

Understanding and Addressing Youth Cannabis Use

Kevin M. Gray, M.D.

Medical University of South Carolina



**YOUTH
COLLABORATIVE**

 **MUSC**
Medical University
of South Carolina

Disclosures

- Research discussed in this presentation is supported by the National Institutes of Health
- Dr. Gray has provided consultation to Indivior and Jazz Pharmaceuticals and has received research support from Aelis Farma
- This presentation will include discussion of off-label pharmacotherapy

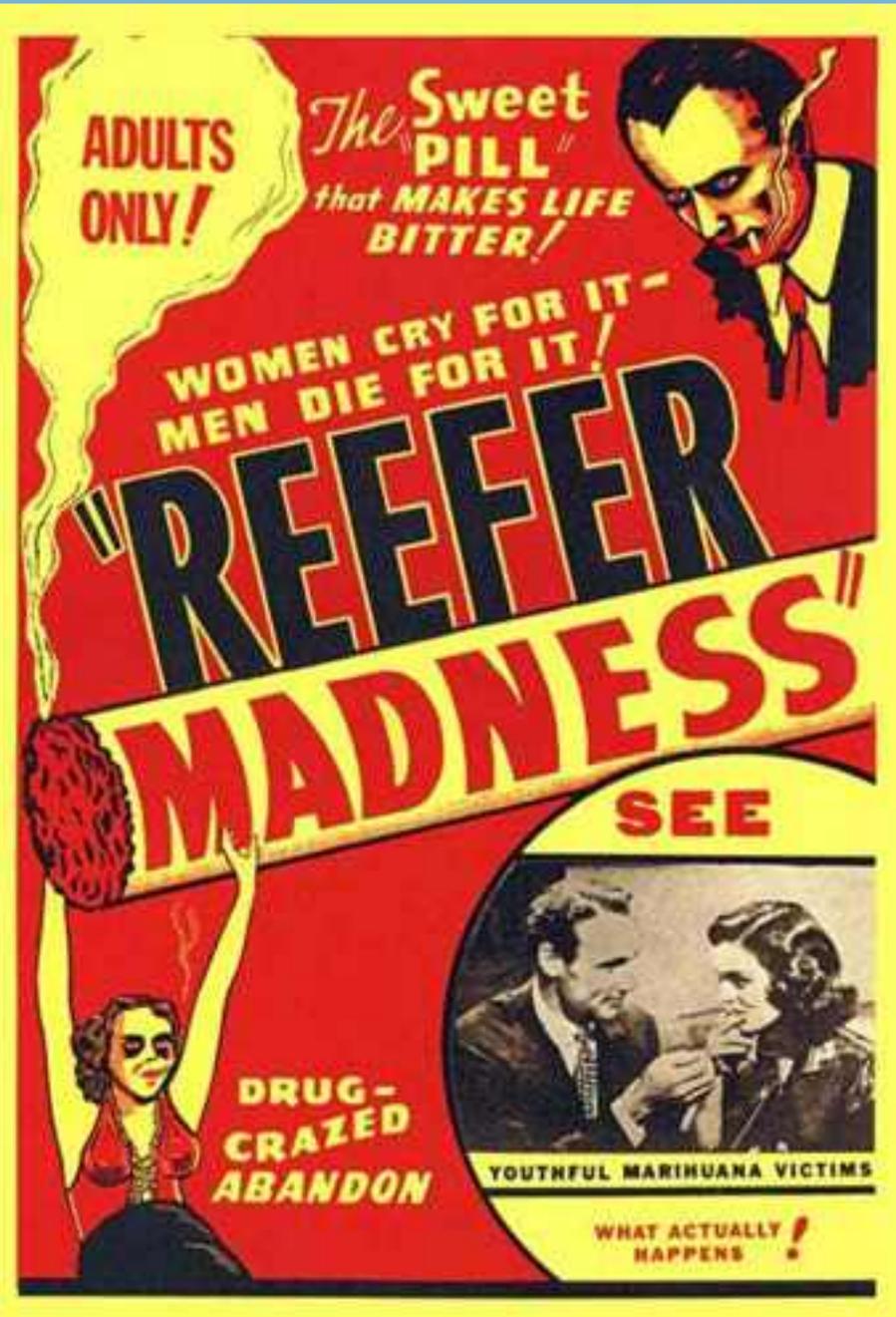
Overview

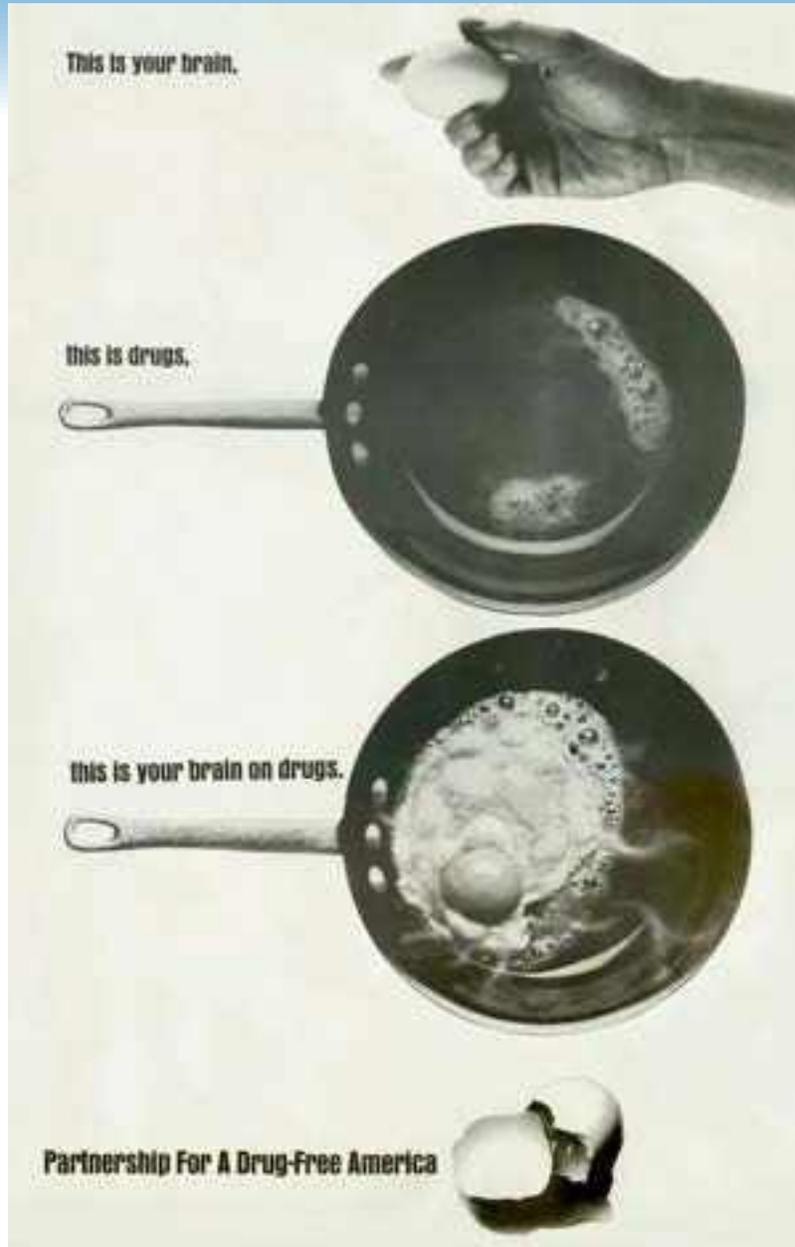


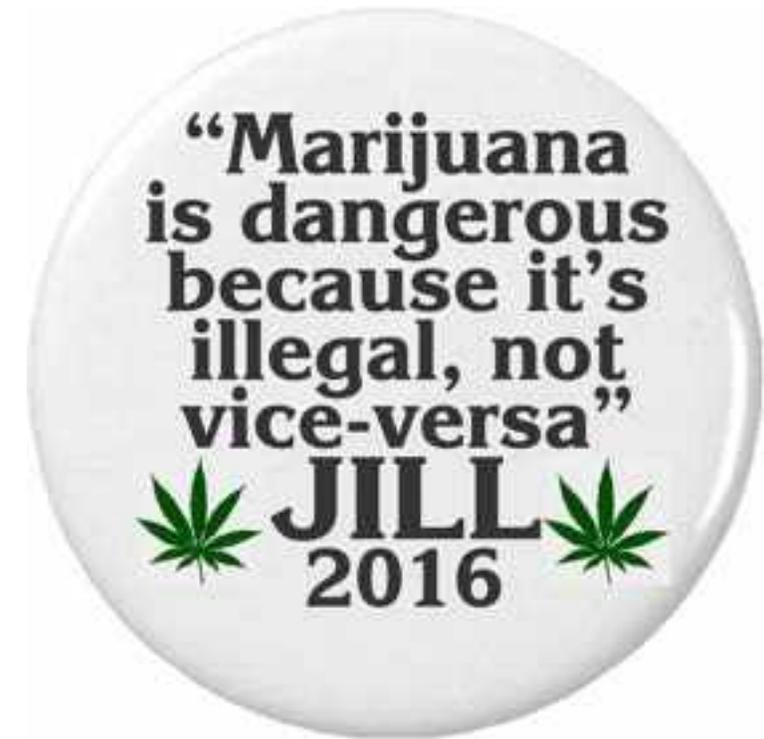
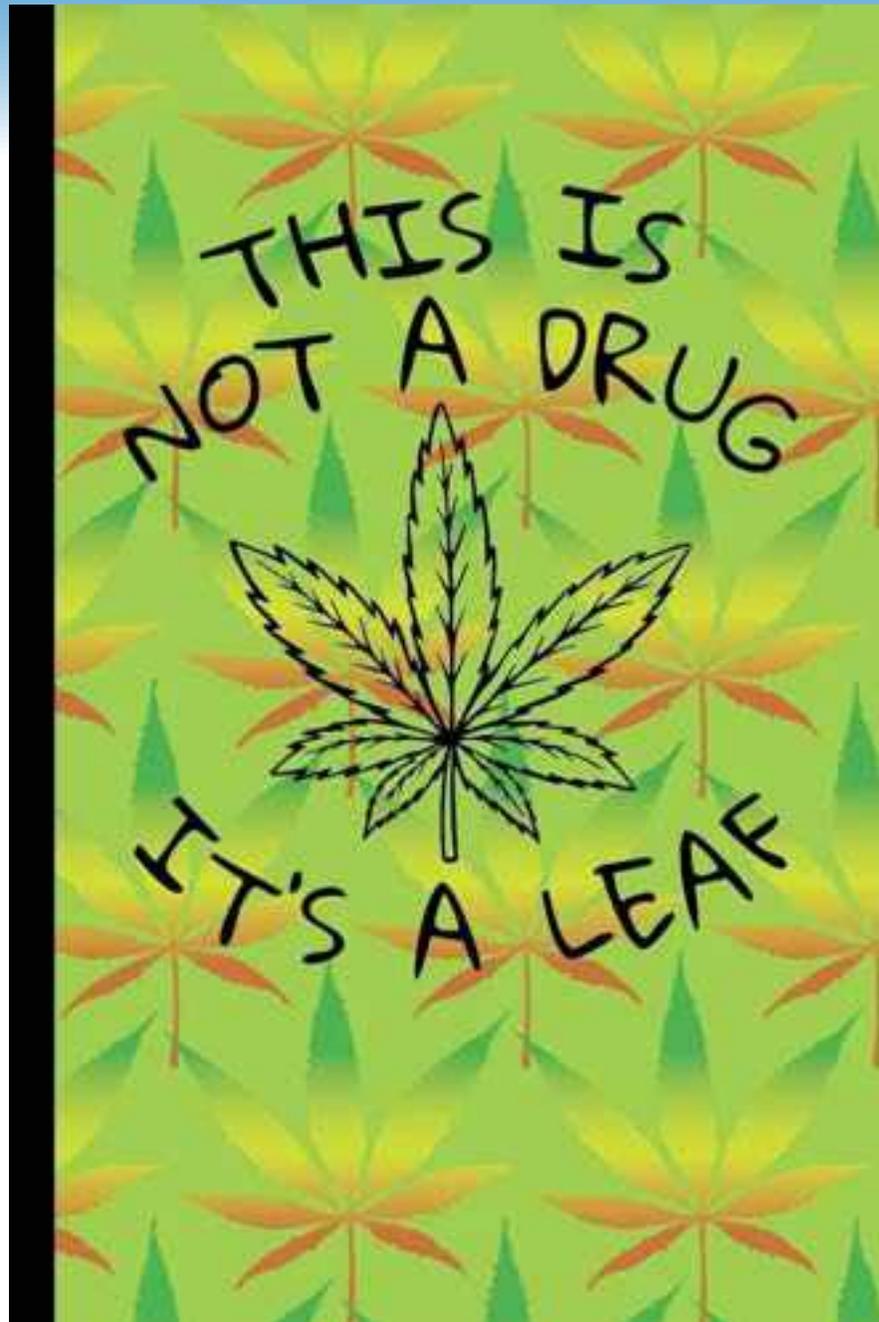
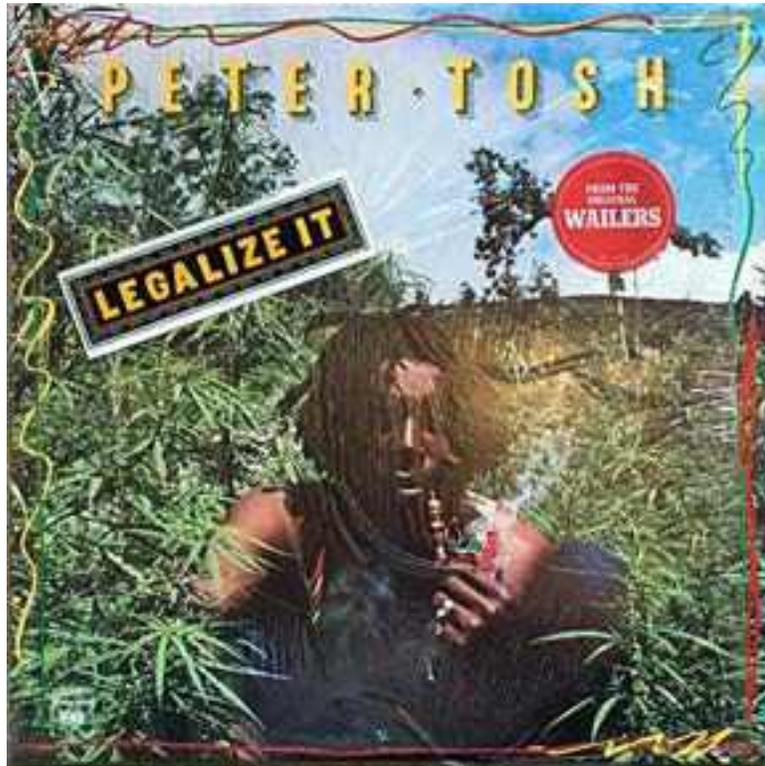
- Grappling with a complicated topic
- What's happening with cannabis?
- What's happening with youth?
- What's happening with cannabis + youth?
- How can we make sense of this and address it?

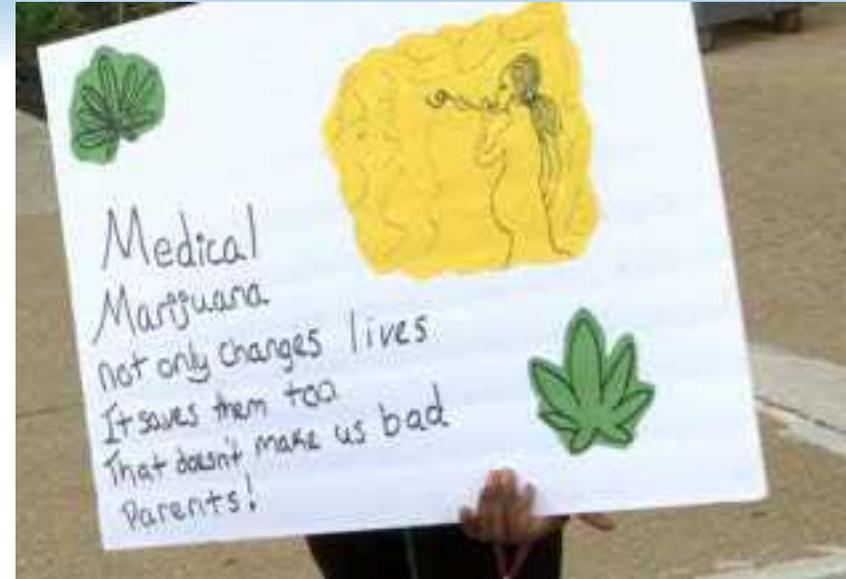
Grappling with a complicated topic





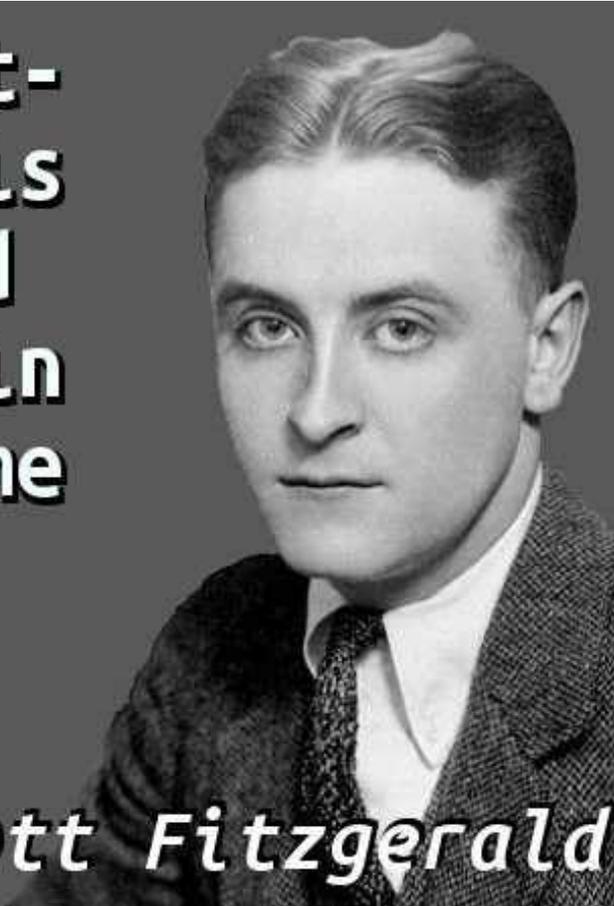






“The test of a first-rate intelligence is the ability to hold two opposed ideas in the mind at the same time, and still retain the ability to function.”

