age particularly problematic for potential structural brain changes and lasting neurocognitive dysfunction**
- **Medical marijuana is not well delineated (approved for pediatric epilepsy)**