

MARIJUANA AND THE DEVELOPING BRAIN

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ADDICTION MEDICINE PHYSICIAN

1

PREVALENCE OF MARIJUANA USE

Cannabis 2023 Past 12 Month Use

8th grade	11% (+15)
10 th grade	21.5% (+1.8)
12 th grade	32.6% (+0.6)

Most students are not using cannabis.

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

National Institute on Drug Abuse, University of Michigan (2009). Monitoring the Future: National survey results on drug use, 1975-2022. National Institute on Drug Abuse, U.S. Dept. of Health and Human Services, National Institutes of Health.

3

YOUTH MARIJUANA USE POST LEGALIZATION

Recreational legalization increased likelihood of youth reporting use of cannabis and alcohol. No impact on tobacco or nicotine use.

Bailey 2020

5

OBJECTIVES

1. Analyze the latest trends in youth marijuana use.
2. Understand the impact of marijuana on the teen brain and adolescent development.
3. Discuss intervention and treatment options for young people who are using marijuana.

2

COMPARISON: PREVALENCE OF ALCOHOL USE

Alcohol 2022 Past 12 Month Use

8th grade	15.2%
10 th grade	31.3%
12 th grade	51.9%

Alcohol is more commonly used than cannabis.

Even among 12th grade, half do not drink.

Alcohol: Trends in Last 12 Months Prevalence of Use in 8th, 10th, and 12th Grade

National Institute on Drug Abuse, University of Michigan (2009). Monitoring the Future: National survey results on drug use, 1975-2022. National Institute on Drug Abuse, U.S. Dept. of Health and Human Services, National Institutes of Health.

4

YOUTH MARIJUANA USE POST LEGALIZATION

Recreational legalization slows projected declines in youth use?

To M 2019

6

WHAT IS MARIJUANA?

Cannabis (Cannabis Sativa) =

- psychoactive cannabinoids → Tetrahydrocannabinol (THC) delta-9, delta-8, delta-10, delta-12, THC-P
- minimally psychoactive cannabinoids → Cannabidiol (CBD) cannabigerol (CBG), cannabivarin (CBV), cannabichromene (CBC), and olivetol
- Other chemical compounds

Hemp: Cannabis plant bred to be <0.3% THC, CBD and levels of other compounds are not regulated "Federally Legal"

Marijuana: Dried flower, leaves of cannabis, varying degrees of THC and other compounds

Psychoactive: Affects thinking, behavior, memory, processing

Bioactive: Impacts a living system or tissue

13

SYNTHETIC CANNABIS PRODUCTS

Lab created THC analog sprayed on plant material

10-200X greater potency
CB 1 and CB 2 R full agonists
>280 compounds

SYNTHETIC CANNABINOIDS (K2/SPICE)
UNPREDICTABLE DANGER
K2/SPICE IS **NOT** MARIJUANA

It's illegal to possess, transport or use synthetic cannabinoids and the federal government is cracking down on those who do.

Produced from plant material | May have chemicals | A "natural" product that may be bad

15

CANNABIDIOL (CBD)

Low affinity partial agonist/antagonist at Cannabidiol 2 Receptor
Minimal action at Cannabidiol 1 Receptor
Partial agonist of 5-HT1A
 buspirone, vilazodone use this mechanism
Modulator of opioid receptors and others
Attenuates impacts of Delta-9 THC

17

WHAT IS DELTA-8 THC?

- Lower affinity for Cannabinoid Receptors compared to Delta-9
- Produced from putting hemp-derived CBD through a chemical process. Also naturally occurring in plant.
- Federally Unregulated
- Restricted or banned in 26 States

How states regulate delta-8 across the US

Source: American Trade Association of Cannabis and more

14

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16

CANNABIDIOL (CBD)

Non-intoxicating
Bioactive, limited bioavailability
Can produce psychoactive effects
Interacts with the Blood Brain Barrier (BBB)
Decreased inflammation
Possibly improved BBB efficacy
Future treatment for dementias associated with stroke, diabetes?