F. Scott Fitzgerald



- Cannabis can
 - be potentially safe and benign in some contexts
 - contain potentially medicinal components
 - be potentially risky and harmful (e.g., use by youth, context of psychiatric and substance use comorbidity, high-concentration THC exposure)
- These can all be simultaneously true
- And there can still be a lot more to learn



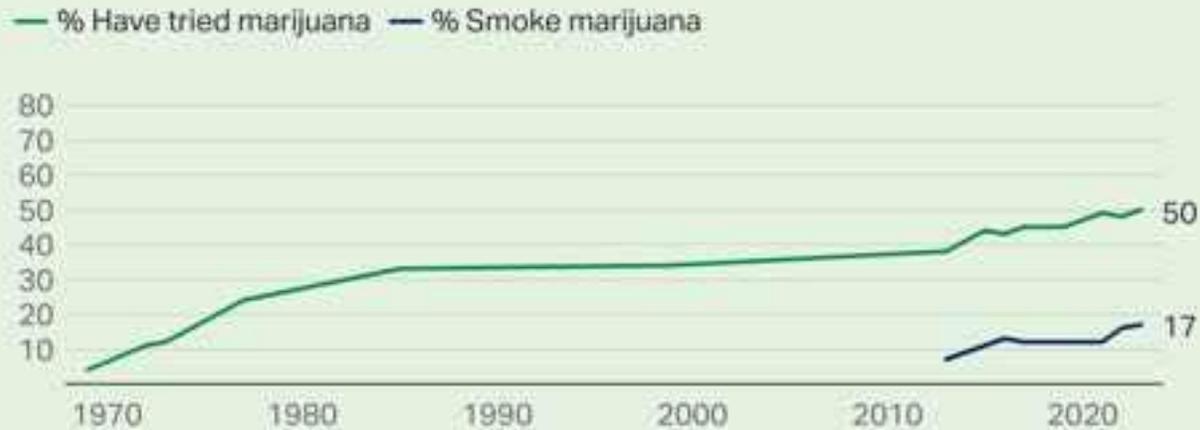


**What's happening with
cannabis?**

What's happening with cannabis?

Marijuana Usage Among U.S. Adults, 1969-2023

Keeping in mind that all of your answers in this survey are confidential, have you, yourself ever happened to try marijuana?^ // Keeping in mind that all of your answers in this survey are confidential, do you, yourself, smoke marijuana?



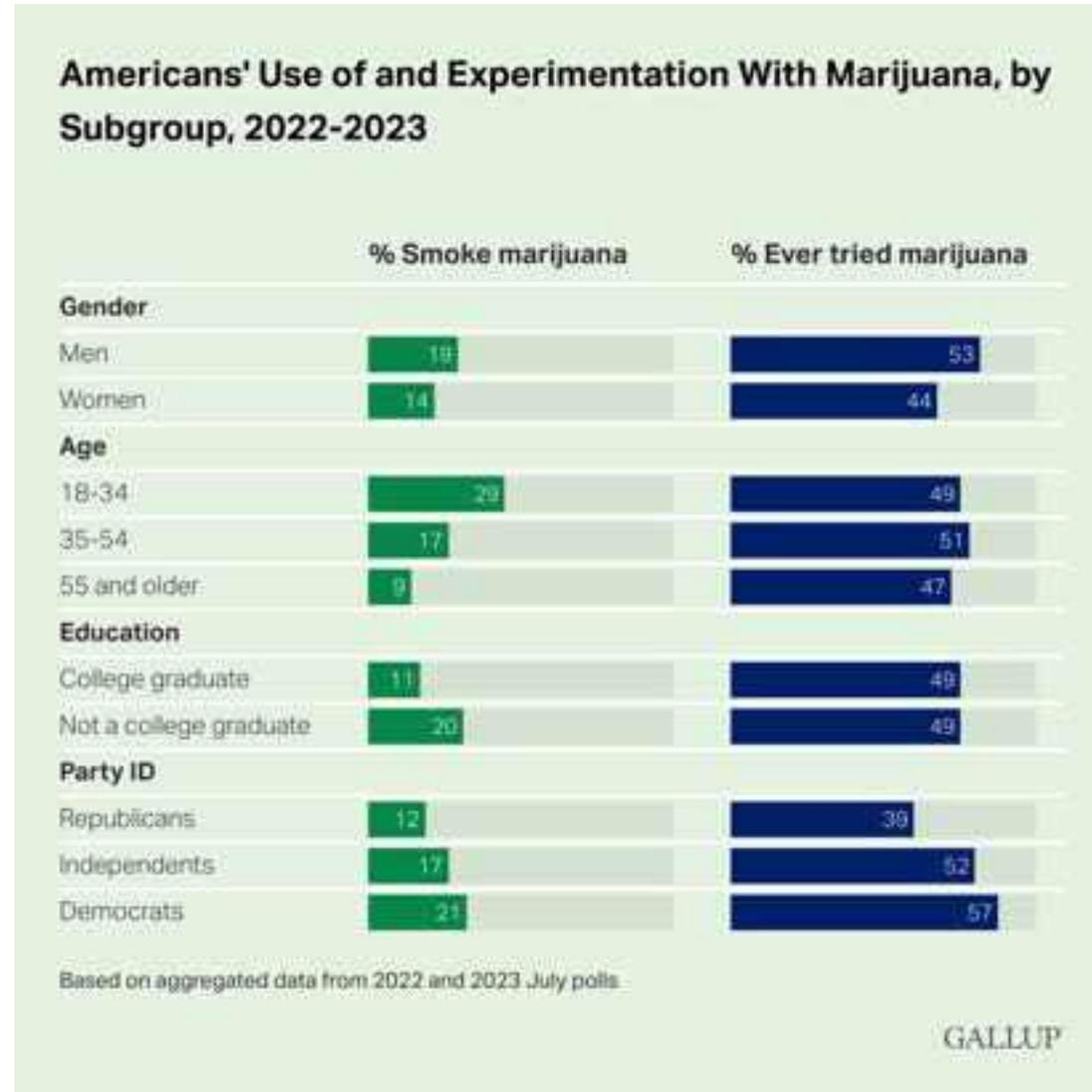
Questions asked of separate randomly selected half-samples since 2013

^ 1969-1985 wording: Have you, yourself, ever happened to try marijuana?

GALLUP

Source: Gallup

What's happening with cannabis?



Source: Gallup

What's happening with cannabis?

The Green Wave: Americans' Support for Marijuana, 1969-2023

Do you think the use of marijuana should be legal, or not?

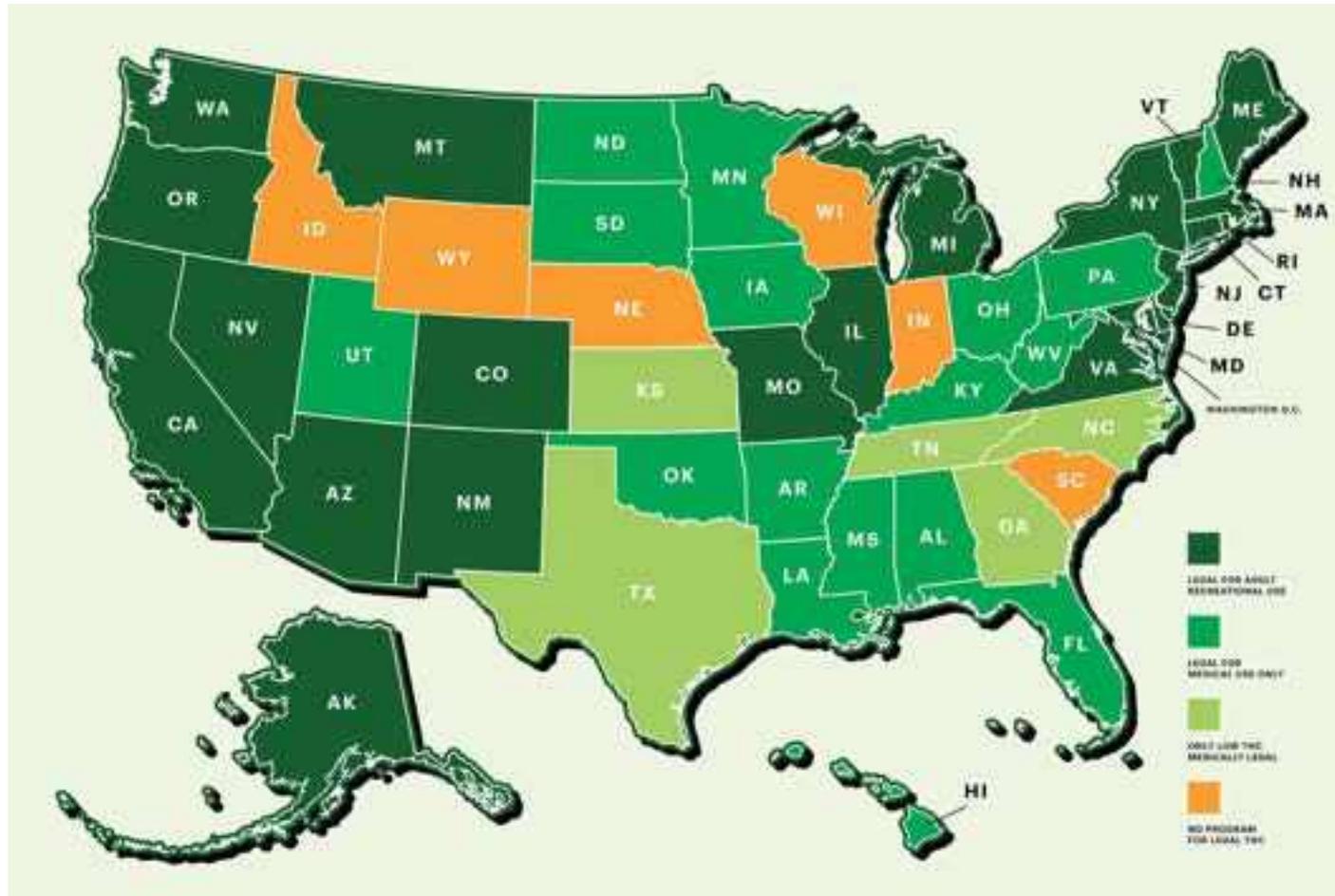
— % Yes, legal



GALLUP

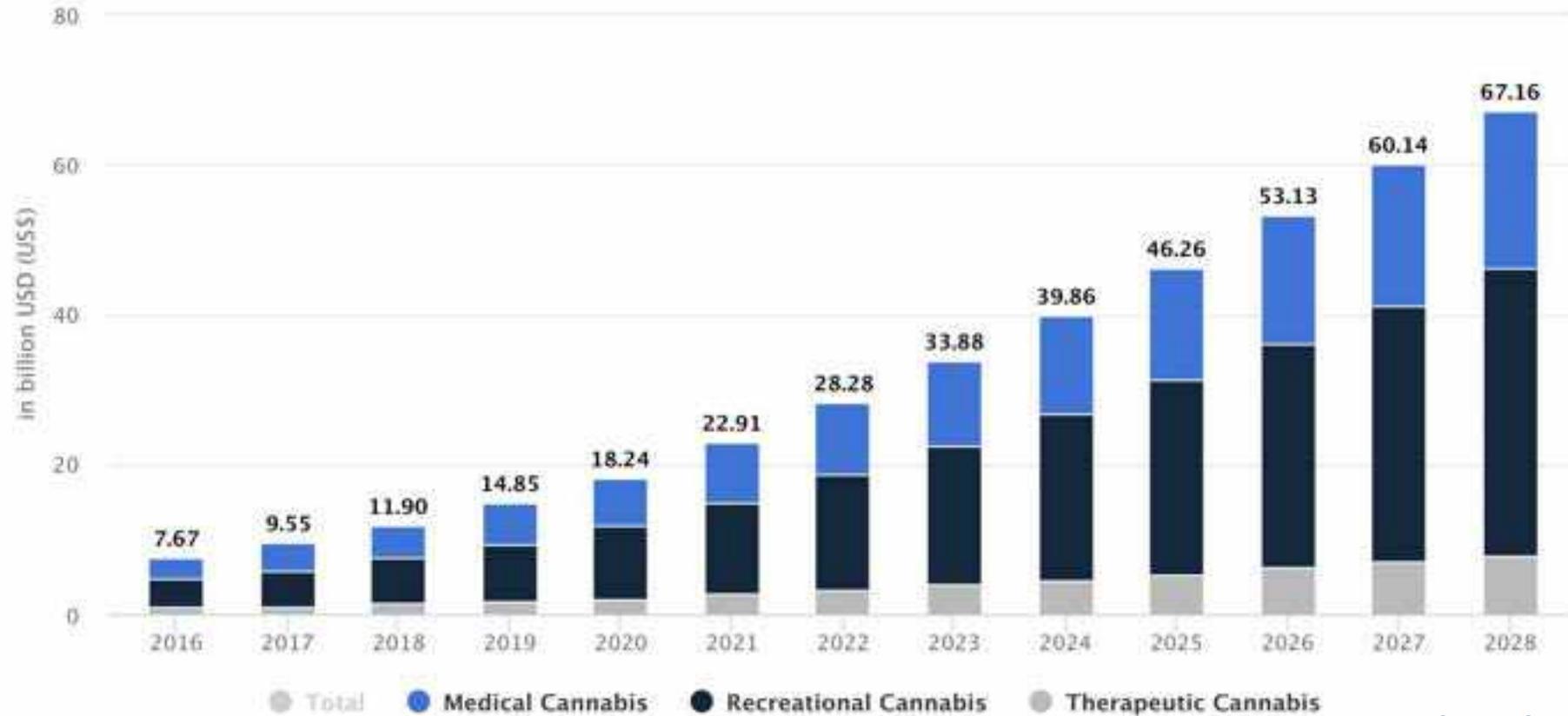
Source: Gallup

What's happening with cannabis?



Source: *Rolling Stone*

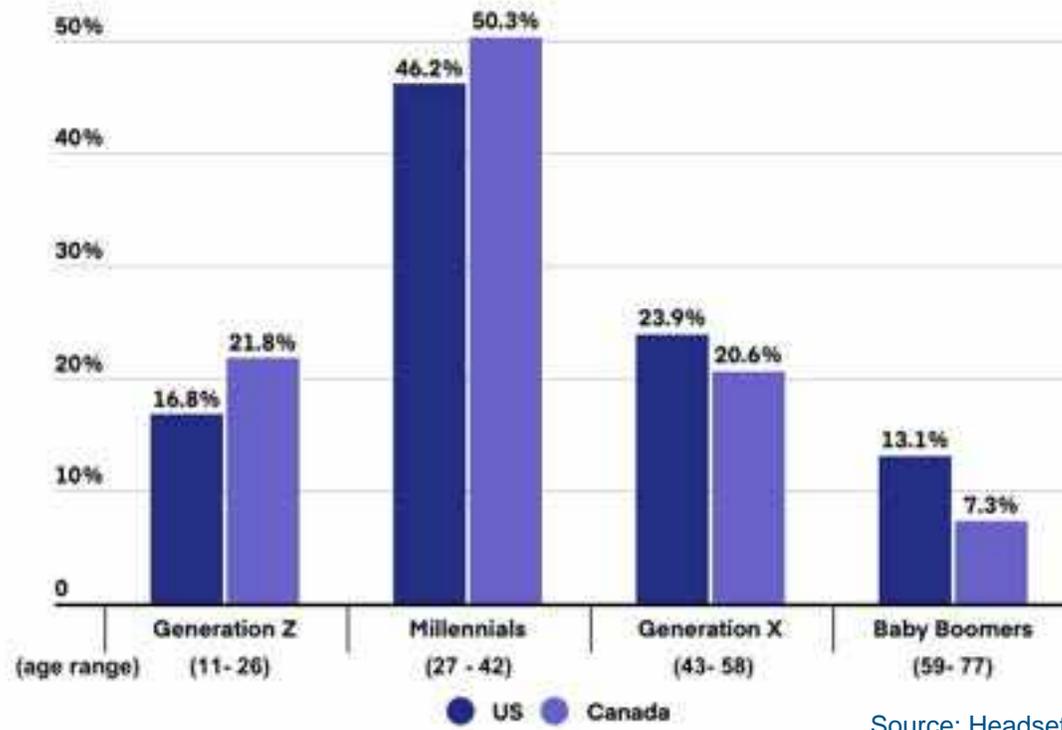
What's happening with cannabis?



Source: Statista

What's happening with cannabis?

