





## Marijuana in Teenagers: A Pandemic in a Pandemic?

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## Faculty Disclosur

e

Timothy Wilens, M.D. has served as a consultant, or has received grant support from the following (past year):

- 3D Therapeutics, NIH (NIDA), Food and Drug Administration (FDA)
- Licensing agreement with Ironshore (Before School Functioning Questionnaire)
- Clinical care: MGH, Bay Cove Human Services, Gavin Foundation, Major/Minor League Baseball
- Royalties: (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); ADHD Across the Lifespan (Cambridge)
- 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)

## **Objectives**

### Learn the basic neurobiology of marijuana

### Understand the use of marijuana in Teenagers

List treatment strategies for Cannabis Use Disorders

### Past Year Illicit Drug Use: Among People Aged 12 or Older; 2020



Rx = prescription.

Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.

#### **PRESCRIPTION/OVER-THE-COUNTER VS. ILLICIT DRUGS**



Past-year misuse of Vicodin<sup>®</sup> among 12th graders has dropped dramatically in the past 5 years. So has misuse of all Rx opioids among 12th graders despite high opioid overdose rates among adults.

#### PRESCRIPTION/OTC



#### STUDENTS REPORT LOWEST RATES SINCE START OF THE SURVEY

Across all grades, past-year use of inhalants, heroin, methamphetamine, alcohol, cigarettes, and synthetic cannabinoids are at their lowest by many measures.





#### DRUGABUSE.GOV

https://www.drugabuse.gov/related-topics/trends-statistics/ir monitoring-future-2016-survey-results

## Past Year Marijuana Use: Among People Aged 12 or Older; 2002-2020



Age	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
12 or Older	11.0	10.6	10.6	10.4	10.3	10.1	10.4	11.4	11.6	11.5	12.1	12.6	13.2	13.5	13.9	15.0	15.9	17.5	17.9
12 to 17	15.8	15.0	14.5	13.3	13.2	12.5	13.1	13.7	14.0	14.2	13.5	13.4	13.1	12.6	12.0	12.4	12.5	13.2	10.1
18 to 25	29.8	28.5	27.8	28.0	28.1	27.5	27.8	30.8	30.0	30.8	31.5	31.6	31.9	32.2	33.0	34.9	34.8	35.4	34.5
26 or Older	7.0	6.9	7.0	6.9	6.9	6.8	7.0	7.7	8.0	7.9	8.6	9.2	10.1	10.4	11.0	12.2	13.3	15.2	16.3

+ Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

### U.S. Students Reporting Any Past-Year Illicit Drug Use\*



Source: 2021 Monitoring the Future Survey

#### Youth Marijuana Use by State

#### Youth Marijuana Use by State

Based on Percentage of Individuals 17 and Younger Reporting Use in the Past Year (2017)



(From SAMSHA NSDUH 2017 (recreated from OxfordTreatment)

## SUD is a Pediatric Disorder: Age at Onset of Drug Use Disorders



•<u>Colorado</u> •<u>Washington</u> •<u>Alaska</u> •<u>Oregon</u> •<u>Washington, D.C</u> •<u>California</u>

•<u>Maine</u> •<u>Mass Huseus</u> •<u>Nevada</u>t drink and drive, •<u>Michicar</u>ioke and fly. •<u>Vermoni</u>

•Gua

•<u>Illinois</u>

•<u>Arizona</u>

Montana

•New Jersey

•<u>New York</u>

•<u>Virginia</u>

<u>New Mexico</u>

<u>Connecticut</u>

•Deleware

Missouri

Maryland



#### As of May 2023

Medical: 39 States+ DC Recreational: 21 States, Guam, DC None: 6 States







Home » <u>Newsroom</u> » Rhode Island

### Governor McKee Signs Legislation Legalizing and Safely Regulating Recreational Cannabis in Rhode Island

Published on Wednesday, May 25, 2022

PROVIDENCE, RI – Governor Dan McKee today signed into law the Rhode Island Cannabis Act, legalizing and safely regulating recreational adult-use cannabis in

#### **Recreational But Not Medical Marijuana Legalization Is Associated With** Increased Cannabis Use Among Youth in the United States: Results of a Aditya K.S. Pawar MD<sup>1,2</sup>Systematio reviewi& metaFanalysis Wilens, MD<sup>3</sup>; Christopher J. Hammond MD PhD<sup>2\*</sup>