18

MEDICINAL USES OF CANNABIDIOL (CBD)

Most evidence for epileptic illnesses

Epidiolex: >98% CBD, FDA approved for pediatric epilepsy in 2018

VS

Improved pain and sleep in pancreatic cancer

Reduction in breast cancer proliferation

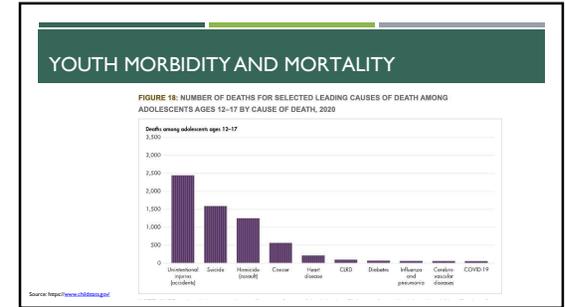
Side Effects: decreased appetite, fatigue, diarrhea, hepatotoxicity

19

MARIJUANA AND BRAIN HEALTH

1. Immediate Impacts
2. Mental Health Vulnerabilities
3. Altered Brain Development

21



23

CBD IN REAL LIFE

Tested 2,946 products, 136 brands

25% no testing of contents

84% outside of allowed variance (10%) of THC/CBD concentration

13% tested for purity

Brands with <7 products most likely to test

Beverages and topicals were least reliable

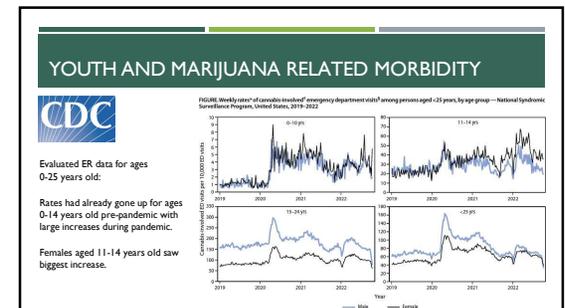
Source: www.healthspan.com/healthspan/insights/cbd-transparency-report

20

I. IMMEDIATE IMPACTS

<p>Normal Teen Brain</p> <p>Pleasure Seeking</p> <p>Impulsive</p> <p>Novelty</p> <p>Instant Gratification</p> <p>Limited Planning</p>	<p>+</p>	<p>Cannabis Intoxication</p> <p>Cognitive slowing</p> <p>Euphoria</p> <p>Decreased IQ</p> <p>Increased risk taking</p> <p>Impaired motor skills</p> <p>Sensation Seeking</p>
		<p>=</p>
		<p>Morbidity and Mortality</p>

22



24

MARIJUANA AND DRIVING

Cannabis Effects on Driving Occasional Users in a Driving Simulator

- Increased variability in speed
- Increased variability in vehicle gap maintenance
- Increased Standard Deviation of Lateral Placement, a measure of weaving
- Reduced speed relative to speed limit

Duration of impairment after consumption (smoking): 4 to 6 hours

Cannabis Effects on Driving Iowa/NIDA Driving Simulator Study

- Greater movement within a lane
- Reduced speed
- Greater lane deviations requiring steering correction
- Missing within the lane

TIC concentration

Hartman RL, et al. Clin Chem. 2013;58:478-482; Hartman RL, et al. Drug Alcohol Depend. 2015;154:35-37; Hartman RL, et al. J Appl Behav. 2016;36:543-547.

25

AMOTIVATIONAL SYNDROME

Unique to regular marijuana use

Characterized by: Anhedonia, Apathy, Decreased Self – Efficacy

Research participants who smoke >3 times a week score lower on measures of initiative and persistence



Lee A, Luk JW. Testing the Amotivational Syndrome: Marijuana Use Longitudinally Predicts Lower Self-Efficacy Even After Controlling for Demographics, Personality, and Alcohol and Cigarette Use. Prev Sci. 2018; 19(2):117-126. doi: 10.1007/s11121-017-0801-6. PMID: 29007220. PMCID: PMC6272061.