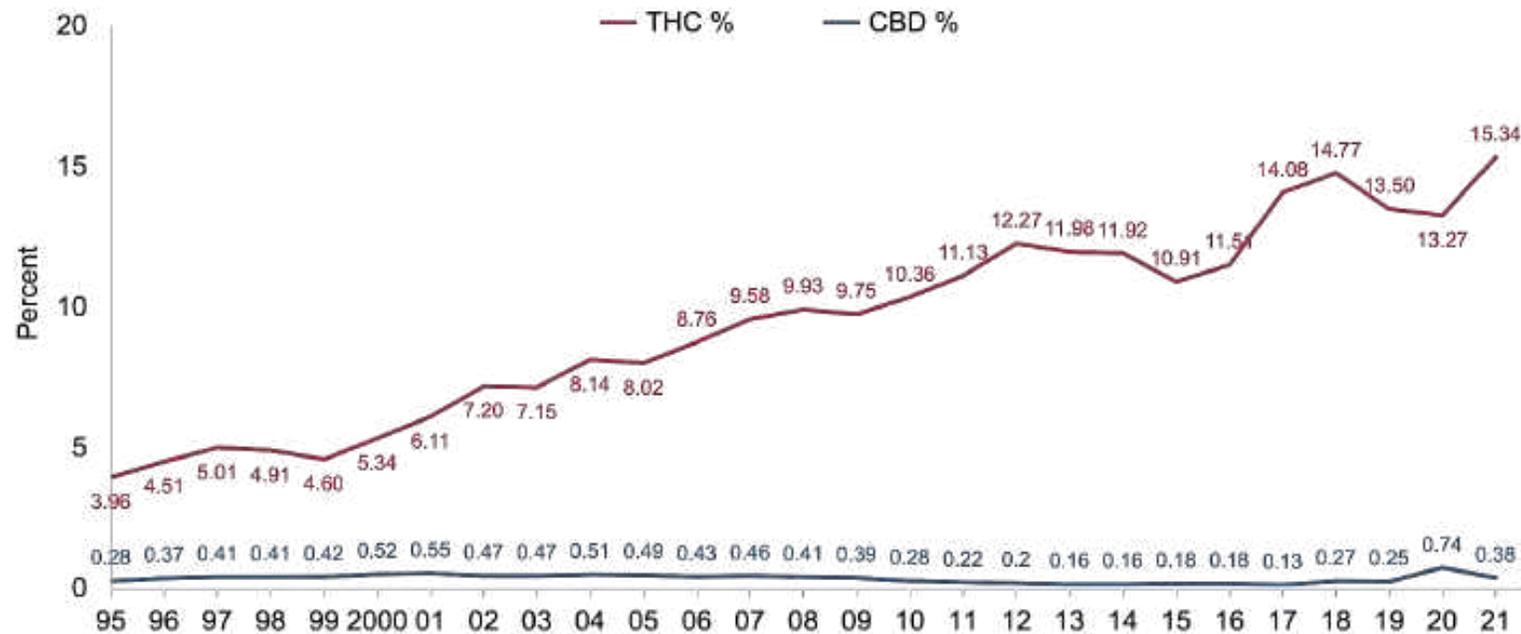
Percent of Total Sales by Age Group
(Jan - Feb 2023)



Source: Headset

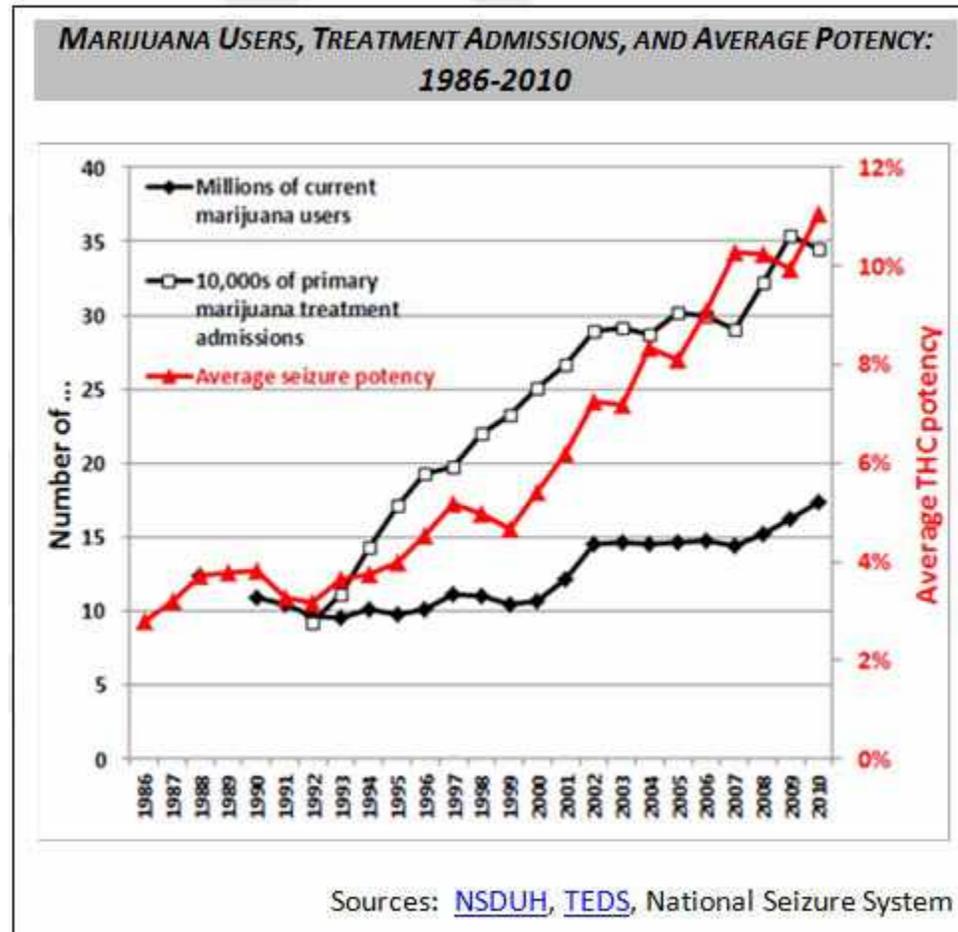
What's happening with cannabis?

Percentage of THC and CBD in Cannabis Samples Seized by the DEA, 1995-2021



SOURCE: U Miss, Potency Monitoring Project

What's happening with cannabis?





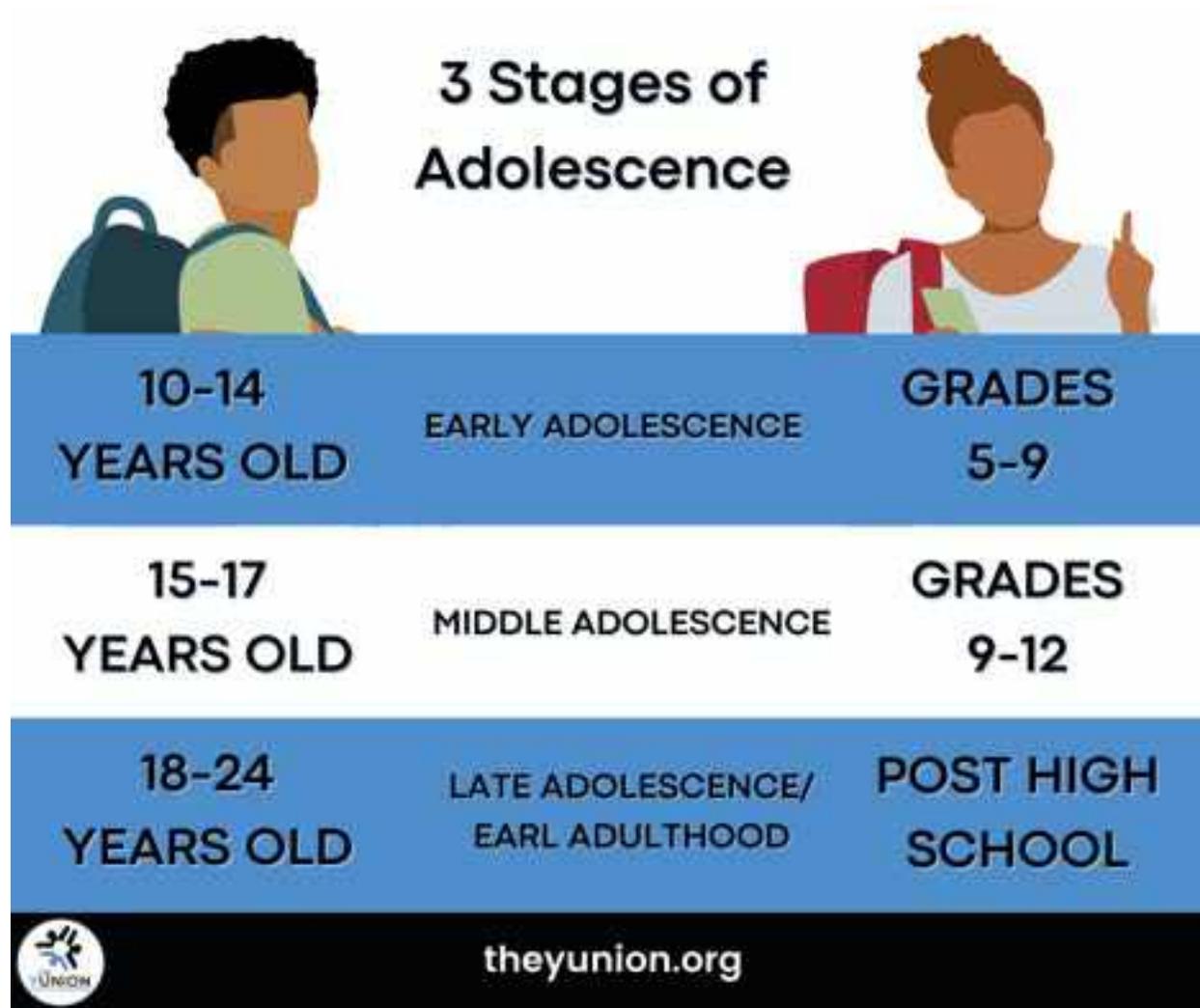
What's happening with youth?

What's happening with youth?



- Teenagers these days are out of control. They eat like pigs, they are disrespectful of adults, they interrupt and contradict their parents, and they terrorize their teachers.
- – Aristotle

What's happening with youth?

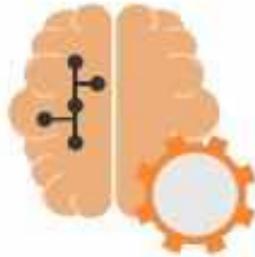


What's happening with youth?



Our adolescent years—from around age 10 to about 25—are a period of remarkable growth and opportunity.

We discover, learn from, and adapt to the world around us, forging our sense of who we are and who we aspire to be.



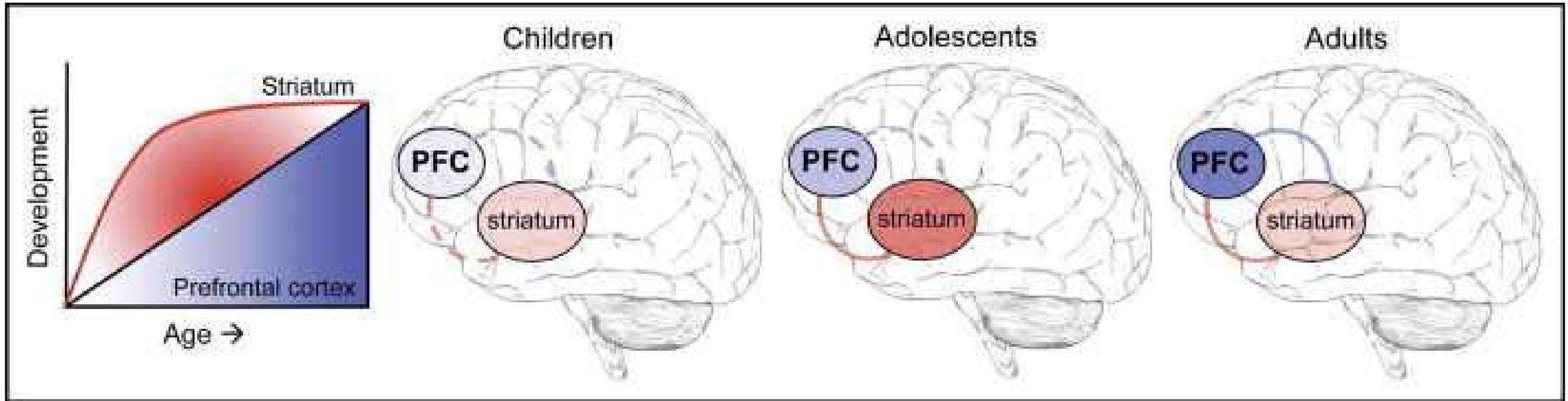
We learn to make decisions, manage our emotions, and create deeper connections with peers and others in our communities.

We also build resilience and develop interests, passions, and meaningful goals that shape our adult lives.



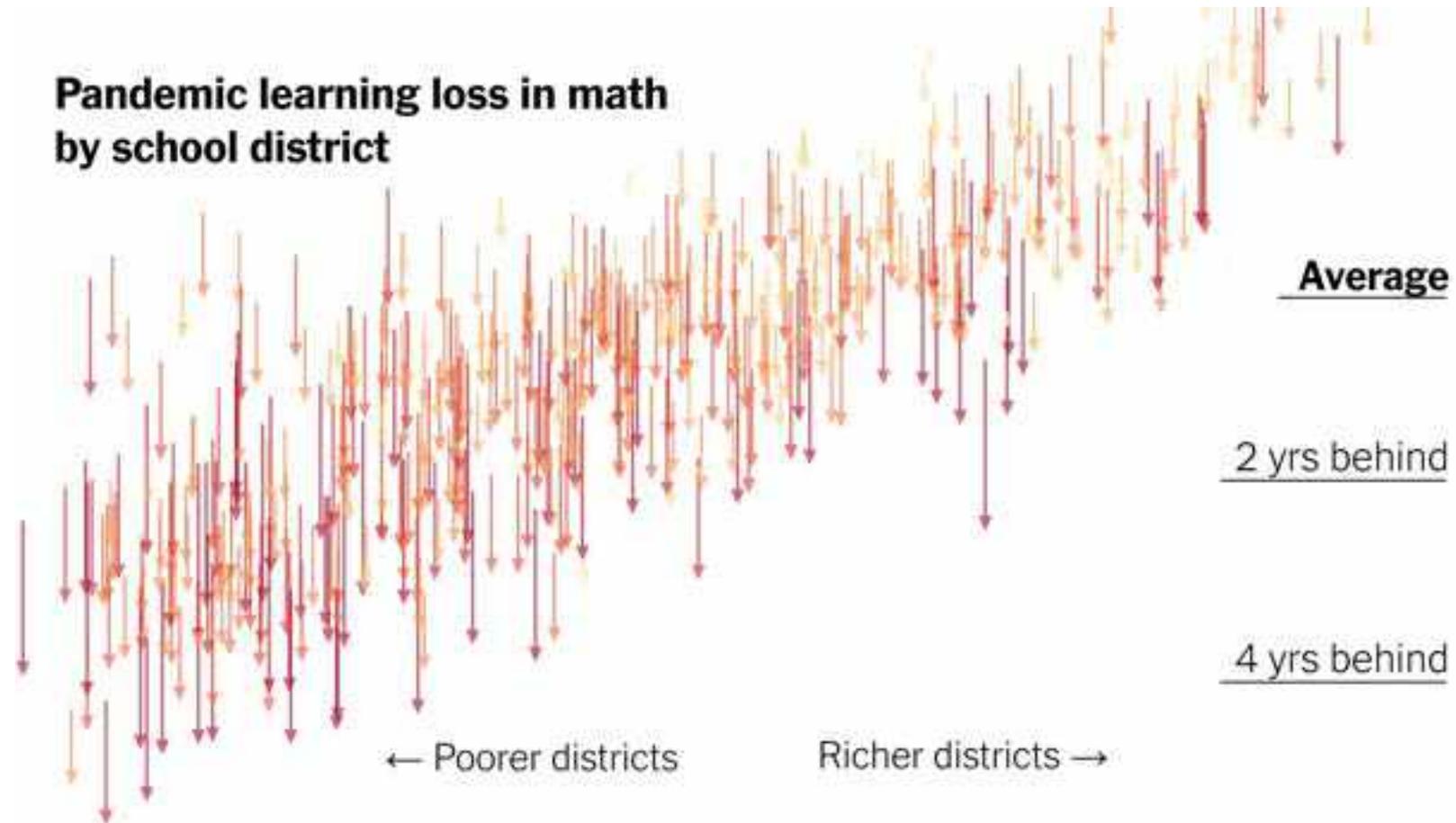
Source: UCLA Center for the Developing Adolescent

What's happening with youth?



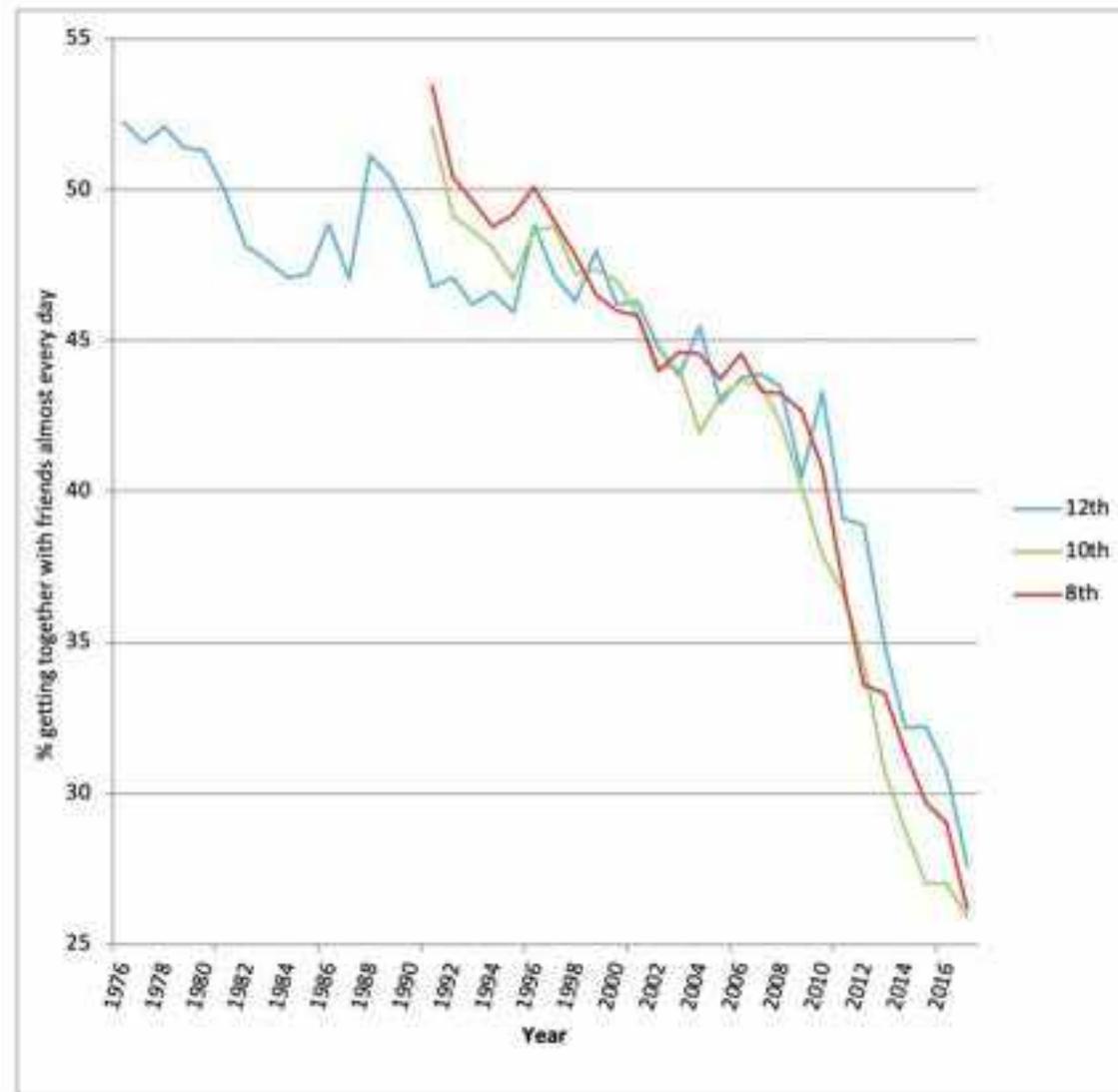
Source: Casey & Jones, 2010

What's happening with youth?