#### 1 Kennedy Krieger Institute Baltimore MD 2 Denartment of Psychiatry & Behavioral Sciences Johns Hopkins University Baltimore MD

#### 3.Departn**Objectives**hiatry, MGH/Harvard Medical School **Results** MA. AACAP Presentatio Fig 3 Effect of MMU on Youth Past-Month Cannabis Use Qualitative analysis showed heterogeneity across studies with limited consistency

Dramatic changes in marijuana laws (ML) over the past 20 years have resulted in shifted societal perceptions and increased availability of cannabis throughout the US with unknown implications for American youth. The objective of this project was to conduct an updated systematic review and meta-analysis estimating the effect of US medical ML (MML) and recreational ML (RML) on past-month cannabis use prevalence among adolescents and young

adults. Methodology

A systematic review was conducted using broad search terms following PRISMA guidelines. Out of 2012 citations reviewed, 69 studies were identified for inclusion in the gualitative review (33 for MML, 28 for RML,

#### and 9 compining MMS MAd RMI,



in outcomes. Twenty-six studies provided 33 data points for MML and 20 data points for RML that were meta-analyzed. Our analysis showed different effects on past month cannabis use for MML and RML. Compared to MML, RML studies were more likely to show significant effects, typically of modest positive associations between RML and adolescent cannabis use. No significant association was found between MML passage and change in past-month adolescent cannabis use, with fixed effect analysis yielding a standardized effect size of -0.003 [-0.009, 0.003, 95% Cl], however RML showed a modest positive association in fixed effect 0.215 [0.214, 0.215, 95% CI], and random effects model 0.061 [0.035, 0.088, 95% CI].

Fig 2. Effect of RML on Youth Past-Month Cannabis Use

Model Study name

Fixed

AND OF

•

Point estimate and 95% CI



The authors report no conflicts of interest related to the content of this poster. Scan the code to view additional details related to our meta-analytic methods, study citations, and full authors' disclosures.

0

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0.25

Increase

0.50

0.00



Point estimate and 95% Cl

#### Conclusions

Marijuana legalization has complex and heterogenous effects on youth cannabis use that may differ across recreational and medical laws. Per our analysis RML has a modest but significant positive effect towards an increase Marijuana use amongst youth in the USA, in contrast to MML, for which our meta-analytic findings are consistent with previous reports showing no significant effects of MML on past-month youth cannabis use. However, given the shift towards recreational legalization, additional focus on RML effects

are warrante

Fixed

Random

Model

Study name



IOHNS HOPKINS



## Data for the price of weed in Rhode Island, United States

#### Social Rating

Law Enforcement:	
Lightly Enforced	Heavily Enforced
Social Acceptance:	
Accepting	Very Intolerant

#### Average Weed Prices

Quality	Average (\$/Oz.)*	Sample Size		
High Quality	\$306.31	953		
Medium Quality	\$255.65	845		
Low Quality	I feel bad for these guys>	54		

\* Averages are corrected for outliers based on standard deviation from the mean.

#### Latest Submissions from Rhode Island



Westerly, Rhode Island	\$180	an ounce	high quality	Jun 29, 2022
Newport, Rhode Island	\$230	an ounce	high quality	Mar 11, 2022
East Providence, Rhode Island	\$35	an eighth	medium quality	Jan 19, 2022

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



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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



### Five years after Massachusetts voters approved marijuana legalization, some lawmakers seek increased restrictions

By Madeleine Pearce, Boston University Statehouse Program Dec 8, 2021





News / Massachusetts Marijuana Establishments Surpass \$2 Billion in Gross Sales

For Immediate Release September 1, 2021

#### Contact

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> Tara Smith Press Secretary 617-549-1166

Press@CCCMass.Com

Massachusetts Marijuana Establishments Surpass \$2 Billion in Gross Sales



## Massachusetts **Cannabis at Lowest Average Price Per Ounce Since** Pandemic Lockdown \$ 340/ ounce

Thu / Jan 6th / by TG Branfalt

**24** ENGAGEMENTS

**f** FACEBOOK

**W**TWITTER

in LINKEDIN

# Basics of Substances of Misuse (Marijuana)

## Marijuana Potency is Increasing Every

Year



#### Major Brain Circuits Involved in Addiction



A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana.