27

CANNABIS WITHDRAWAL

Cannabis Withdrawal Scale
24 hours period
Good sensitivity and specificity

Prevalence: JAMA 2020 Review
47% of cannabis users
Increased risk with tobacco users, SUD diagnoses, daily use

	Not at all	Slightly	Moderately	Very much	Relative frequency (%)	
1. The only thing I could think about was smoking cannabis	0	2	3	4	4	10
2. Had a headache	0	2	3	4	4	10
3. Had no appetite	0	2	3	4	4	10
4. Had trouble falling asleep	0	2	3	4	4	10
5. Had nausea	0	2	3	4	4	10
6. Had trouble concentrating	0	2	3	4	4	10
7. Had mood swings	0	2	3	4	4	10
8. Had decreased energy	0	2	3	4	4	10
9. Had trouble staying motivated	0	2	3	4	4	10
10. Had trouble staying focused	0	2	3	4	4	10
11. Had trouble staying alert	0	2	3	4	4	10
12. Had trouble staying awake	0	2	3	4	4	10
13. Had trouble staying interested	0	2	3	4	4	10
14. Had trouble staying motivated	0	2	3	4	4	10
15. Had trouble staying focused	0	2	3	4	4	10
16. Had trouble staying alert	0	2	3	4	4	10
17. Had trouble staying awake	0	2	3	4	4	10
18. Had trouble staying interested	0	2	3	4	4	10
19. Had trouble staying motivated	0	2	3	4	4	10
20. Had trouble staying focused	0	2	3	4	4	10
21. Had trouble staying alert	0	2	3	4	4	10
22. Had trouble staying awake	0	2	3	4	4	10
23. Had trouble staying interested	0	2	3	4	4	10
24. Had trouble staying motivated	0	2	3	4	4	10
25. Had trouble staying focused	0	2	3	4	4	10
26. Had trouble staying alert	0	2	3	4	4	10
27. Had trouble staying awake	0	2	3	4	4	10
28. Had trouble staying interested	0	2	3	4	4	10
29. Had trouble staying motivated	0	2	3	4	4	10
30. Had trouble staying focused	0	2	3	4	4	10

29

2. MENTAL HEALTH VULNERABILITY

- Number of mental health diagnoses, suicidality
- Diagnostic Complexity
- Trauma exposure
- Treatment resistance
- Medication toxicity or inefficacy
- Psychosis risk with regular cannabis use
- Decreases use of health coping skills

26

CANNABIS WITHDRAWAL

Three or more within 1 week of stopping

- Irritability, anger, aggression
- Anxiety, nervousness
- Sleep difficulty
- Decreased appetite, weight loss
- Restlessness
- Depressed Mood

+ one physical symptom:
abdominal pain, shakiness/tremor, sweating, fever, chills, headache

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5). https://doi.org/10.1177/08980101135005642006

28

CANNABIS HYPEREMESIS SYNDROME

Subset of Cyclic Vomiting Syndrome
More common in young adults and adolescents
Associate with >2 years of use, >3 times a week

Prodromal Phase: morning nausea, abdominal cramps
Hyperemetic Phase: intractable NV, diffuse stomach pain
Recovery Phase: weeks to months, even with ongoing use
Prolonged Relief: after 1-3 months of cessation of cannabis

Pearny JL, Lockwood B. Cannabinoid Hyperemesis Syndrome. MedSurg. 2017 Oct;34(10):33-36. PMID: 28762026. PMCID: PMC5754416.

30

MEDICATION TOXICITY AND INEFFECTACY

Risk of Drug-THC Interactions

Impacts from CBD, THC and others:

- Largely liver enzyme metabolism inhibitors
- Inhibition means drug levels go up
- Increased drug levels means side effects and toxicity

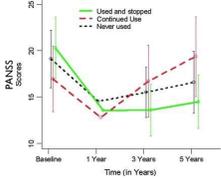


Source: Google Image search, July 2023

31

MARIJUANA AND PSYCHOSIS

- First episode psychosis and mania when combined with marijuana use had worse outcomes.
- Chronic use of marijuana after diagnosis caused greater structural brain changes.
- Stopping use of marijuana after diagnosis led to improved outcomes.