Source: *New York Times*, based on findings from Stanford University and Harvard University

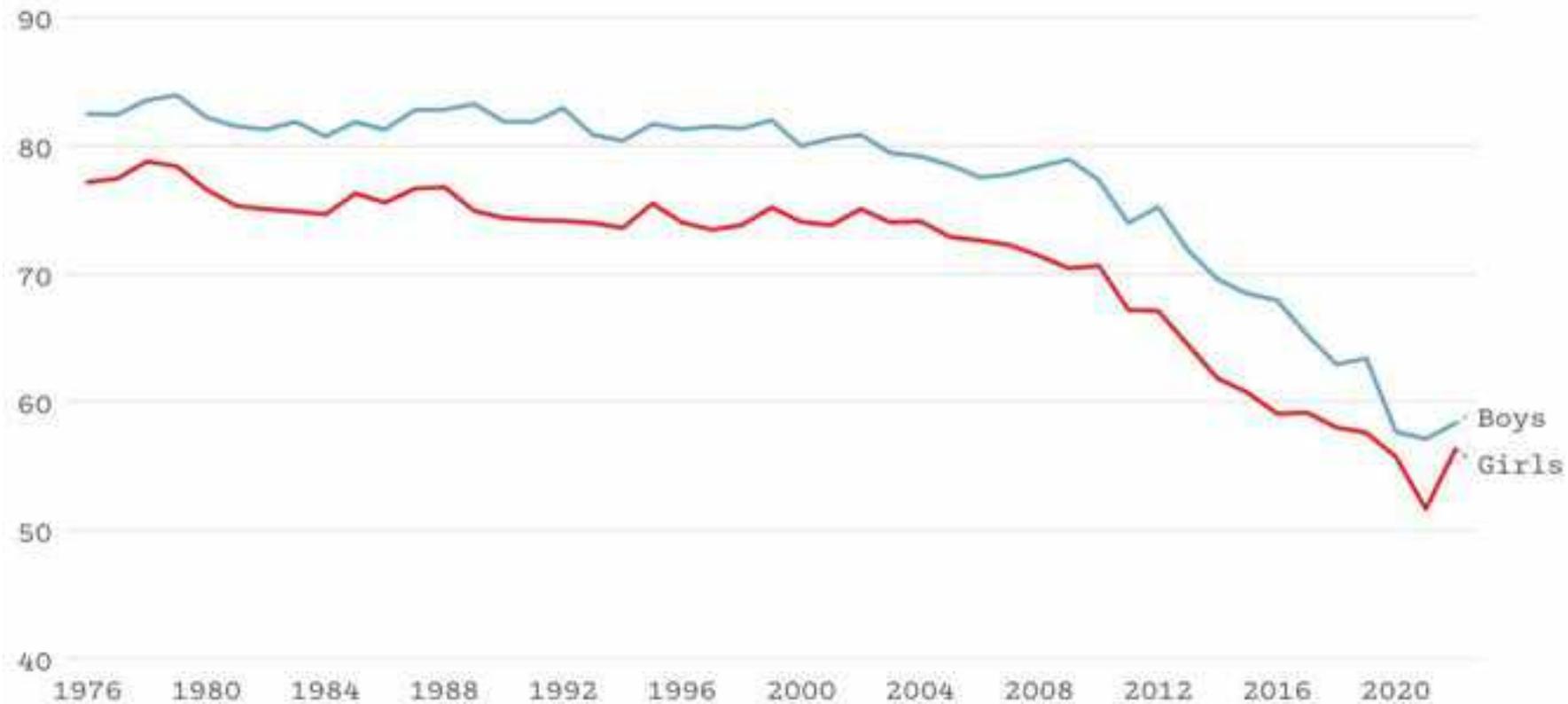
What's happening with youth?



Source: Monitoring the Future survey

What's happening with youth?

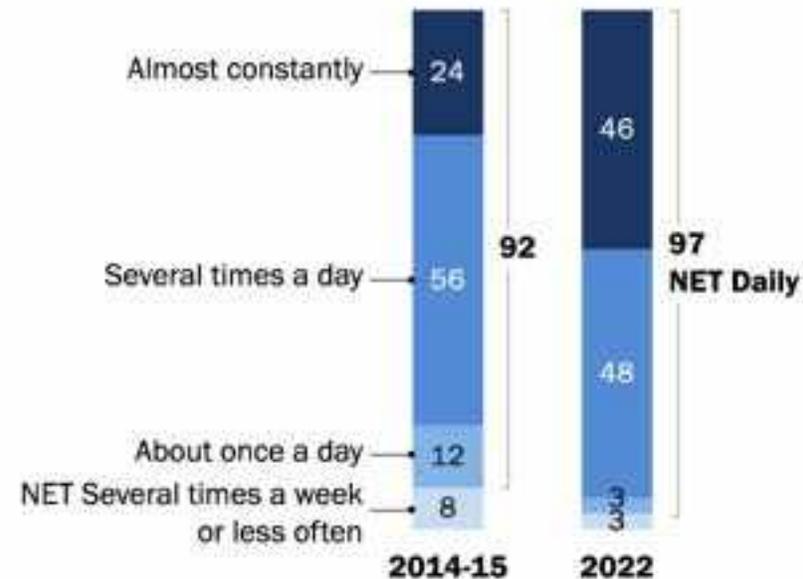
Percent of 12th graders who say they go out with friends 2+ times per week (Monitoring the Future survey)



What's happening with youth?

Nearly half of teens now say they use the internet 'almost constantly'

% of U.S. teens who say they use the internet ...



Note: Teens refer to those ages 13 to 17. Figures may not add up to the NET values due to rounding. Those who did not give an answer are not shown.

Source: Survey conducted April 14-May 4, 2022.

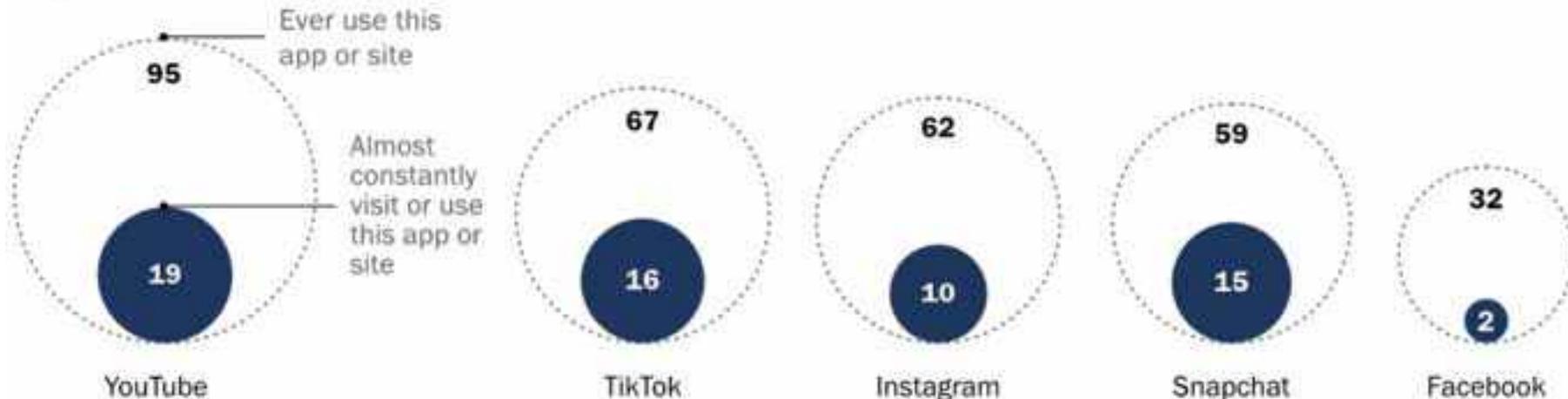
"Teens, Social Media and Technology 2022"

PEW RESEARCH CENTER

What's happening with youth?

About one-in-five teens visit or use YouTube 'almost constantly'

% of U.S. teens who say they ...



Note: Teens refer to those ages 13 to 17. Those who did not give an answer or gave other responses are not shown.

Source: Survey conducted April 14-May 4, 2022.

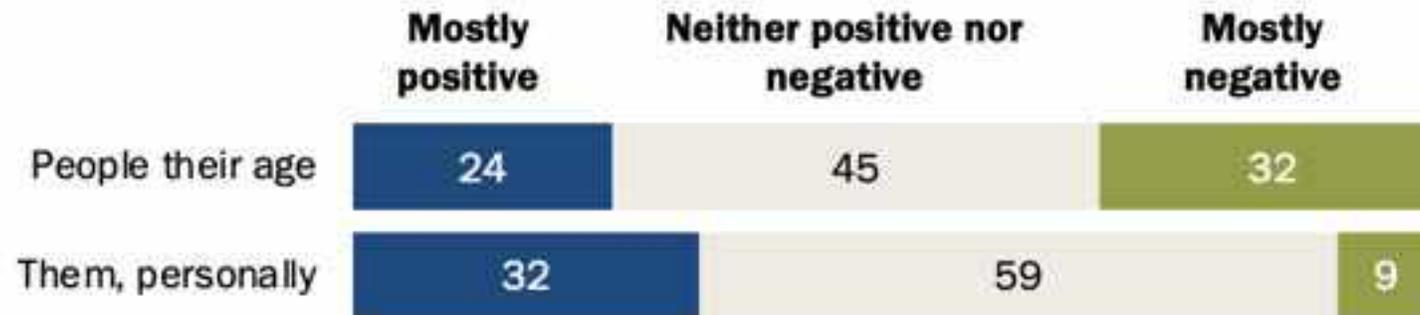
"Teens, Social Media and Technology 2022"

PEW RESEARCH CENTER

What's happening with youth?

Teens more likely to see potential negative effects of social media for other teens than for themselves

% of U.S. teens who say social media has had a ___ effect on each of the following



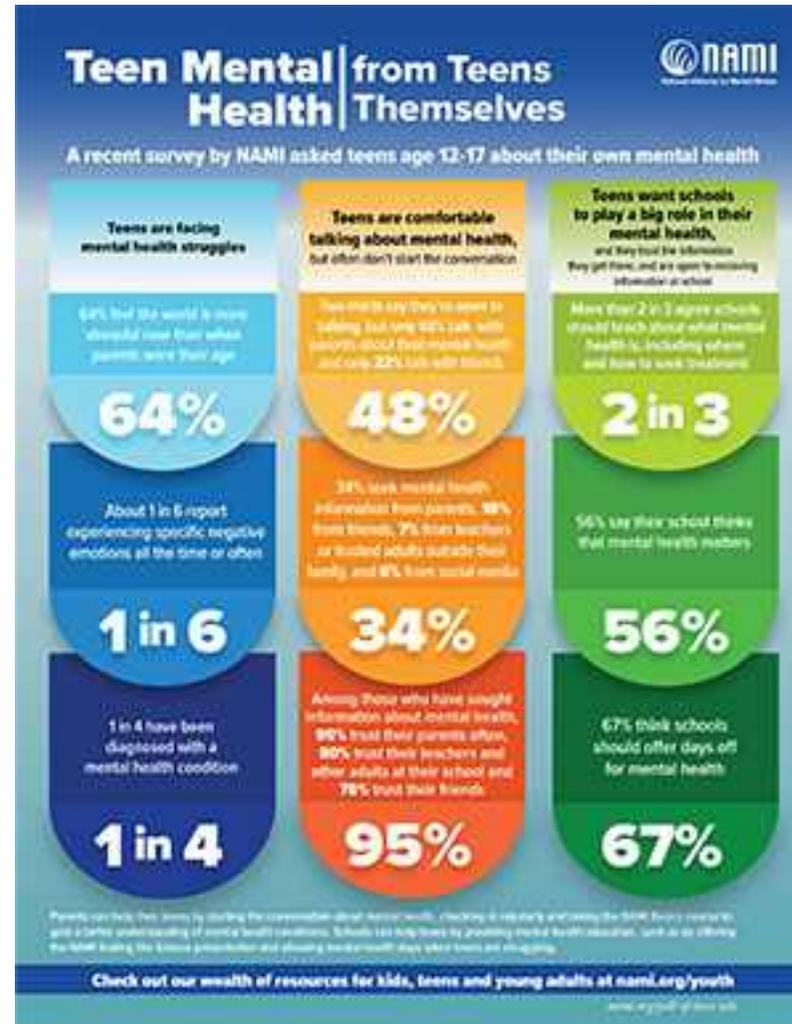
Note: Teens are those ages 13 to 17. Those who did not give an answer are not shown.

Source: Survey conducted April 14-May 4, 2022.

"Connection, Creativity and Drama: Teen Life on Social Media in 2022"

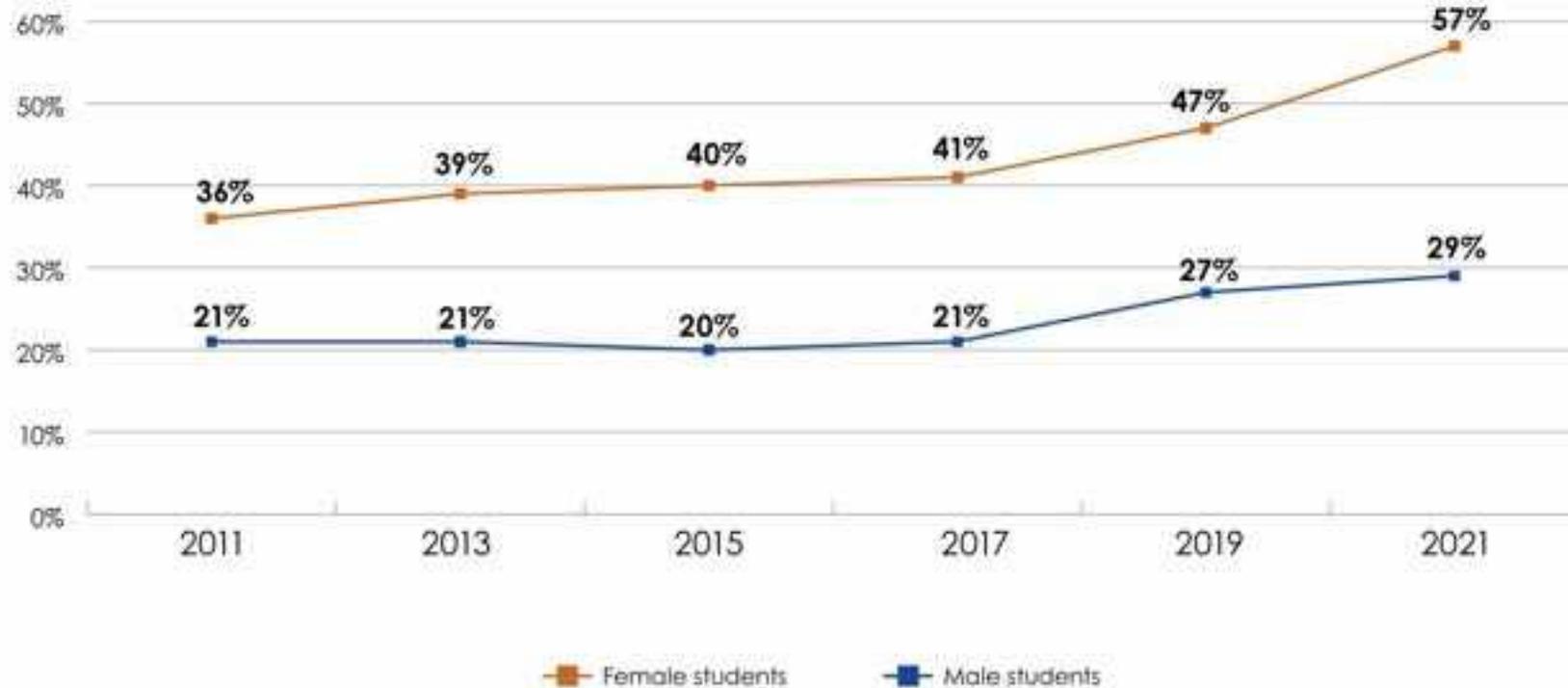
PEW RESEARCH CENTER

What's happening with youth?



What's happening with youth?

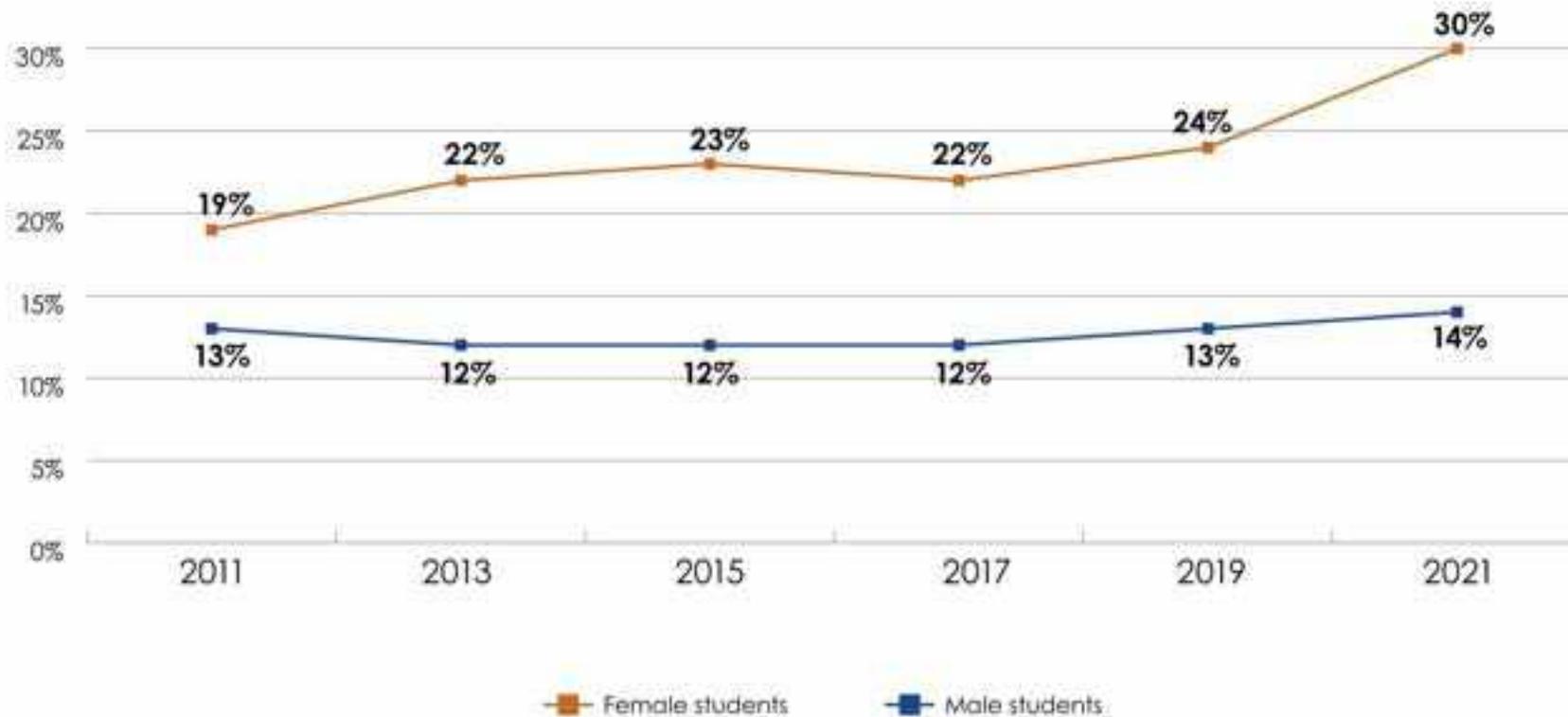
**PERSISTENT FEELINGS OF SADNESS OR HOPELESSNESS
AMONG U.S. HIGH SCHOOL STUDENTS, BY SEX, 2011-2021**



Source: CDC

What's happening with youth?