## **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

### Main Effects of Marijuana

- Molecular mechanisms
  - Inhibitory to many neurotransmitters (e.g. GABA, 5HT, etc)
  - CB1-inhibits adrenergic, cholinergic, serotonergic neurons
  - Stimulates dopamine release in "reward centers"



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; Szabo & Schlicker, Handb Exp Pharmacol. 2005;(168):327-65.

https://www.google.com/search?q=cannabinoid+receptor&source=lnms&tbm=isch&sa=X&ved=0ahUKEwiOzv y\_6lbiAhWGY98KHbOyAioQ\_AUIDygC&biw=1493&bih=1239#imgrc=89HFOLT47pNtgM:&spf=1557142676517

## Main Effects of Marijuana

Agonist to the cannabinoid (CB) receptors: CB<sub>18</sub> CB<sub>2</sub>



### 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

https://www.google.com/search?q=location+of+cb1+and+cb2+receptors&tbm=isch&source=iu&ictx=1&fir=KyG1MZsuZDhgBM%253A%252C rbj4iywrNvRO7M%252C\_&vet=1&usg=AI4\_-kSbJDhTGhs4VR\_sKJWPmavG7HMSCg&sa=X&ved=2ahUKEwinp8rOkP3hAhWim-AKHc2EAC IQ9QEwBHoECAkQDA#imgrc=RaxQJOsslt1peM:&vet=1&spf=1556809858557

## **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







## Marijuana Vaping



- Heating cannabis flower or concentrates to a temperature that turns the active compounds (cannabinoids and terpenes) into vapor
- Heating ranges between 180 -190 degrees F
- Vaporization increases the amount of cannabis consumed
- Types
  - Tabletop-mouthpiece/tube, heating element, chamber
  - Portable chamber, heating element, battery
  - Vape/"hash oil" pens battery, cartridge [compound+heating element]
  - Dab pens- same as vape pens but self-loaded no cartridge

The most common cutting agents include polyethylene glycol (PEG), propylene glycol (PG) and vegetable glycerin (VG).

Vitamin E Acetate banned (CDC suspect for pulmonary distress)

## Costs of Vaping (cigs/MJ)

- Disposable vapes: \$3 \$7 (cigs); 15-25\$ (device)
- Pod systems: \$15 \$50
- Vape pens: \$15 \$35
- Replacement coils: 1-5\$
- Vape juice: 3-7\$ (device) 10-30\$ (bottle); MJ: 20-60\$ (device)
- Overall cost: \$30-60 per month for coils and juice



## Medical Marijuana May Not Contain CBD or THC



<u>JAMA Netw Open.</u> 2021 Apr; 4(4): e215490. Published online 2021 Apr 12. doi: <u>10.1001/jamanetworkopen.2021.5490</u> PMCID: PMC8042519 PMID: <u>33844003</u>

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

Jodi M. Gilman, PhD,<sup>12,3</sup> William A. Schmitt, AB,<sup>1</sup> Grace Wheeler, BA,<sup>1</sup> Randi M. Schuster, PhD,<sup>1,2</sup> Jost Klawitter, PhD,<sup>4</sup> Cristina Sempio, PhD,<sup>4</sup> and A. Eden Evins, MD, MPH<sup>1,2</sup>

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This article has been cited by other articles in PMC.

This cohort study examines the association between medical cannabis product use and exposure to  $\Delta 9$ -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

### 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

### **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)

### Marijuana distribution after smoking

Marijuana rapidly re-distributes from blood to brain and other tissues. Distribution to fat is delayed

From Sapiensoup.com (Marlene Rupp)



### Euphoria, Performance, and THC Levels

Higher THC Levels, Euphoira (VAS) More Deficits,



CLINICAL TRIAL published: 13 November 2020 doi: 10.3399/fpsyt.2020.576877



Cashir .

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

Timo Woelfi<sup>1</sup>, Cathrin Rohleder<sup>1,2</sup>, Juliane K. Mueller<sup>1,3</sup>, Bettina Lange<sup>1</sup>, Anne Reuter<sup>1</sup>, Anna Maria Schmidt<sup>1</sup>, Dagmar Koethe<sup>2,4</sup>, Martin Hellmich<sup>5</sup> and F. Markus Leweke<sup>1,2\*</sup>