Legend:
 - Used and stopped (solid green line)
 - Continued Use (dashed red line)
 - Never used (dotted black line)

Y-axis: PANSS Scores (20-80)
 X-axis: Time (in Years) (Baseline, 1 Year, 3 Years, 5 Years)

Quedano-Polo A, Meehan S, Suterich S, Guterich S, Hager P, Bohns A, Hesse M, Yoon E, Anong C, Canales and the International Cannabis Use Research Network. Association of cannabis use with outcomes in psychosis. *Am J Psychiatry*. 2017;174(12):1217-1224. doi: 10.1176/appi.ajp.2016.16.09.1118. Epub 2016 Dec 11. PMID: 28019482. <https://doi.org/10.1176/appi.ajp.2016.16.09.1118>
 Bohns A, Hesse M, Hager P, Suterich S, Guterich S, Hager P, Bohns A, Hesse M, Yoon E, Anong C, Canales and the International Cannabis Use Research Network. Association of cannabis use with outcomes in psychosis. *Am J Psychiatry*. 2017;174(12):1217-1224. doi: 10.1176/appi.ajp.2016.16.09.1118. Epub 2016 Dec 11. PMID: 28019482. <https://doi.org/10.1176/appi.ajp.2016.16.09.1118>

33

MARIJUANA AND PSYCHOSIS

- Cannabis induced psychosis increases risk of further unprovoked psychotic episodes.
- Earlier age of onset for psychotic disorders in those with family history.
- Influenced by genetic and environmental factors.
- THC potency, CBD/THC ratio of product, duration of use.



Starzer 2017, Murrin 2020, Kessler 2019, Chester 2021, Ortiz 2018

35

MEDICATION TOXICITY AND INEFFECTACY

CYP1A2 Substrates
 clozapine, propranolol, caffeine, clopidogrel, warfarin, tacrine, verapamil, melatonin, duloxetine

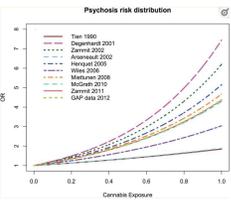
CYP3A4 Substrates
 escitalopram, amlodipine, simvastatin, codeine, warfarin, buspirone, venlafaxine, mirtazapine

32

MARIJUANA AND PSYCHOSIS

- 4X population risk for heavy users
- 2X population risk for moderate use
- 1.5x population risk with any use

Population Risk: 3%

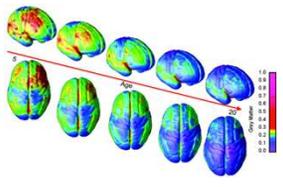


Legend:
 - Finn 1990 (solid red)
 - Degenhardt 2001 (dashed blue)
 - Zammit 2002 (dotted green)
 - Aasen et al 2002 (dash-dot purple)
 - Henquet 2005 (long-dash orange)
 - Vollen 2006 (short-dash yellow)
 - Mittleman 2008 (solid black)
 - Mclellan 2010 (dashed grey)
 - Zammit 2011 (dotted light blue)
 - GIP-USA 2012 (dash-dot dark blue)

Sullivan SA, Kessler D, Cannon M, David AS, French PC, Holmans P, et al. A Population-Based Cohort Study Investigating the Incidence and Impact of Psychotic Experiences From Childhood to Adulthood and Prediction of Psychotic Disorder. *Am J Psychiatry*. 2022;179(1):28-37. <https://doi.org/10.1176/appi.ajp.2021.18.07.210788>
 Mclellan A, Chouinac J, Leck K, Hwang M, Yoon E. Prevalence of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophrenia Bulletin*. 2014; Sep 40(3):523-9. doi: 10.1093/schbul/sbu014. Epub 2014 Feb 15. PMID: 24488165. <https://doi.org/10.1093/schbul/sbu014>

34

3: ALTERED BRAIN DEVELOPMENT



Caudal → Rostral
 Deep Centers → Cortex

Image courtesy of V.J. Weiden and L.L. Wald, Maricopa Center for Biomedical Imaging at MGH

36

THE BRAIN AS A HOUSE



Incomplete construction increases risk of derailment by the environment.

George Heggen, November 14th 1, 2022

37

MARIJUANA AND COGNITIVE PERFORMANCE

↓ Executive Functioning Skills

- cognitive flexibility
- working memory
- declarative memory
- attention span
- inhibitory control

These symptoms may persist beyond acute use depending on THC concentration, duration, age of cessation

Associated most often with use at or before 16yo

39

WHAT IF YOU USE MARIJUANA AND HAVE ADHD?