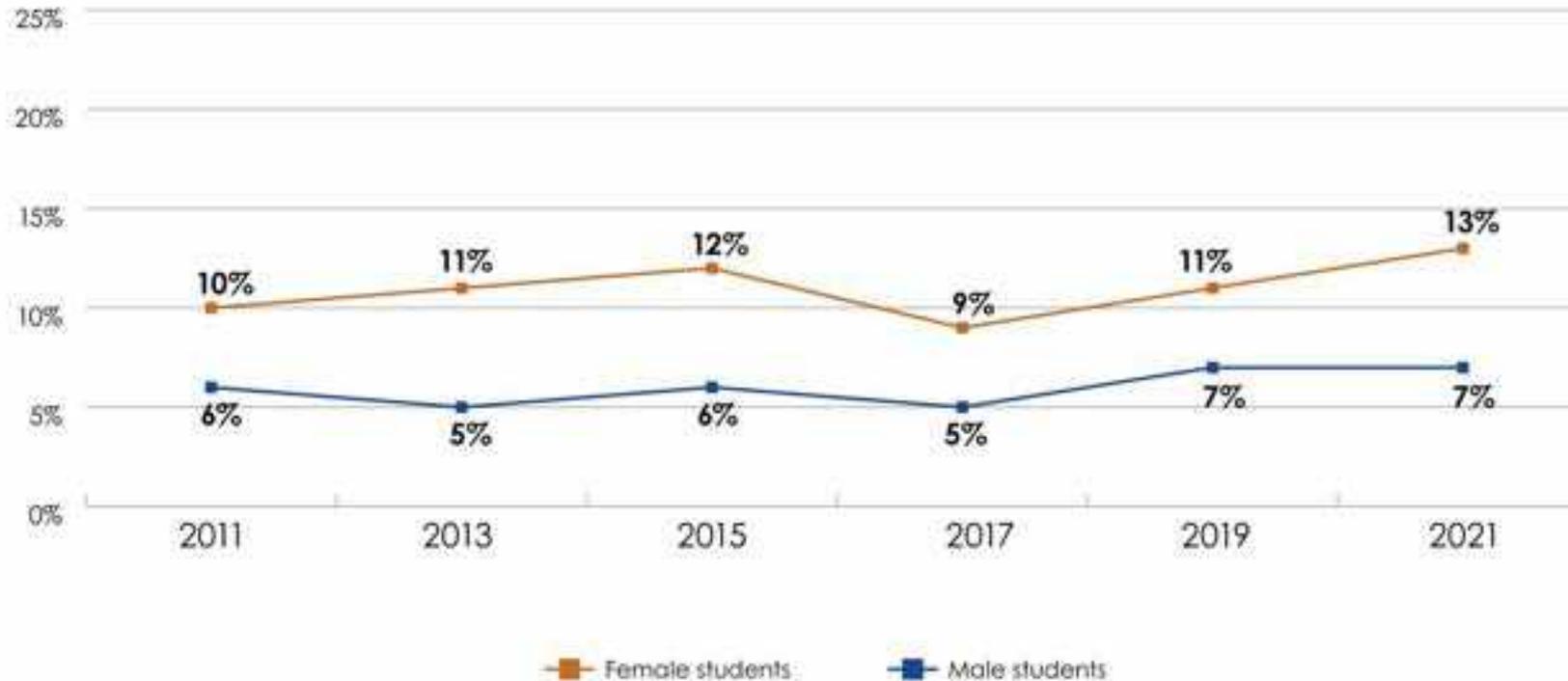
**SERIOUSLY CONSIDERED ATTEMPTING SUICIDE
AMONG U.S. HIGH SCHOOL STUDENTS, BY SEX, 2011-2021**



Source: CDC

What's happening with youth?

ATTEMPTED SUICIDE AMONG U.S. HIGH SCHOOL STUDENTS,
BY SEX, 2011-2021



Source: CDC

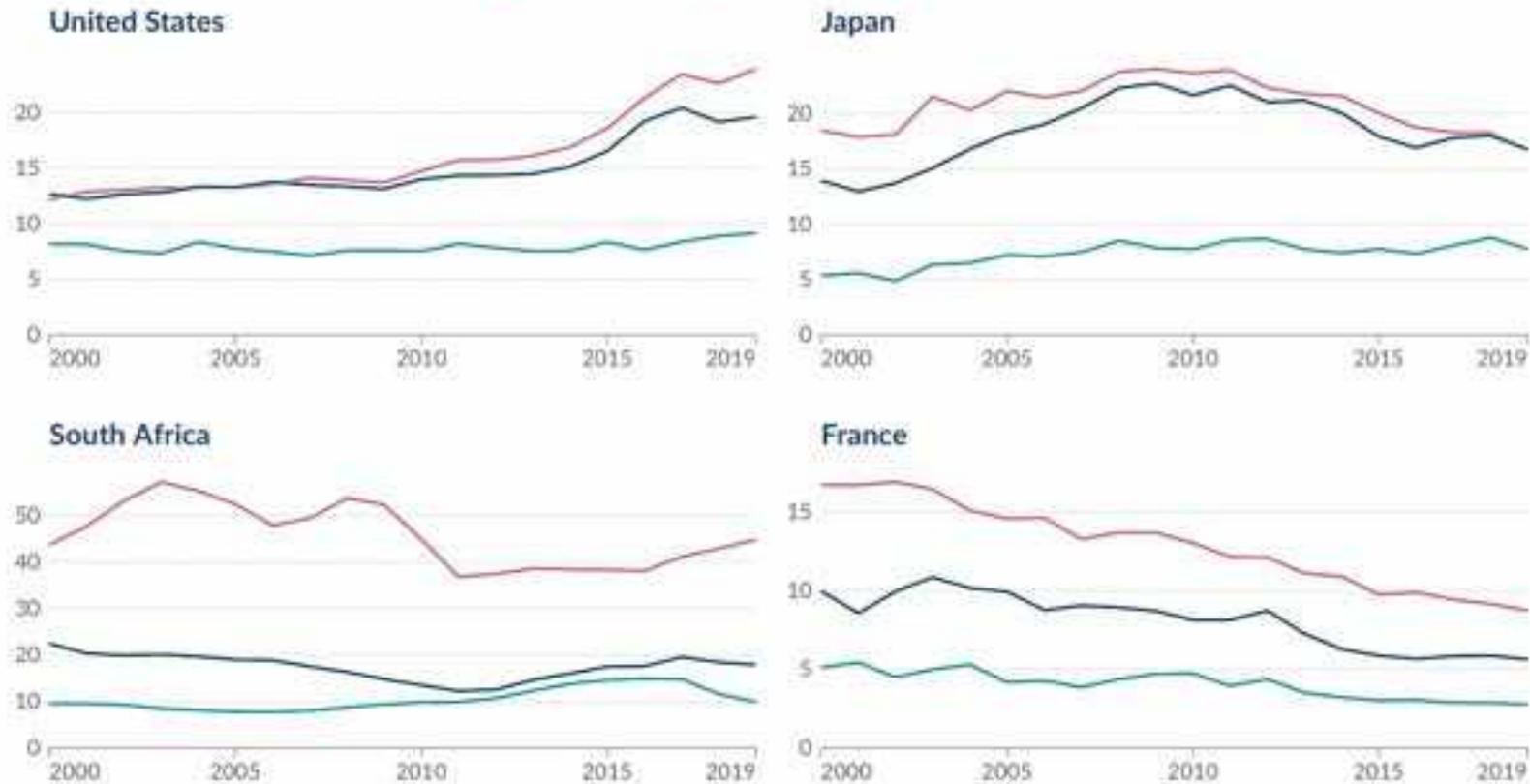
What's happening with youth?

Suicide rates among young people, 2000 to 2019

Our World
in Data

Number of deaths by suicide per 100,000 individuals in each age group. Suicide deaths are underreported in many countries due to social stigma and cultural or legal concerns.

■ 15-19 years ■ 20-24 years ■ 25-34 years



Data source: WHO, Global Health Estimates (2020)

OurWorldInData.org/suicide | CC BY



What's happening with cannabis + youth?

What's happening with cannabis + youth?

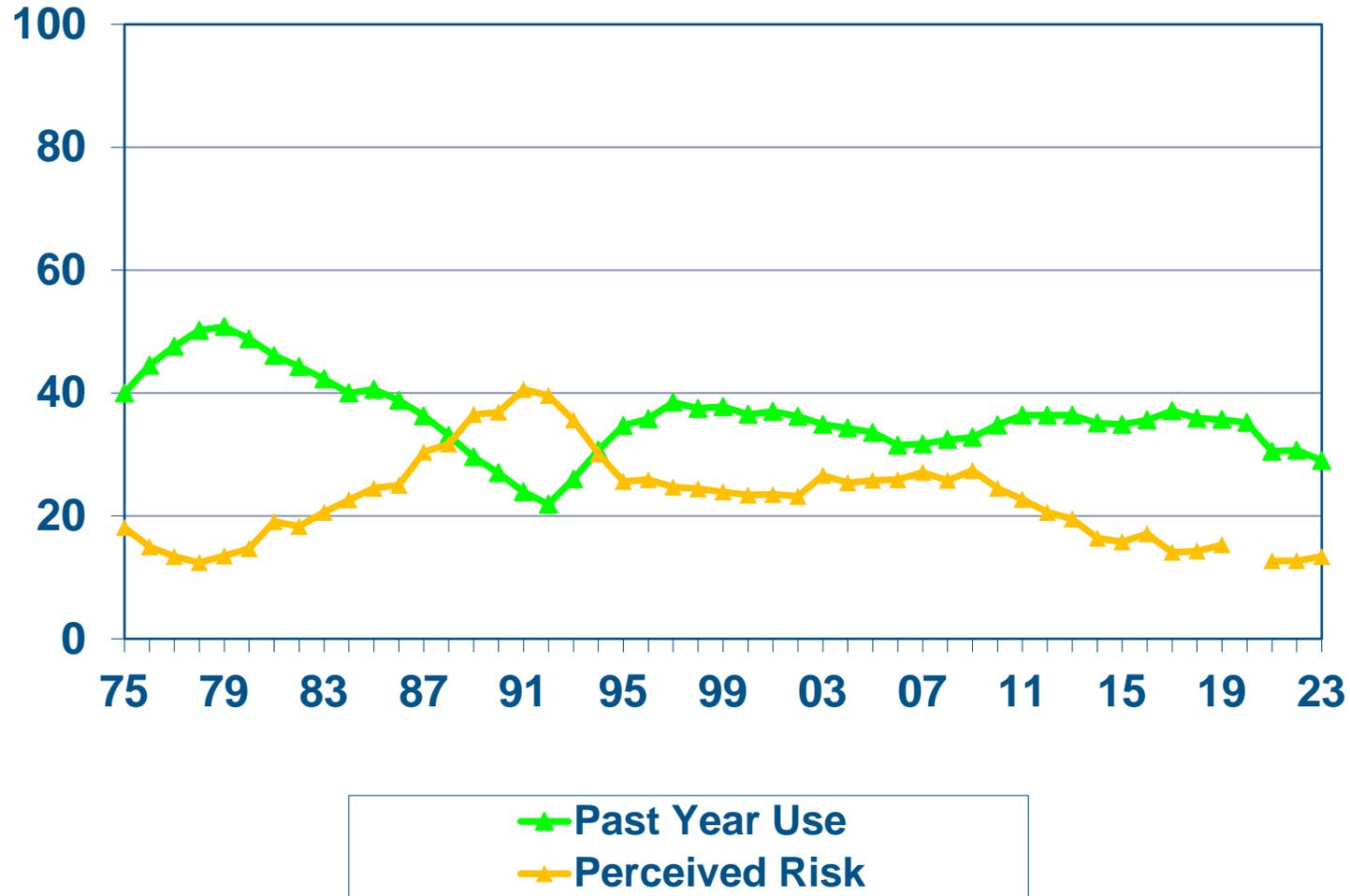


Caitlin Gibson

The Washington Post, May 3, 2023

<https://www.washingtonpost.com/parenting/2023/05/01/teen-pot-use/>

What's happening with cannabis + youth?



SOURCE: 2023 Monitoring the Future survey

- Cannabis use among adolescents is strongly correlated with perceived risk of cannabis use-related harm (Monitoring the Future)
- State-level legalization does not correlate with adolescent cannabis use within a given state (Bailey et al., 2023)
- Legalization does not appear to have a cause-and-effect relationship with adolescent cannabis use; both may stem from reduced perception of cannabis-related risks (“attitudes cross state lines”)

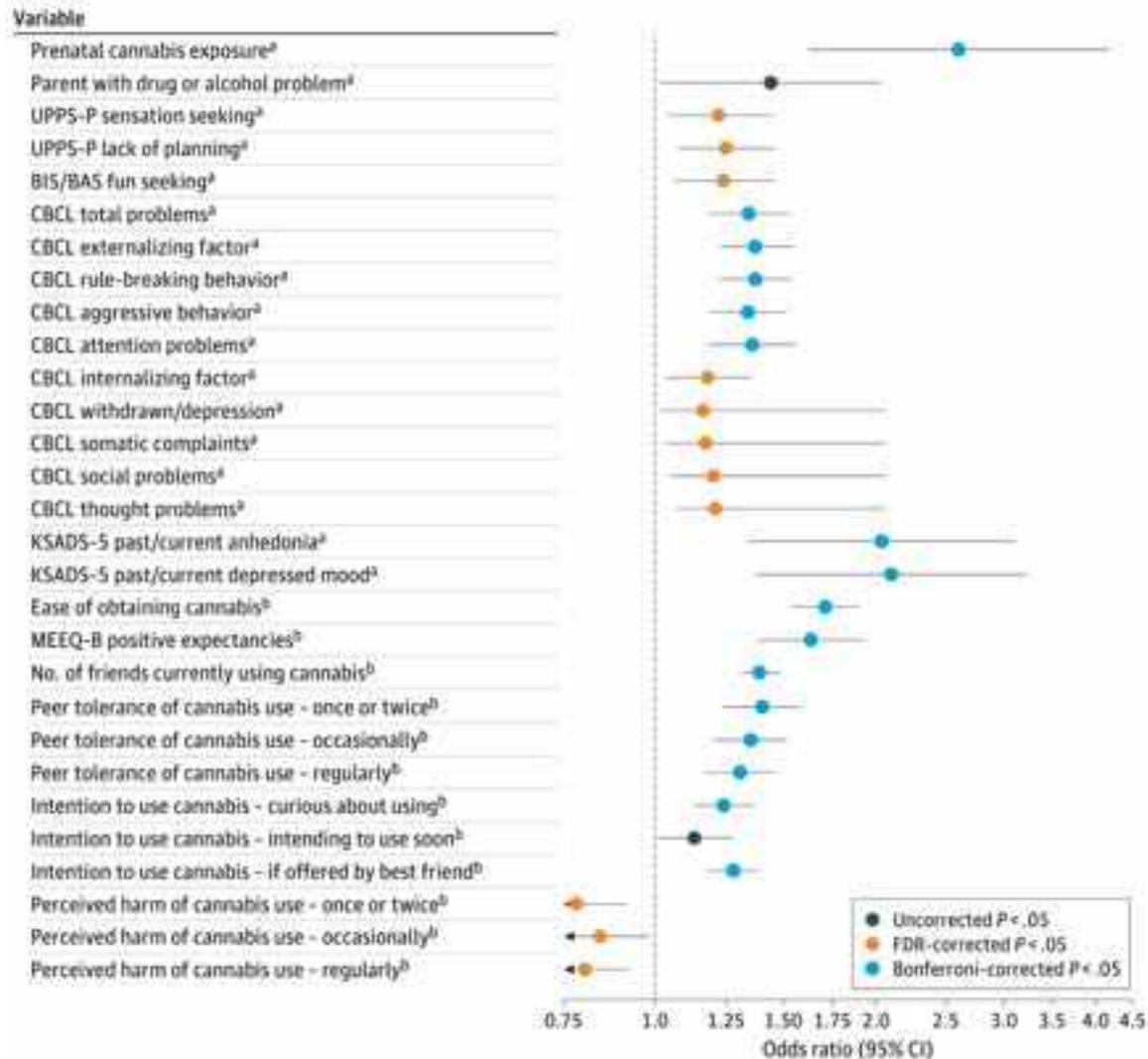
What's happening with cannabis + youth?

12 th graders in USA	Marijuana (in general)	Vaping Marijuana
Ever used	38.3%	27.5%
Used in past year	30.7%	20.6%
Used in past 30 days	20.2%	14.8%
Daily use in past 30 days	6.3%	2.1%

Source: Monitoring the Future 2023

Social media use is associated with cannabis vaping initiation among US youth (Lee et al., 2023)

What's happening with cannabis + youth?



Miller et al., 2023, *JAMA Pediatrics*

Predictors of early cannabis initiation in the ABCD Study cohort

- Initiation of alcohol OR 17.46
- Initiation of tobacco use OR 35.85
- Prenatal cannabis exposure OR 2.60 (controlling for potentially confounding factors OR 2.16)
- Ease of obtaining, positive expectancies, number of friends using, greater peer tolerance
- Greater externalizing symptomatology, depressed mood, and anhedonia

What's happening with cannabis + youth?

Why worry about cannabis use?

- **Acute/intoxication**
 - Impaired driving performance and decision-making (Manning et al., 2024, Dellazizzo et al., 2022)
- **Chronic/repeated use**
 - Cannabis use disorder (CUD)
 - More prevalent than previously thought
 - 1/5 lifetime users, of whom 23% are symptomatically severe, of whom 48% are not functioning in any role (e.g., work, school) (Hasin, 2018; Leung et al., 2020)
 - Primary driver of global disease burden of cannabis use (Degenardht et al., 2013)
- **Use during pregnancy – effects on neonate/child** (Baranger et al., 2022; Hiraoka et al., 2023; Paul et al., 2021)
- **Exposure/use during childhood/adolescence**
 - Higher (~2x) rate of CUD than in adult cannabis users (Hasin, 2018)
 - Effects on cognition, emotion, and development

What's happening with cannabis + youth?

Why worry about cannabis use among youth?