<sup>1</sup>Department of Psychiatry and Psychiatherapy, Cantral Institute of Montel Health, Medical Faculty Marnheim, Heidelberg University, Marnheim, Germany, <sup>2</sup> Youth Montel Health Team, Brain and Mind Centre, Central Clinical School, Faculty of Medicine and Health, The University of Syching, Syching, NSW, Nastralia, <sup>2</sup> Department of Psychiatry, Psychiaszmatics and Psychotherapy, Coatha University Frankfurt, Frankfurt, Garmany, <sup>4</sup> Department of Psychiatry, Beychiatra, Bernheim, Garmany, <sup>4</sup> Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Mannheim, Garmany, <sup>4</sup> Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Garmany

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Woall T, Rohladar C, Muallar JK, Lango B, Routar A, Schmidt AM, Koatha D, Halminh M and Lavaka FM (2020) Effacts of Cannabidol and Dalta-9-Totnthydrocannabidol an Emotion, Cognition, and Attantion: A Double-Bind, Placabach-Controlled, Randomized Experimental Trial in Healthy Voluntaons. Front. Psychiatry 11:52877. doi: 10.3380/jbsyz.2020.576877 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.

#### CBD -> No Effects

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

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

# Medical Marijuana

ICAL USA

DICA



## Chemotherapy Induced Nausea & Vomiting: Pediatric Studies of Medical Cannabinoids

Study by Indication Authors, y	Sample Size	Diagnoses (Inclusion Criteria)	Mean Age (Range)	Design	Medication	Measures	Findings
CINV							
Elder and Knoderer, <sup>7</sup> 2015	58	Childhood cancer	13.9 (6–18)	Retrospective chart review	Dronabinol	Episodes of vomiting	Positive response (0–1 bouts of vomiting) in 60% of children
Abrahamov et al, <sup>8</sup> 1995	8	Hematologic cancers	6.6 (3–13)	Open-label trial	Δ-8-THC	Episodes of vomiting	Prevented vomiting in all 480 total treatment cycles
Chan et al, <sup>9</sup> 1987	30	Childhood cancer	11.8 (3.5–17.8)	Double-blind, crossover RCT	Nabilone	Episodes for retching and vomiting	Reduced retching and vomiting compared with prochloperazine
Dalzell et al, <sup>10</sup> 1986	23	Childhood cancer	7.9 (0.8–17)	Double-blind, crossover RCT	Nabilone	Episodes of vomiting, nausea scale (0–3)	Reduced nausea severity and vomiting compared with domperidone
Ekert et al, <sup>11</sup> 1979	19 and 14	Childhood cancer	12.5 (5–19)	Two double-blind RCTs	Δ-9-THC	Episodes of nausea and vomiting	Reduced nausea and vomiting compared with metoclopramide or prochloperazine

## Pediatric Epilepsy Studies of Medical Cannabinoids

Study by Indication Authors, y	Sample Size	Diagnoses (Inclusion Criteria)	Mean Age (Range)	Design	Medication	Measures	Findings
Epilepsy		1 1 43 34 64 6555 Ve 1444 69					
Devinsky et al, <sup>12</sup> 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, <sup>13</sup> 2017	7	FIRES <sub>a</sub>	7.1 (3.9–8.5)	Open-label trial	CBD	Seizure frequency and duration, EEG	Reduced seizures in 86% of patients
Kaplan et al, <sup>14</sup> 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, <sup>15</sup> 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, <sup>16</sup> 2016	137	Treatment-refractory epilepsy	10.5 (1–22.2)	Open-label trial	CBD	No. of seizures, LAEP, PESO	37% decrease in monthly motor seizures
Tzadok et al, <sup>17</sup> 2016	74	Treatment-refractory epilepsy	1–18	Retrospective chart review	CBD-enriched OCE	Seizure frequency	Reduced seizures in 89% of patients
Hussain et al. <sup>18</sup> 2015	117	Treatment-refractory epilepsy	6 (3-10)	Parent survey	CBD-enriched OCE	Seizure frequency	Reduced seizures in 85% of patients
Press et al, <sup>19</sup> 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, <sup>20</sup> 2015	1	MMPSI <sup>a</sup>	10 mo	Case report	CBD	Seizure frequency, EEG	Reduced seizure frequency
Porter and Jacobson, <sup>21</sup> 2013	19	Treatment-refractory epilepsy	9.1 (2–16)	Parent survey	CBD-enriched OCE	Seizure frequency	Reduced seizures in 84% of patients
Lorenz, <sup>22</sup> 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).