Qualitative Self Report:
25% adults felt it helped
8% adults felt it worsened symptoms

One RCT assessed pharmaceutical THC in 30 adults with strictly ADHD for 6 wks:

- No change in primary outcome measures
- Decreased hyperactivity

15 Total Cross-Sectional Studies:

- No change or worsened attention, concentration, impulsivity
- Tolerance to Benefits

Francisco AP, Luthi-Kluger C, Paterson R, et al. Cannabis use in attention-deficit/hyperactivity disorder (ADHD): A scoping review. J Psychosom Res. 2023;157:229-56.

41

MARIJUANA AND COGNITIVE PERFORMANCE

Disentangling the lasting effects of adolescent cannabinoid exposure

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Progress In Neuro-psychopharmacology & Biological Psychiatry 104 (2021) 110867

* Human and Rodent Studies, Human only reviewed here
 * Most studies have mainly male participants

38

MARIJUANA AND COGNITIVE PERFORMANCE

↓ Intellectual Ability – Verbal IQ

modified by social, economic and psychologic factors

Cortical Thickening

Impairments in myelination

Excess gray matter

Increased fMRI signaling

These symptoms may persist beyond acute use depending on THC concentration, duration, age of cessation

Associated most often with use at or before 16yo

40

MARIJUANA AND ADDICTION

Marijuana Addiction

Contrary to popular belief, marijuana is addictive. Research shows that:

- 1-in-6 people who start using the drug before the age of 18 can become addicted.
- 1-in-10 adults who use the drug can become addicted.

Among 18yo with severe SUD – 60% still met criteria for SUD at 50yo

Among 18yo with mild SUD – 45% still met criteria for SUD at 50yo.

Population risk is 15%

McGee 2022

TABLE 3.1 DSM-5 Criteria for Substance Use Disorder	
Criterion	Severity
Use in larger amounts or for longer periods of time than intended	Severity is designated according to the number of symptoms endorsed: 0-1 No diagnosis 2-3 Mild SUD 4-5 Moderate SUD 6 or more Severe SUD
Unsuccessful efforts to cut down or quit	
Excessive time spent using the drug	
Continue to use despite clear negative consequences	
Failure to fulfill major obligations	
Continued use despite social/interpersonal problems	
Activities/hobbies reduced/abandoned	Recurrence of physical or psychological problems caused by or worsened by use
Recurrence of legal problems	
Recurrence of family or social problems	
Continued use despite physical or psychological problems caused by or worsened by use	

McGee 2022

42



43

MARIJUANA USE: INTERVENTION AND TREATMENT

Develop a relationship with a community referral site:

<https://www.psychologytoday.com>
<https://findtreatment.gov/>
<https://www.hazeldenbettyford.org/referrals>

45

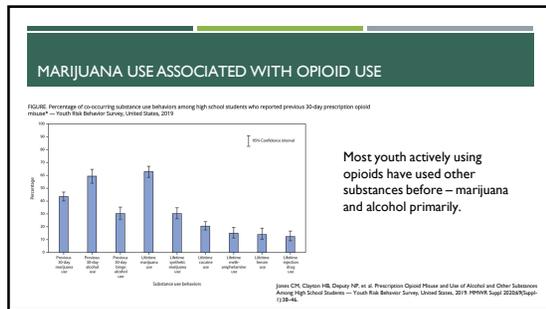
CANNABIS USE DISORDER TREATMENT

FIGURE 2. A Theoretical Treatment Algorithm for CUD With the Goal of Abstinence

	Withdrawal management			
	Sleep	Appetite	Mood	Other use
Zolpidem/benzos	+++			
Mirtazapine	++	+++		
Clonidine	+++	+++		
Quetiapine	++		+	
Nabiximols and dronabinol	++	++	++	++

Loebel, Bryan C. et al. Current Treatments for Cannabis Use Disorder. Psychiatric Times, Dec 22, 2022, Vol 39, Issue 12.