- Lichenstein et al. (2022). Systematic review of structural and functional neuroimaging studies of cannabis use in adolescence and emerging adulthood: Evidence from 90 studies and 9441 participants. *Neuropsychopharmacology*, 47(5), 1000-1028.
 - Preliminary evidence for functional and structural alterations in frontoparietal, frontolimbic, frontostriatal, and cerebellar regions among adolescent cannabis users
- Solmi et al. (2023). Balancing risks and benefits of cannabis use: Umbrella review of meta-analyses of randomised controlled trials and observational studies. *BMJ*, 382, e072348.
 - “Convincing converging evidence supports avoidance of cannabis use during adolescence and early adulthood, in people prone to or with mental health disorders, in pregnancy, and before and while driving.”

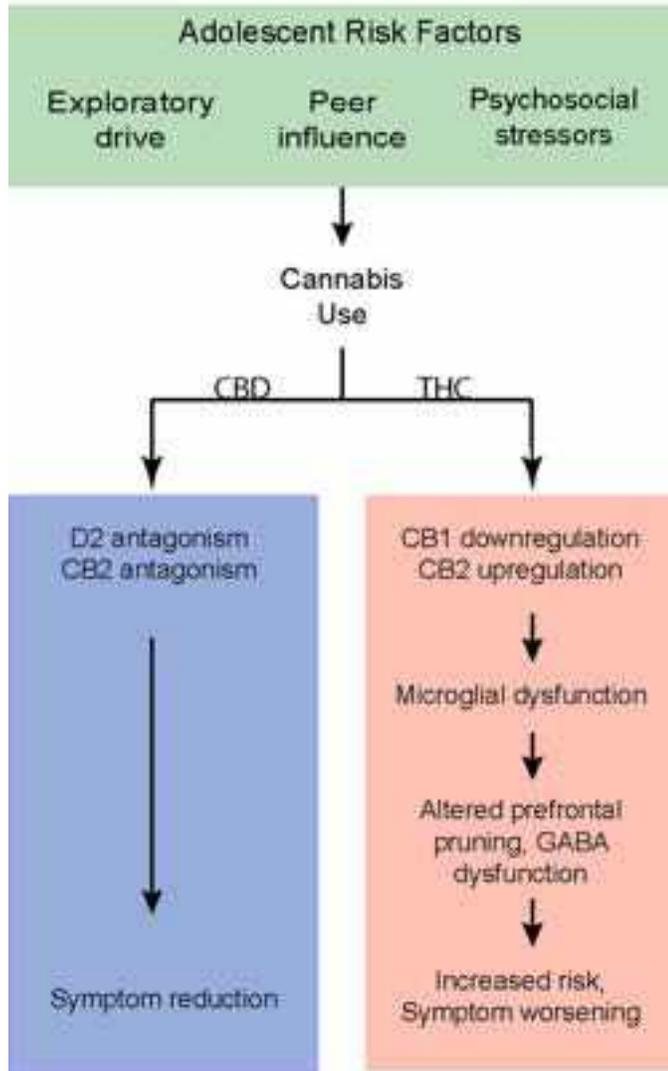
What's happening with cannabis + youth?

Why worry about cannabis use among youth?

- **Cognitive performance** (Lorenzetti et al., 2020; Scott et al., 2018; Wallace et al., 2020)
 - Impairment occurs beyond intoxication, though it appears to largely resolve with sustained abstinence
 - Academic and occupational attainment (Ferguson et al., 2015; Maggs et al., 2015; Melchior et al. 2017; Schaefer et al., 2021)
- **Mental health**
 - The relationship between cannabis use and mental health symptoms in youth is complex, with ample evidence of bidirectional associations
 - Gobbi et al. (2019). Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: A systematic review and meta-analysis. *JAMA Psychiatry*, 76(4), 426-434.
 - Depression OR 1.37; Anxiety 1.18 (NS); Suicidal ideation 1.50; Suicide attempt 3.46

What's happening with cannabis + youth?

Cannabis Use and Psychosis Risk



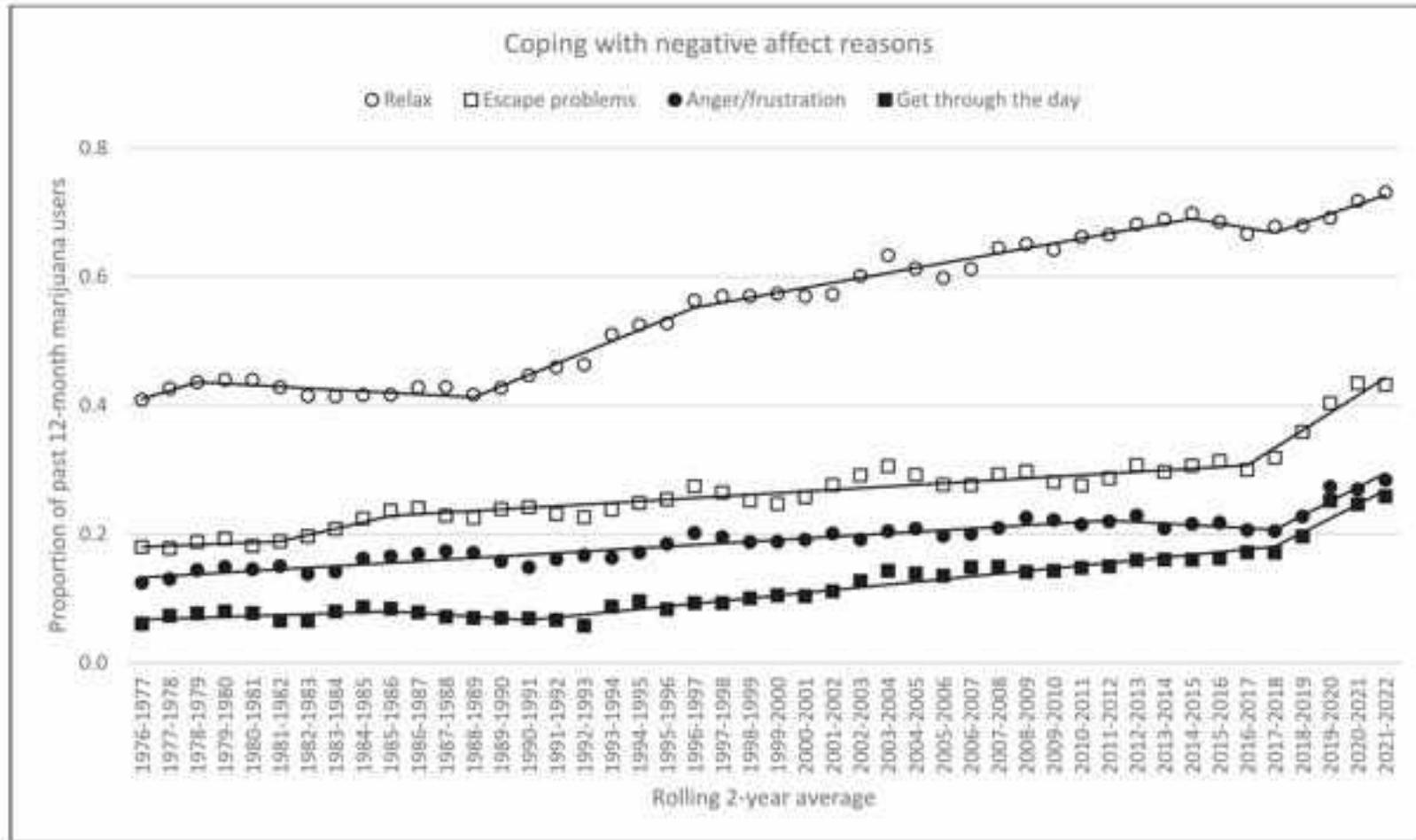
- Cannabis use and psychosis have a bidirectional relationship (Patel et al., 2021)
- Cannabis use at age 16 predicted psychosis vulnerability at age 19; psychosis vulnerability at ages 13 and 16 predicted cannabis use at ages 16 and 19 (Griffith-Lending et al., 2013)
- Cannabis use increases risk of psychotic outcomes independently of confounding of transient intoxication effects, baseline prodromal symptoms, parental psychosis, and other substance use (Moore et al., 2007; Mustonen et al., 2018)
- Meta analysis: heaviest users vs non-users OR 3.9 in risk of schizophrenia and other psychosis-related outcomes (Marconi et al., 2016)
- Population attributable fraction of cannabis for schizophrenia is almost 10% (Dragioti et al., 2022)

What's happening with cannabis + youth?

How do we know which youth are more at risk than others?

- We've reviewed predictors of early cannabis initiation (Miller et al., 2023)
- What's an important clinical predictor of escalation from use to adverse consequences?
 - **Using to cope with negative emotions**
 - Emotional distress motives are associated with greater problematic cannabis use (Conn et al., 2024)
 - Coping motives related to escalating use and negative consequences (Schultz et al., 2023)
 - Sex differences in coping motives and craving (Gex et al., 2023)
 - Patrick et al., 2024. Trends in coping reasons for marijuana use among US adolescents from 2016 to 2022. *Addictive Behaviors*, 148, 107845.
 - **Consistent increase in coping reasons for adolescent cannabis use over time**
 - Those who use frequently (versus less often) had higher odds of endorsing all coping reasons

What's happening with cannabis + youth?



Patrick et al., 2024

How can we make sense of this and address it?

How to make sense of this?

- “At a cardiac arrest, the first procedure is to take your own pulse.” – Saul Shem, *House of God*
- We are all awash in an environment of information overload, and it’s easy to become paralyzed or to tune out when grappling with a complicated topic



Prevention: Cannabis-related messaging to youth

- Messaging must reflect the evidence base, be developmentally appropriate, and be salient to the target audience(s)
 - Approaches that exaggerate or minimize risks may ultimately fail
 - A one-size-fits-all approach often falls flat, as history suggests
- What messages can stand out and yield meaningful positive effects amid a cluttered information environment?
- There are roles for both messaging and modeling of behavior
 - Is it possible that the most powerful messages might not even mention cannabis?
- Responsibility for messaging and modeling can be shared by many adults and systems, though the optimal messaging may necessarily require peer-to-peer transmissibility
- We have a unique position as clinical providers; it is important to leverage this position of authority thoughtfully and effectively

Early intervention: Youth-targeted cannabis brief interventions

What do we know about the effect of cannabis-focused brief interventions?

- Across platforms and strategies, including Screening, Brief Intervention, and Referral to Treatment (SBIRT), effects have been limited (Gette et al., 2023)
- A shortcoming of brief interventions to date is that many were adapted from alcohol brief interventions, without substantial consideration of cannabis-specific factors (Gex et al., in press)
- Work is underway to yield tailored early intervention strategies for youth that are in early stages of cannabis use

Treatment: Youth-targeted cannabis use disorder interventions

Psychosocial and behavioral approaches supported by evidence

- Motivational Interviewing (Walker et al., 2011)
- Cognitive Behavioral Therapy (Hendriks et al., 2011)
- Family Therapy (Rigter et al., 2012)

While these treatments are effective, long-term abstinence outcomes are generally poor (Compton & Pringle, 2004; Dennis et al., 2004; Waldron & Turner, 2008; Hogue et al., 2014)

Contingency Management (CM) can be used to reinforce abstinence (and other desired behaviors) and enhance outcomes (Stanger et al., 2009; Stanger et al., 2015)

There is room for improvement!

How can we improve treatment outcomes?

Bolstering psychosocial and behavioral treatments

- Integrated strategies for concurrently treating CUD and co-occurring mental health disorders
- Approach avoidance training (Jacobus et al., 2018)

Employing treatment tailoring based on clinical presentation

- Using machine learning algorithms to determine who is most likely to respond to a given treatment (Tomko et al., 2023)

Potential somatic or pharmacologic approaches

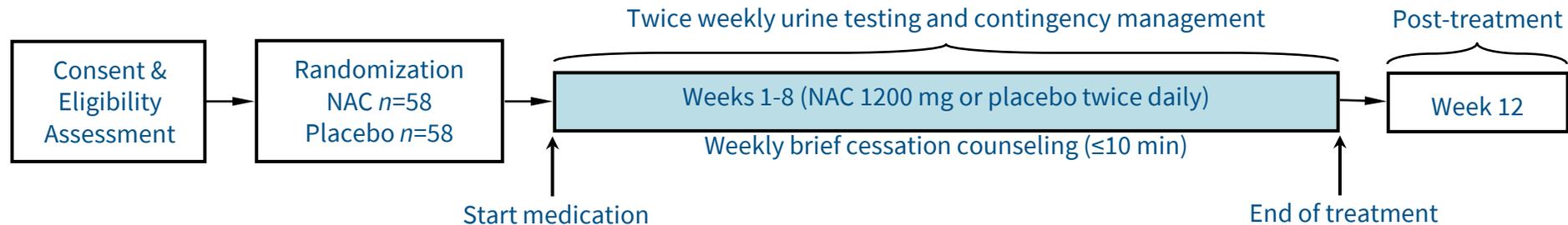
- Transcranial magnetic stimulation (Sahlem et al., 2024)
- Pharmacotherapies (for review: Kondo et al., 2020)

Human Laboratory Controlled Trials		Pilot Controlled Trials		Fully Powered Controlled Trials	
Discouraging	Encouraging	Discouraging	Encouraging	Negative/Null	Positive or Mixed
Bupropion SR (N=10) (Haney et al., 2001)	Rimonabant (N=63, 36) (Huestis et al., 2001; Huestis et al., 2007)	Divalproex (N=25) (Levin et al., 2004)	Buspirone (N=50) (McRae-Clark et al., 2009)	Dronabinol (N=156) (Levin et al., 2011)	<i>N</i> -acetylcysteine (N=116 adolescents) (Gray et al., 2012)
Nefazodone (N=7) (Haney et al., 2003)	Dronabinol (N=7, 8) (Haney et al., 2004; Budney et al., 2007)	Bupropion SR (N=106, 22) (Carpenter et al., 2009; Penetar et al., 2012)	Gabapentin (N=50) (Mason et al., 2012)	Venlafaxine XR (N=103) (Levin et al., 2013)	Nabiximols (N=128) (Lintzeris et al., 2019, 2020)
Divalproex (N=7) (Haney et al., 2004)	Lofexidine+ Dronabinol (N=8) (Haney et al., 2008)	Nefazodone (N=106) (Carpenter et al., 2009)	Oxytocin (N=16) (Sherman et al., 2017)	Buspirone (N=175) (McRae-Clark et al., 2016)	Quetiapine (N=130) (Mariani et al., 2021)
Baclofen (N=10) (Haney et al., 2010)	Zolpidem CR (N=20) (Vandrey et al., 2011)	Atomoxetine (N=78) (McRae-Clark et al., 2010)	Nabiximols (N=9, 40) (Trigo et al., 2016, 2018)	Lofexidine+ Dronabinol (N=122) (Levin et al., 2016)	
Mirtazapine (N=11) (Haney et al., 2010)	Nabilone (N=11) (Haney et al., 2013)	Escitalopram (N=52) (Weinstein et al., 2014)	PF-04457845 FAAH inhibitor (N=70) (D'Souza, 2019)	<i>N</i> -acetylcysteine (N=302) (Gray et al., 2017)	
Naltrexone (N=14, 31, 29) (Wachtel & de Wit, 2000; Haney et al., 2003; Cooper & Haney, 2010)	Nabiximols (N=51) (Allsop et al., 2014)	Lithium (N=41) (Johnston et al., 2014)	Cannabidiol (N=48) (Freeman et al., 2020)	Gabapentin (N=150) (Mason, clinicaltrials.gov)	
Quetiapine (N=14) (Cooper et al., 2013)	Naltrexone (N=51) (Haney et al., 2015)	Vilazodone (N=76) (McRae-Clark et al., 2016)	Varenicline (N=72) (McRae-Clark et al., 2021)	PF-04457845 FAAH inhibitor (N=228) (D'Souza, clinicaltrials.gov)	
Cannabidiol (N=31) (Haney et al., 2016)	Zolpidem+Nabilone (N=11) (Herrmann et al., 2016)	Topiramate (N=66 adolescents) (Miranda et al., 2016)			
Tiagabine (N=12) (Wesley et al., 2018)	Guanfacine (N=15) (Haney et al., 2019)	Nabilone (N=18) (Hill et al., 2017)			
Celecoxib (N=15) (Haney et al., 2022)	Lorcaserin (N=15) (Arout et al., 2021)				
	AEF0117 signaling-specific CB1 inhibitor (N=15) (Haney et al., 2023)				

N-acetylcysteine (NAC) as an example

- Glutamate plays an important role in addictive processes across multiple substances, including cannabis (Gass & Olive, 2008)
- Glutamate dysregulation in the nucleus accumbens underlies drug seeking (LaLumiere & Kalivas, 2008; McFarland et al., 2003, 2004)
- NAC administration activates the cystine/glutamate exchanger and upregulates the GLT-1 receptor, leading to reduction in reinstatement of drug seeking in animal models (Baker et al., 2003; Madayag et al., 2007; Moran et al., 2005; Reissner et al., 2015)
- NAC administration directly normalizes a drug-induced pathology (Kalivas et al., 2008)