## Medical Cannabis in Children and Adolescents: A Systematic Review

- Evidence for benefit was strongest for chemotherapy-induced nausea and vomiting; and refractory epilepsy.
- At this time, there is insufficient evidence to support use for spasticity, neuropathic pain, posttraumatic stress disorder, Tourette's syndrome, or psychiatric disorders in childhood.



**Review** article

A scoping review of the use of cannabidiol in psychiatric disorders

Anna E. Kirkland<sup>a,\*</sup>, Matthew C. Fadus<sup>b</sup> Staci A. Gruber<sup>c,d</sup> Kevin M. Grav<sup>a</sup> Timothy E. Wilens<sup>b,e</sup>,

<sup>a</sup> Department of Psychiatry and Behavi <sup>b</sup> Division of Child and Adolescent Psy <sup>c</sup> Cognitive and Clinical Neuroimaging <sup>d</sup> Department of Psychiatry, Harvard M <sup>e</sup> Center for Addiction Medicine Co-Div

#### A R T I C L E I N F O

Keywords: Psychiatry Anxiety Psychosis Treatment CBD Clinicians

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

re challenged is review is to is the current containing the articles. Only or psychiatric = 6), anxiety

Check for

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.

### Behavioral Disorders Pediatric Studies of Medical CBD

**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

<u>Retrospective study (Barchel et al., Front Pharm 2019)</u> -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%

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

Pain Nausea/Vomiting Spasticity Glaucoma Insomnia Appetite CBD

Seizures Pain Migraines Anxiety Depression Aggression Inflammatory diseases (IBD)

## How Practitioners Can Help Prevent Marijuana Use

- Encourage discussion within families (>5th graders/10 YO)
- Parental monitoring
  - Children's activities
  - Friends
  - Personal space
- Parental marijuana use 
   Children's use (Yule et al)
- Advocate for sensible public laws around marijuana
  - Legalization issues
  - "0" tolerance policies
- Screen & Treat Mental Health issues



Drug and Alcohol Dependence Available online 19 September 2022, 109641 In Press, Journal Pre-proof (7)



The Influence of Parent and Peer Disapproval on Youth Marijuana Use Mediated by Youth Risk Perception: Focusing on the State Comparison

Eunbyeor Sophie Yang ª , Su-Kyung Oh <sup>b</sup>ळ, Seohyun Kim ºळ, Ick-Joong Chung <sup>d</sup> 옷 쩝

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https://doi.org/10.1016/j.drugalcdep.2022.109641

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#### Highlights

- Parent and peer disapproval directly reduces marijuana use.
- Parent and peer disapproval indirectly influences marijuana use via risk perception.
- Parent disapproval has a higher direct effect on youth marijuana use.
- Peer disapproval has a higher indirect effect on youth marijuana use.
- Mechanisms in MML and non-MML states show similar based on significance and direction.

 2019 National Survey of Drug Use and Health in adolescents aged

- 12 to 17 years (N = 2,293)
- Examination of "Risk Perception" by Adolescents
- Comparisons of states with medical marijuana legalization (MML) vs non-MML

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

• PRISMA based search of the literature examining the long-term impact of treating psychopathology with pharmacotherapy in childhood

Journal of

larold S. Koplewicz, M.D.

Child and Adolescent

Psychopharmacology Developmental Psychopathology and Therapeutics

- N= 21 studies in ADHD, 2 studies on Major
   Depression, and 3 studies on psychotic disorders
- Majority reported <u>reductions</u> 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

## MTF Study: Early ADHD Treatment Reduces Marijuana Use in HS Seniors

10 Cohorts of Senior Years 2005 to 2014

(N=40,358; ca. 10% with ADHD)



McCabe, West, Dickinson, Wilens. J Am Acad Child Adoles Psych 2016: 55:479-486

## Marijuana Potential Harm



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

## 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

### Teratogenicity of Cannabinoids

#### Pre-clinical research with mice showed exposure to CBs during early pregnancy can cause malformations in developing embryo

Co-exposure to CBs and alcohol increased likelihood of birth defects involving the face and brain

National Institute on Alcohol Abuse and Alcoholism. (2019, November 15). Using both marijuana and alcohol during early pregnancy may increase the likelihood of disrupting fetal development [Press release].

Retrieved from https://www.niaaa.nih.gov/news-events/news-relea ses/marijuana-and-alcohol-use-during-pregnancy-and-f etal-development

#### Fetal Mouse Brains at 8<sup>th</sup> Day of



(Dr. Scott Parnell, UNC Chapel Hill)

The CBD amounts administered were within what is considered a therapeutic range for several medical conditions in humans.