47



44

MARIJUANA USE: REFERRAL TO TREATMENT

DETERMINING WHEN A REFERRAL IS INDICATED

S2BI SCREENING RESULT	BI FOCUS	REFERRAL INDICATED
No Use (Prevention Opportunity)	Provide anticipatory guidance.	No
Once or Twice Use (Low Risk of Substance Use Disorder)	Provide cessation advice.	No
Monthly Use (Moderate Risk of Substance Use Disorder)	Reduce use and reduce risky behaviors.	Use clinical judgment.
Weekly Use or More (High Risk of Substance Use Disorder)	Facilitate linkage to mental health or substance use treatment	Yes

46

MOTIVATIONAL ENHANCEMENT FOR USE

O Open-ended questions that allow patients to give more information including their feelings, attitudes and understanding.

A Affirmations to help overcome self-sabotaging or negative thoughts.

R Reflections as a way to express ambivalence.

S Summarize to let your patient know that they are being heard.

MI is a collaborative, goal-oriented style of communication with particular attention to the language of change. It is designed to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion.

(Miller & Rollnick, 2013, p. 29)

Miller, W., & Rollnick, S. (2002). Motivational Interviewing: Preparing for Change. New York: Guilford.

48

COGNITIVE BEHAVIORAL THERAPY FOR USE



Evidence-Based Behavioral Treatment

- Use alone or in combination with other things
- Individual or group
- Self-help, peer led, clinician guided

Resource: <https://www.smartrecovery.org/>

McHugh BK, Hearns BA, Ode HW. Cognitive behavioral therapy for substance use disorders. Psychiatr Clin North Am. 2010 Sep;33(5):11-23. doi: 10.1016/j.psc.2010.04.012. PMID: 20599130; PMCID: PMC297895.

49

MARIJUANA HARM REDUCTION

Goal: Decrease Exposure

Delay initiation of use	Try other coping skills first
Reduce frequency	Less risky route of administration
Reduce number of settings when used	Less concentrated products
	THC/CBD ratio

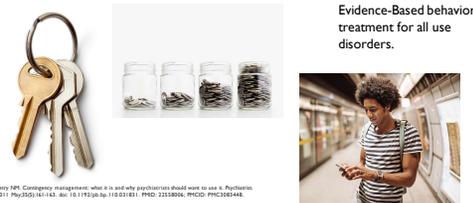
51

SUMMARY

- Youth are using marijuana. Most teens do not use. Youth are more likely to use new products, products that are easily accessible, and those that are viewed as low risk. This is why legalization increases use among teenagers.
- Marijuana impacts the brain of youth differently than adults. It increases risk of immediate death and harm, it causes worsening of mental health, it can change brain development, and it increases the risk of addiction.

53

CONTINGENCY MANAGEMENT FOR USE



Evidence-Based behavioral treatment for all use disorders.

Photo 549. Contingency management: when to use and why. Psychiatric Services. 2011 May;62(5):611-13. doi: 10.1176/appi.ps.110.021181. PMID: 21558066; PMCID: PMC3108448.

50

MARIJUANA WITHDRAWAL MANAGEMENT

Comfort Measures:

- Anti-nausea medications
- Fluids, electrolyte drinks
- Topical capsaicin cream 0.1% (applied to abdomen)
- Hot showers
- Dopamine antagonists: haloperidol 0.5mg/kg
- Gastritis medications
- Stool softeners or anti-diarrheal medications
- Sleep aids
- As needed anxiety medications



52

SUMMARY

- Regarding youth mental health, marijuana use in teens can make diagnosis and treatment difficult and increases the severity of underlying mental illness.
- After screening for and identifying use in a young person, brief intervention strategies can be employed to help a young person consider the benefits and drawbacks of their marijuana use.
- If a teen is being referred to treatment, there are many evidence-based interventions including behavioral treatment and medication treatment for helping them through withdrawal and afterward.

54

QUESTIONS

Thank you!

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Addiction Medicine Physician

55

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<https://www.events.samhsa.gov/2021ASAMPreventionStateoftheUnionV3.aspx?MTA=HDBRHTwN6AS5M6t1N6Q1N7L4R9wPQ=483d4eD193k16> PowerPoint Presentation.

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SE McCabe, JE Schulenberg, TS Scheep, VM McCabe, PT Velting. Longitudinal analysis of substance use disorder symptom severity at age 18 and substance use disorder at adulthood. *JAMA Network Open*. DOI: 10.1001/jamanetworkopen.2022.5224 (2022)

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57

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59

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56

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58