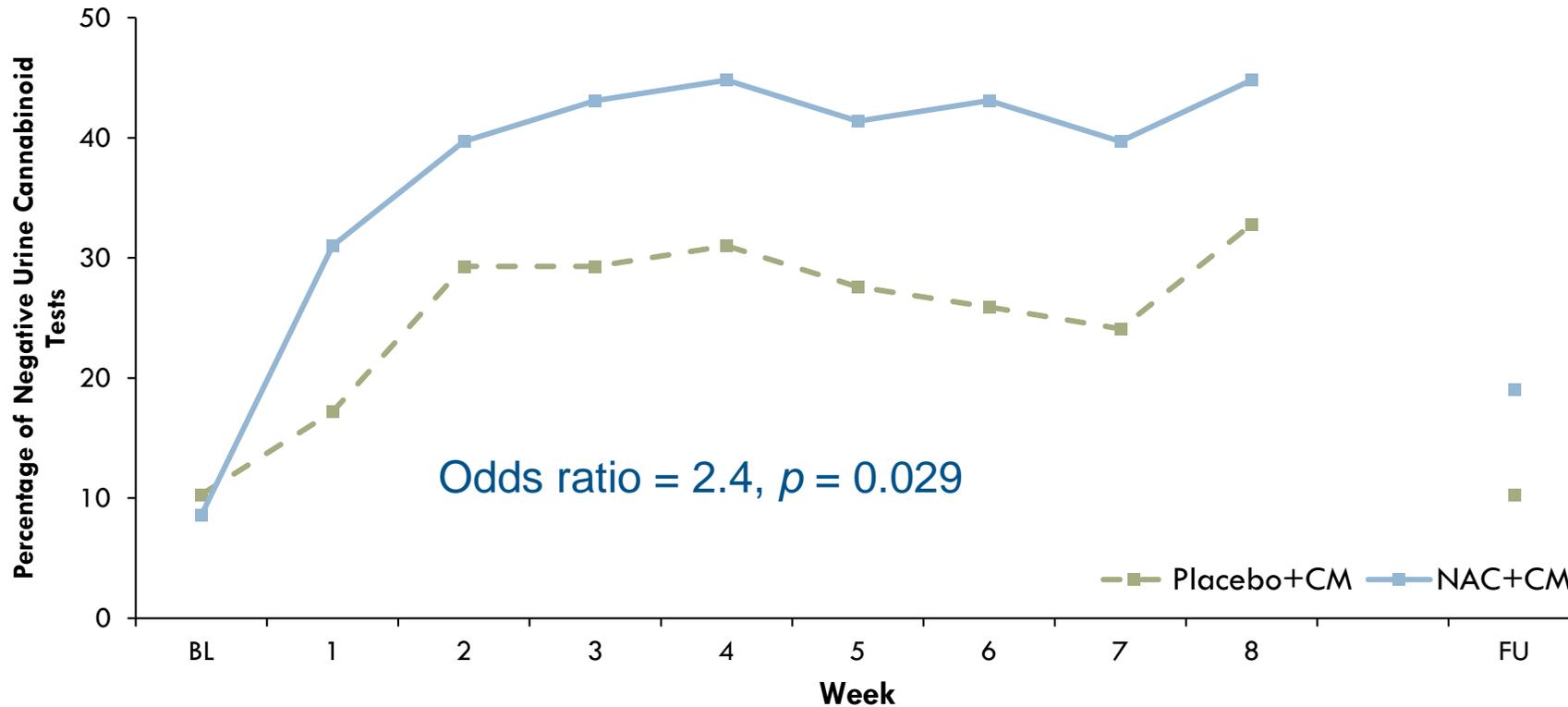
Youth NAC+CM trial (Gray et al., 2012)



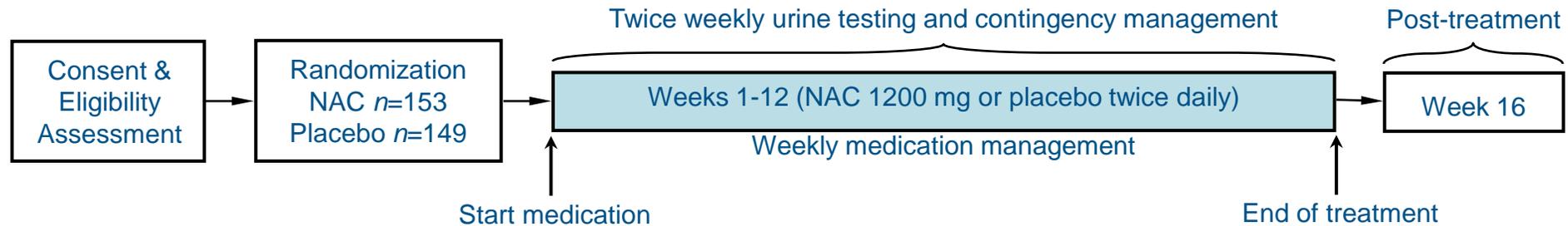
- Adolescents with DSM-IV cannabis dependence ($n=116$; ages 15-21)
- Eight weeks of active treatment
 - Double-blind placebo-controlled NAC 1200 mg BID
- All participants received weekly brief cessation counseling and twice-weekly contingency management (CM)
 - Two-tiered escalating reinforcement schedule with resets, rewarding both study retention and cannabis abstinence (Carroll et al., 2006)

Youth NAC+CM trial: primary outcome

Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit†



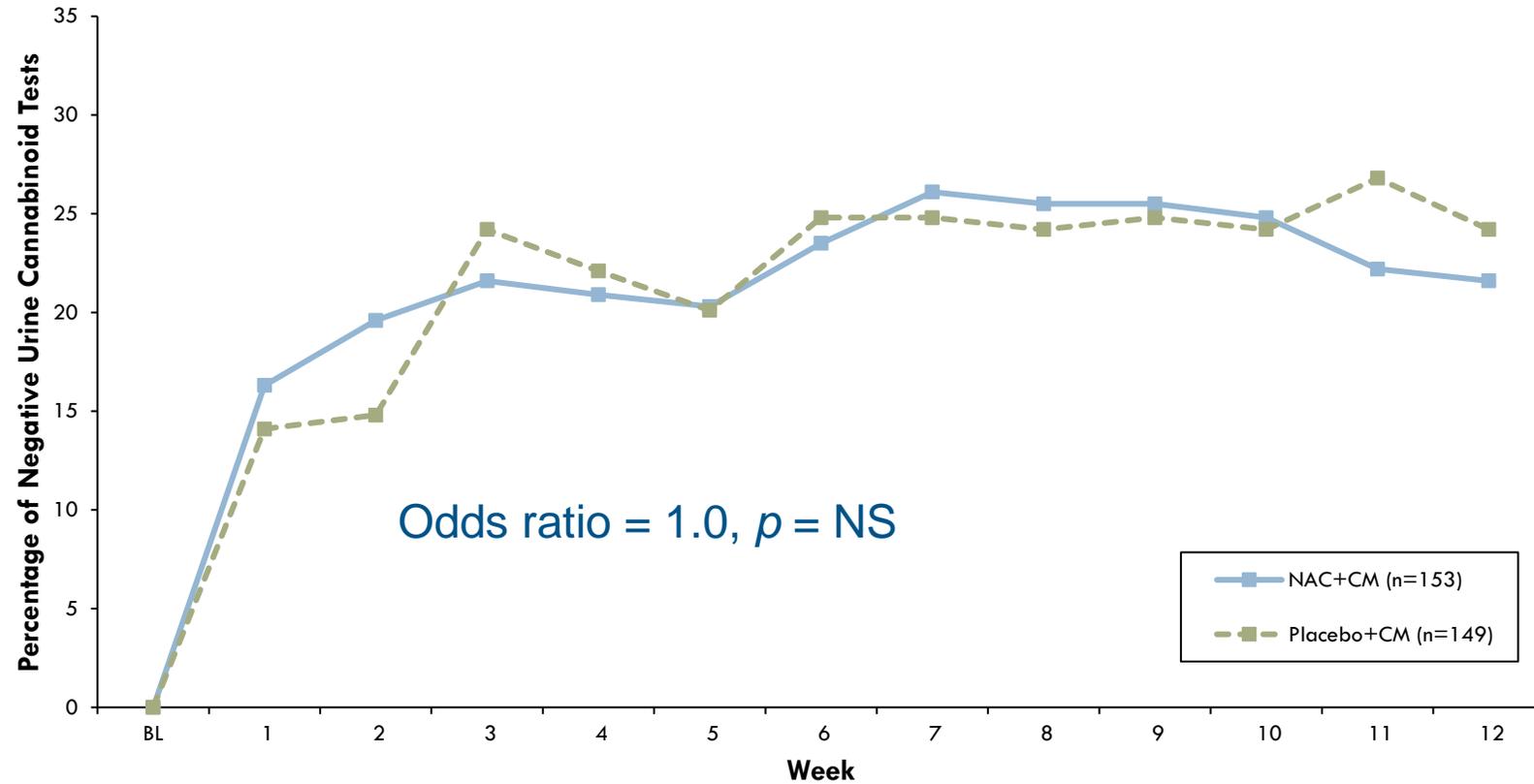
Adult NAC+CM trial (Gray et al., 2017)



- National Drug Abuse Treatment Clinical Trials Network (CTN) effort to see if positive adolescent findings extend to adults (CTN-0053) (Gray et al., 2017)
- DSM-IV cannabis-dependent adults ($N=302$; ages 18-50; recruited across six CTN sites)
- Twelve weeks of active treatment
 - Double-blind placebo-controlled NAC 1200 mg BID
- All participants received weekly medication management and twice-weekly contingency management
 - Two-tiered escalating reinforcement schedule with resets, rewarding both study retention and cannabis abstinence (Carroll et al., 2006)

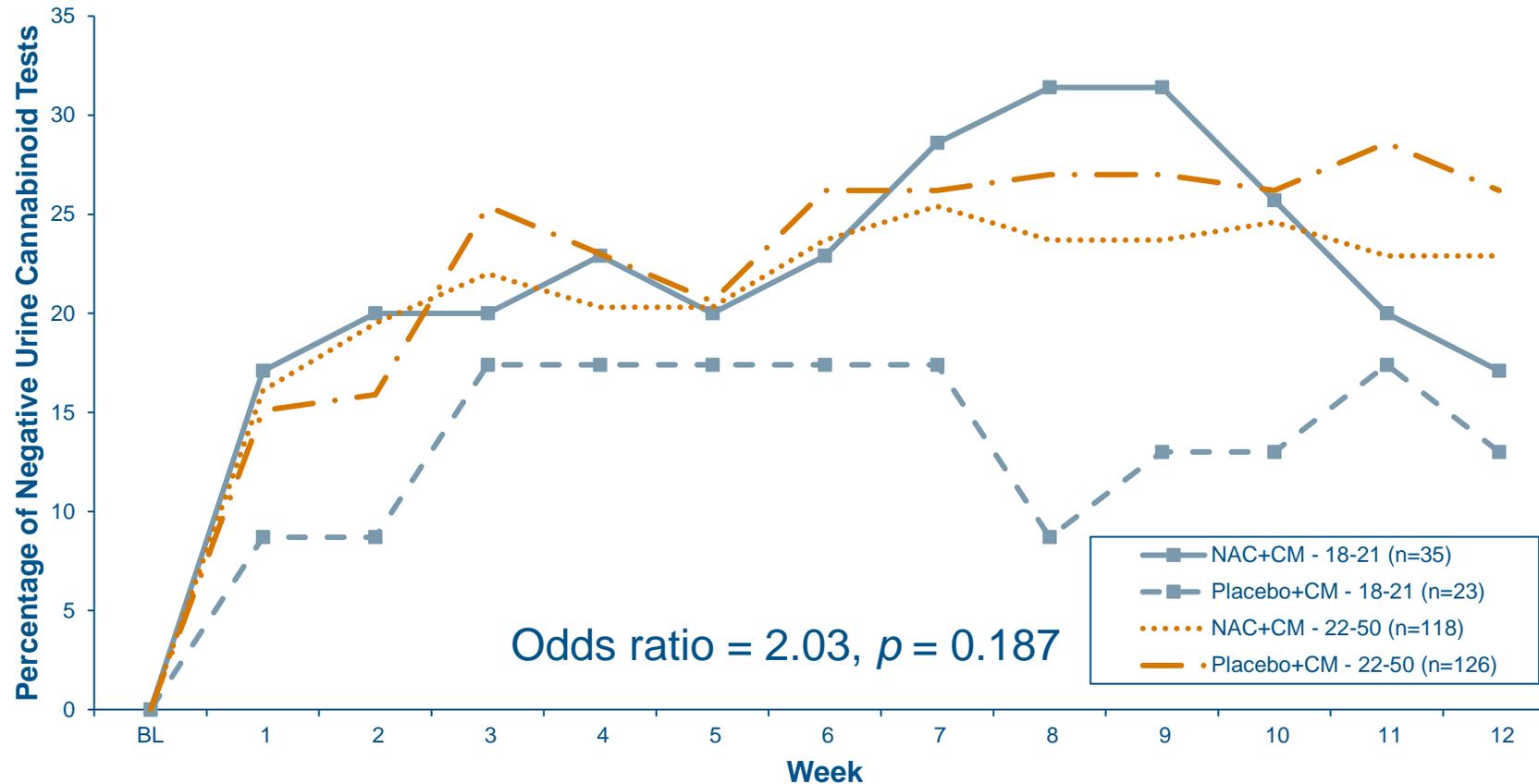
Adult NAC+CM trial: primary outcome

Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit

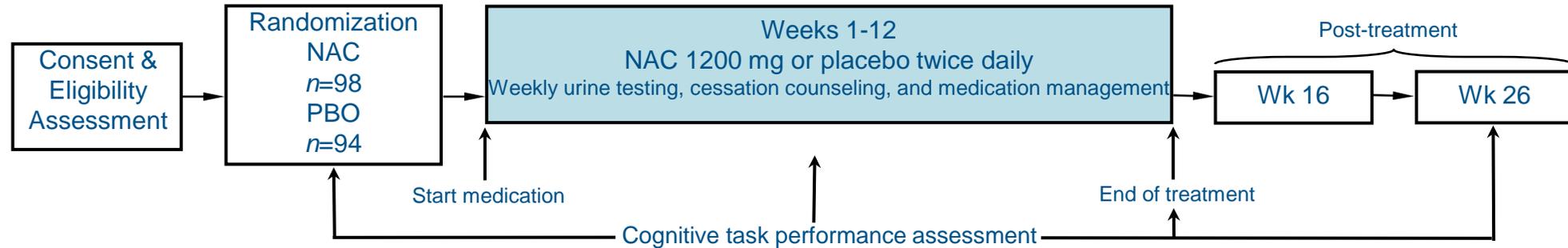


Adult NAC+CM trial: *post-hoc* comparison of ages 18-21 versus 22-50

Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit



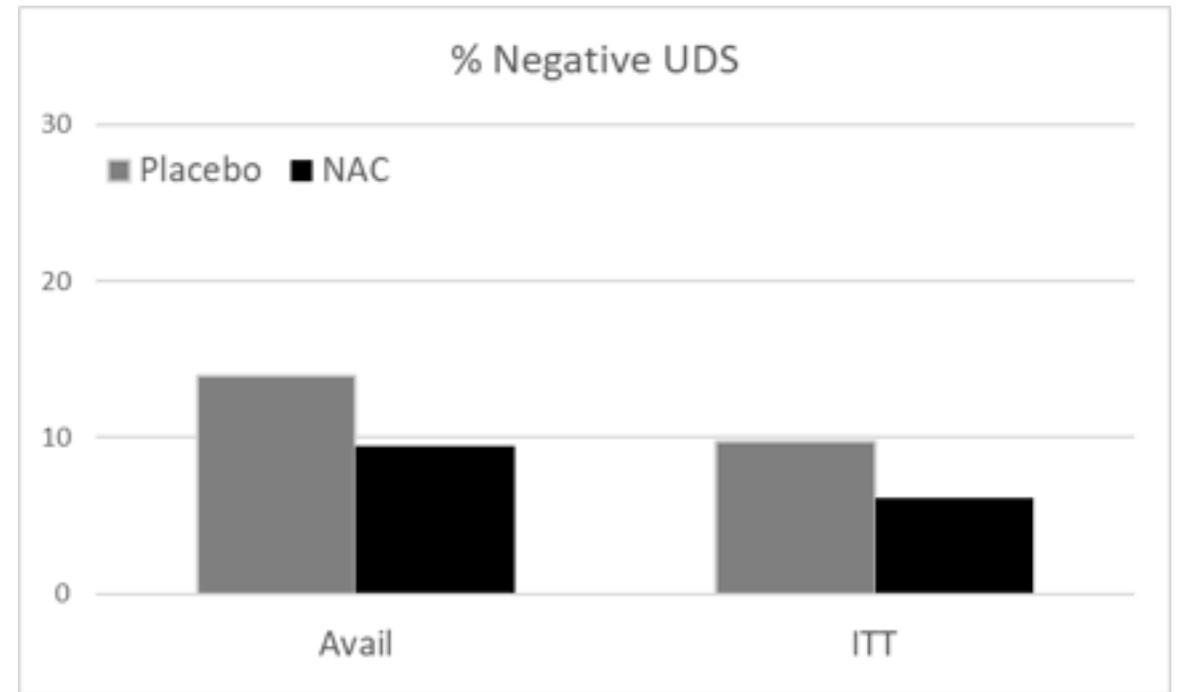
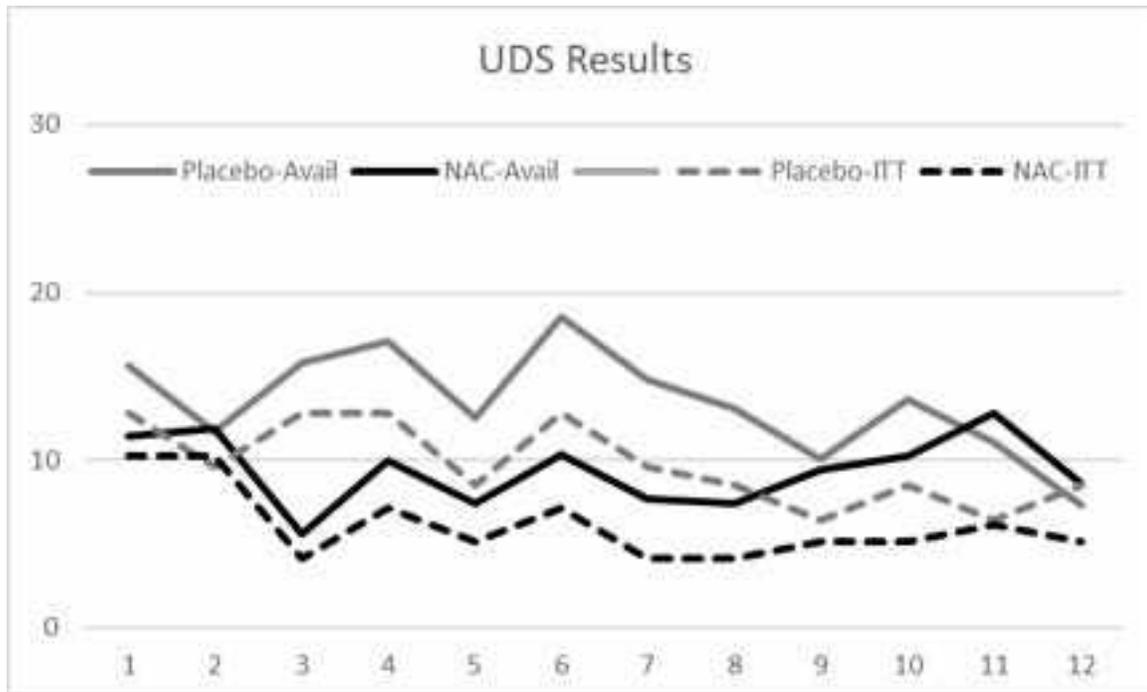
Youth NAC (no CM) trial



Does NAC work for youth CUD in the absence of contingency management (CM)?