The THC concentration administered was similar to levels. reached by a person smoking marijuana.



Adolescent marijuana use negatively effects cognition, **brain structure**, and **function**; especially when started before 16 years of age



FIGURE 5 | Bivariate relationship between younger age of regular marijuana (MJ) use onset (range 11–20 years of age) and decreased white matter integrity (reduced FA measured by diffusion tensor imaging) in 15 MJ users in the left frontal region of interest (adapted from Gruber et al., 2011). MSIT fMRI contrast analyses: Early Onset vs. Late Onset MJ smokers



Early MJ > Late MJ

Late MJ > Early MJ

FIGURE 6 | Whole brain inhibitory processing results demonstrating significant differences between adolescent early onset (n = 9) and late adult onset (n = 14) MJ users, early onset MJ users demonstrated increased middle right cingulum and decreased anterior cingulate BOLD response to an inhibitory processing (multisource interference task, MSIT) fMRI task (adapted from Gruber et al., 2012).

Lisdahl et al. *Frontiers in Psychiatry.* 2013. 4(53). Gruber et al. *Drug Alcohol Depend.* 2012 121, 159–162 Gruber et al. *Exp. Clin. Psychopharmacol.* 2011 19, 231–242.

### Relationship Between Substance Use and Adolescent Cognitive Development

**Results:** Common vulnerability effects were detected for cannabis and alcohol on all domains. Cannabis use, but not alcohol consumption, showed lagged (neurotoxic) effects on inhibitory control and working memory and concurrent effects on delayed memory recall and perceptual reasoning (with some evidence of developmental sensitivity). Cannabis effects were independent of any alcohol effects.

Marijuana Use in Adolescents Causes Executive Functioning Deficits

Pairwise Comparisons: <sup>a</sup> p < 0.05 vs. Controls; <sup>b</sup> 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 acute psychotic episodes and future psychotic disorders Casadio et al, 2011; Semple et al, 2005; Wilkinson et al, 2014; Moore et al, 2007
- Regular marijuana use might increase risk for experiencing subclinical psychotic symptoms Kuepper et al, 2011

Bechtold J, et al Concurrent and Sustained Cumulative Effects of Adolescent Marijuana Use on Subclinical Psychotic Symptoms. *Am J Psychiatry.* Aug 01 2016;173(8):781-789.

### Characteristics of Cannabinoid Hyperemesis Syndrome (Excessive Cyclical Vomiting)





- Regular cannabis use
- Cyclical nausea and vomiting
- •Resolution of symptoms after stopping cannabis
- •Compulsive hot baths/showers with symptomatic relief
- Abdominal pain
- •Male predominance
- •Usually < 50 years; often young people

### 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) 
   <p>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. <u>The Relationship Between Cannabis Use and Self-Reported Trait</u> <u>Anger in Treatment-Seeking Young People</u>. Cannabis Cannabinoid Res. 2022 Jul 12. doi: 10.1089/can.2021.0239

### **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<sup>1</sup>, Hughes JR.; Curr Opin Psychiatry. 2006 May;19(3):233-8.

## **Treatment**

## Substance Use Disorder: Treatment

### Motivational interviewing

- Engage/collaborative connection with patient
- Discuss issues that are problematic (don't focus only on SUD)

### Cognitive Behavioral Therapies

- Reduction in impairing behaviors
- Reduce SUD "cues"
- Coping skills (e.g., anger, anxiety, boredom)

### 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

# Pharmacotherapy for Marijuana Use Disorders

• N-Acetyl Cysteine (NAC)-natraceuticaldosing 1200 mg BID RCT; Grey et al. Am J Psych 2012; 2017 (in young adults only)

 Buspirone *Pilot RCT; McRae-Clark et al., 2009*

- Gabapentin
   Pilot RCT; Mason et al., 2012
- Topirimate
   Adult addiction studies
- Rimonabant- experimental (CB-1 receptor blocker; EU approval and withdrawal: mood/SI) *Huestis MA, et al. Psychopharm 2007*

### Cannabis Use Disorders: Summary

- Marijuana is big business and here to stay!
- Marijuana use in teens appears relatively stable over time
- 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
- Prevention is helpful
- Medical marijuana is not well delineated in youth
- Treatment of marijuana is multimodal in nature

## **QUESTIONS**?