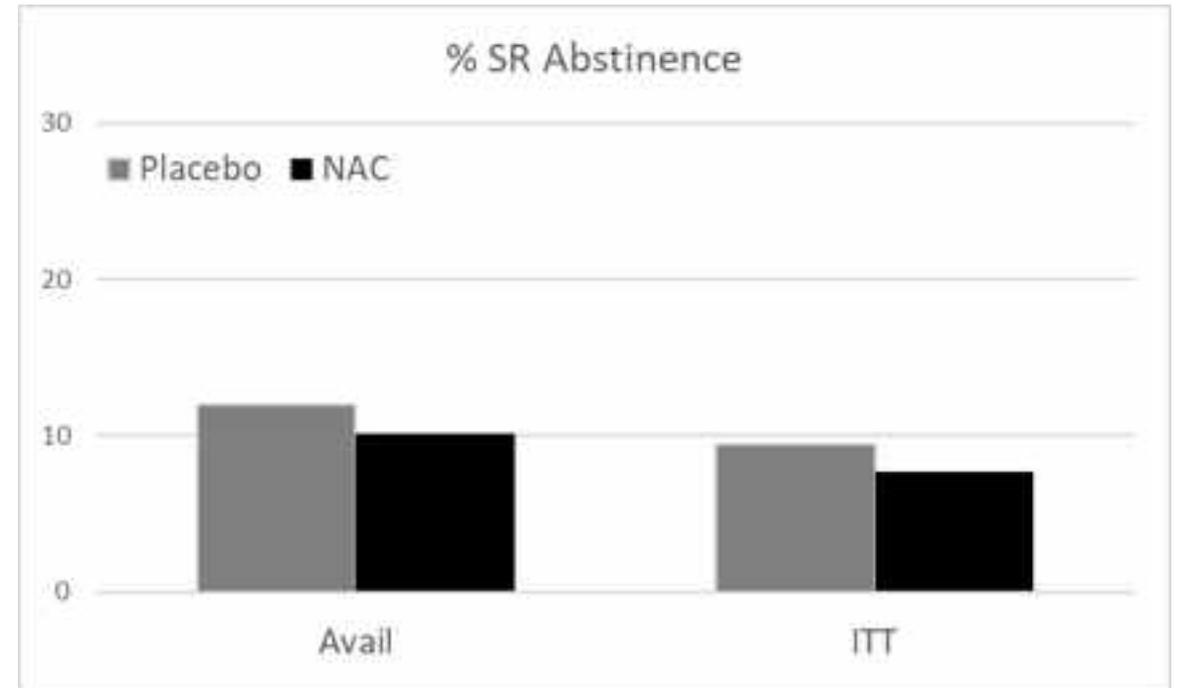
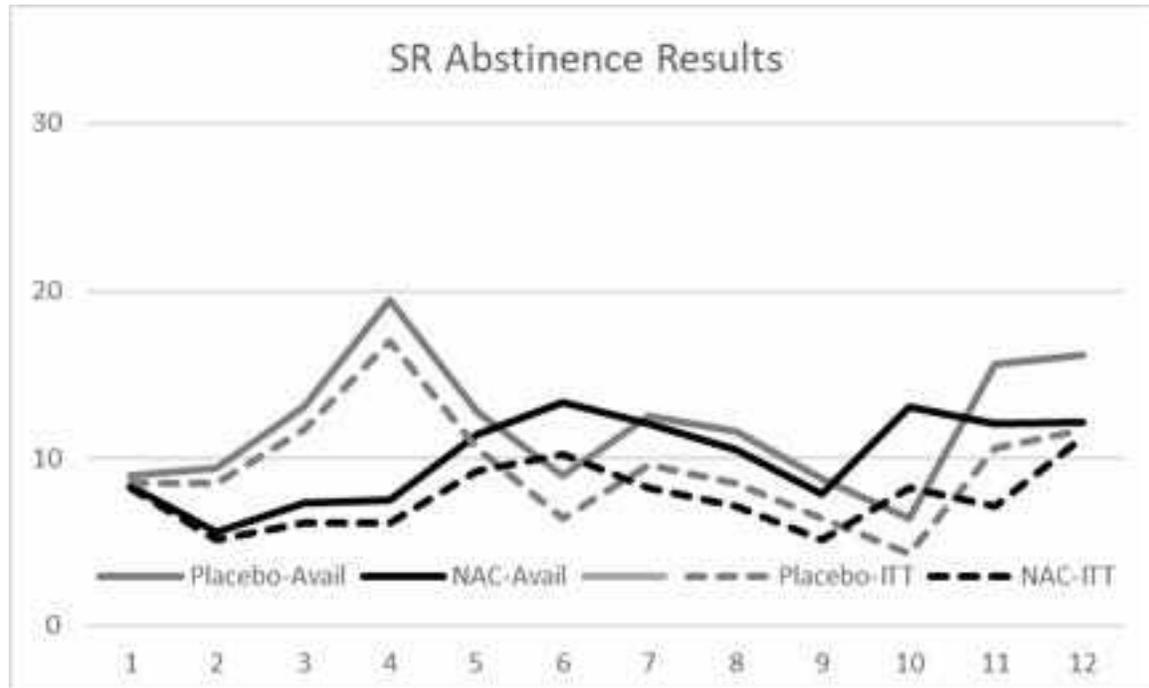
- R01 DA042114 “N-acetylcysteine for youth cannabis use disorder” (PI: Gray)
- Adolescents with DSM-5 cannabis use disorder ($N=192$, ages 14-21)
- Twelve weeks of active treatment
 - Double-blind placebo-controlled NAC 1200 mg BID
- All participants received weekly medication management and medical clinician-delivered cessation counseling (contingency management was *not* included in this trial)
- Data collection completed in early 2024 and not yet published

Youth NAC (no CM) trial: urine cannabinoid tests



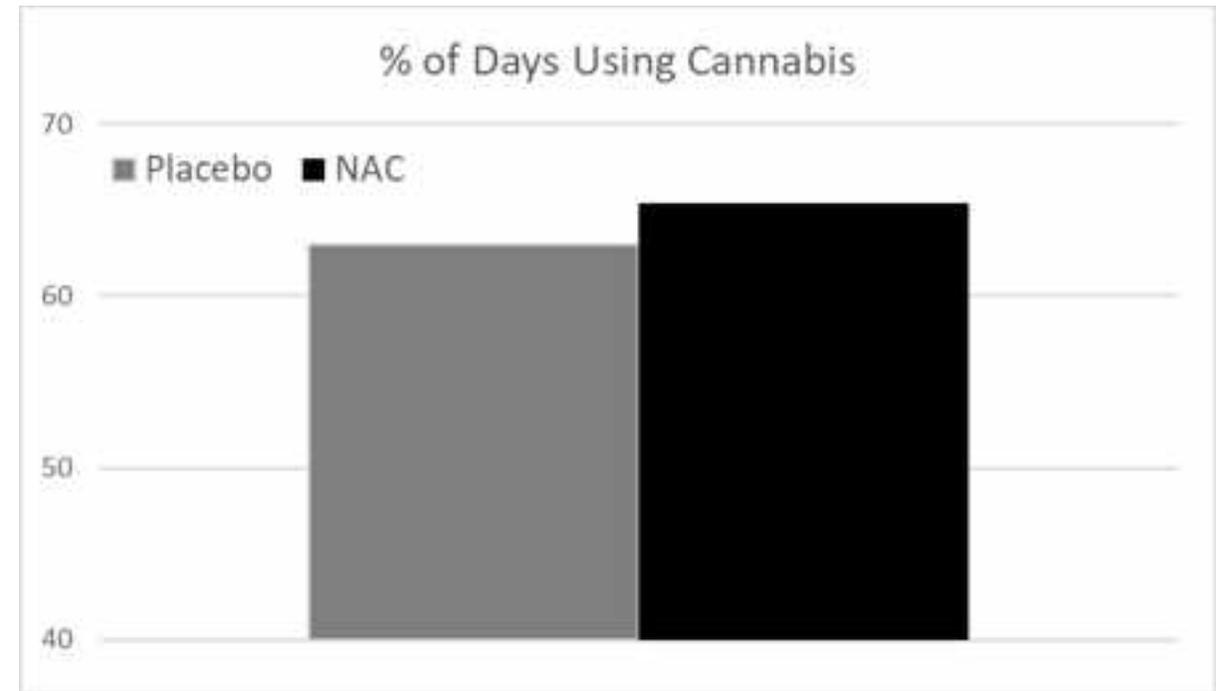
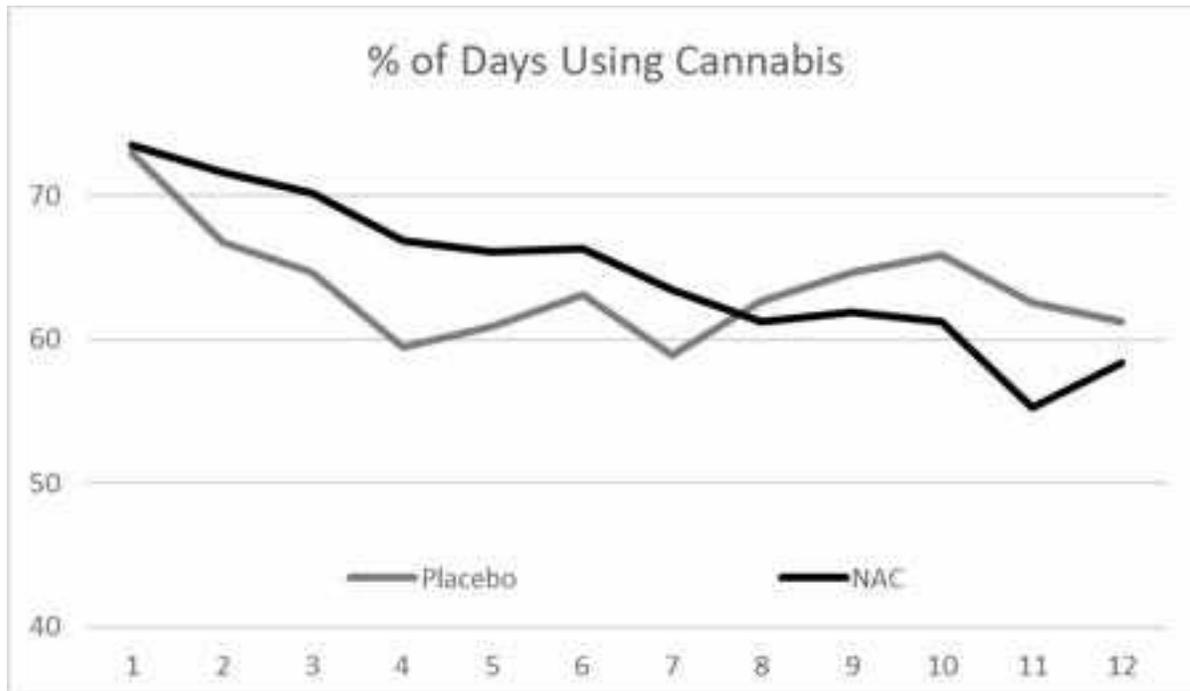
No significant difference in the proportion of negative UDS between Placebo and NAC.

Youth NAC (no CM) trial: self-reported abstinence



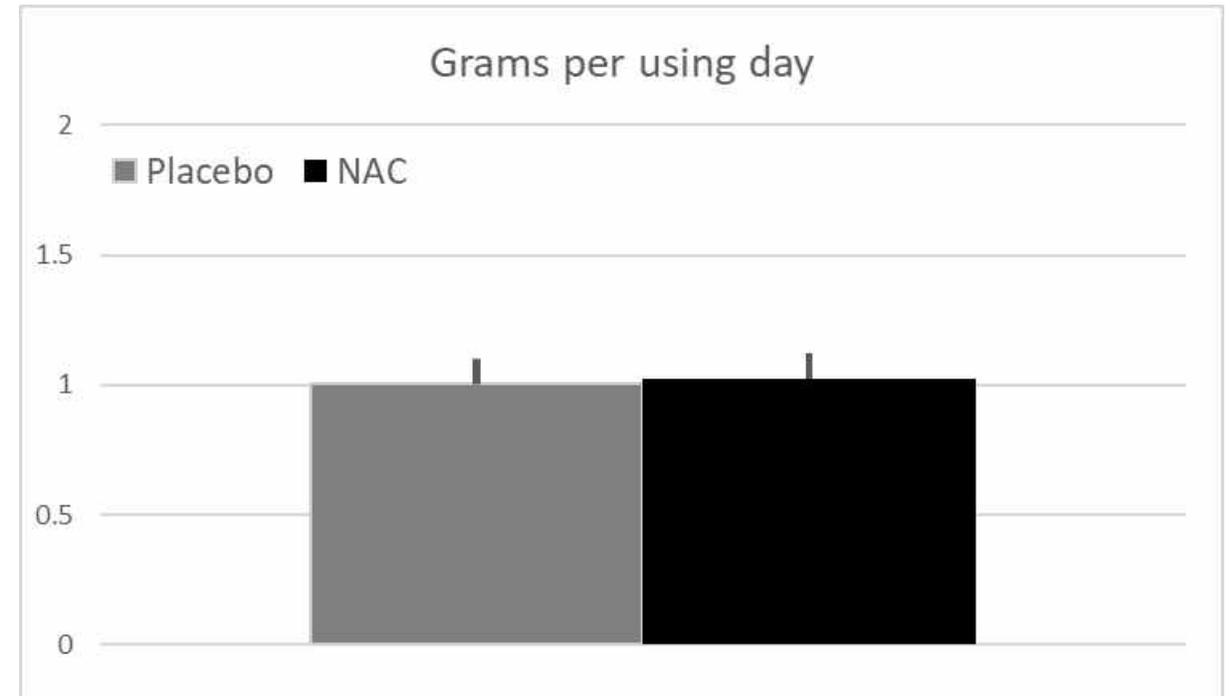
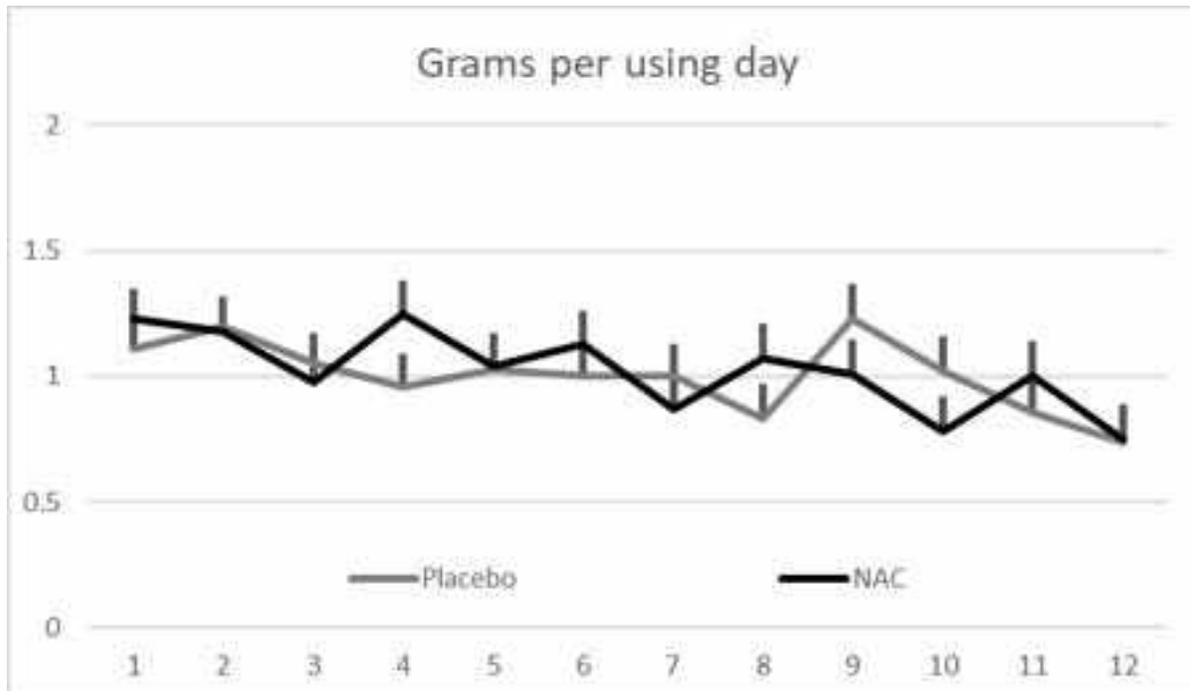
No significant difference in self-reported abstinence between Placebo and NAC.

Youth NAC (no CM) trial: self-reported percent days using cannabis



No significant difference in the proportion of days using cannabis between Placebo and NAC.

Youth NAC (no CM) trial: self-reported grams of cannabis use



No significant difference in cannabis use per using day between Placebo and NAC.

Youth NAC (no CM) trial: predictors of negative urine cannabinoid tests during treatment

Baseline Characteristic	Beta	SE	P Value	
Cannabis Use Days	-0.122	0.017	0.002	Increasing baseline CU Days is associated with lower prob of abstinence
Daily Cannabis Use (yes)	-1.741	0.356	0.003	Baseline daily cannabis users have lower prob of abstinence
Positive CO at BL (yes)	-1.237	0.393	0.010	Those with positive carbon monoxide breathalyzer at baseline have lower probability of abstinence
Age at first cannabis use	-0.077	0.122	0.528	
Any cannabis quit attempts	0.429	0.427	0.291	
Nicotine Use Days	-0.007	0.019	0.721	
Regular Ecig use (yes)	0.255	0.438	0.598	
Alcohol Use Days	-0.154	0.047	0.742	
Sex (female)	0.571	0.439	0.173	
Age	-0.119	0.135	0.463	

How do we make sense of these discrepant findings?

- Adolescents but not adults respond to NAC for CUD when added to contingency management (CM); however, without CM this effect is not evidenced
- Whether the adolescent vs adult discrepant findings are due to developmental differences in the course and phenomenology of CUD, differential effects of NAC based on stage of brain development, potential need for dose adjustment based on age, differences in medication adherence, and/or other factors remains unclear
- The medication effect seen in adolescents when combined with CM vs no-CM is consistent with our prior work (bupropion SR + CM for youth tobacco use disorder) (Gray et al., 2011)
- Indirect comparison of findings between studies occurring years apart holds inherent limitations, especially given the many changes over this time in cannabis use-related attitudes, patterns, and contexts

Conclusions

- We are all navigating a complicated environment, and cannabis is a particularly complex topic
 - One area of increasing clarity is that we should be concerned about adolescent cannabis use, particularly among adolescents with co-occurring mental health symptoms
 - Youth cannabis use and mental health symptoms are increasingly intertwined
 - We must employ a collective approach to prevention and treatment, and clinicians are in a unique position to deliver effective messages to youth and families
- We have evidence-based approaches to youth cannabis use disorder, though effect sizes are small to modest, and enhancements are needed
 - Among the potential pathways for enhanced treatments is pharmacotherapy, though findings to date are mixed
- Several lines of research are underway to help us better understand and address youth cannabis use
 - Stay tuned and stay engaged in front-line evidence-based practice!



muschealth.org/youthcollab • 843-792-9257 • youth@musc.edu