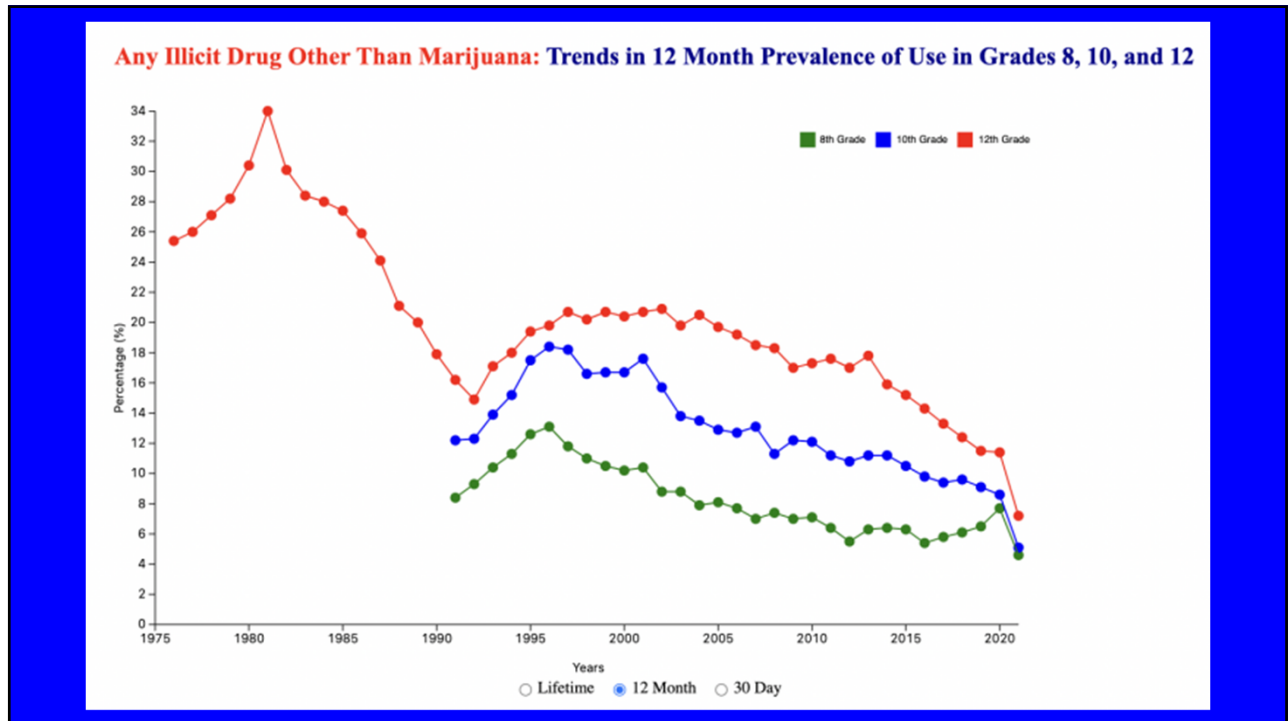


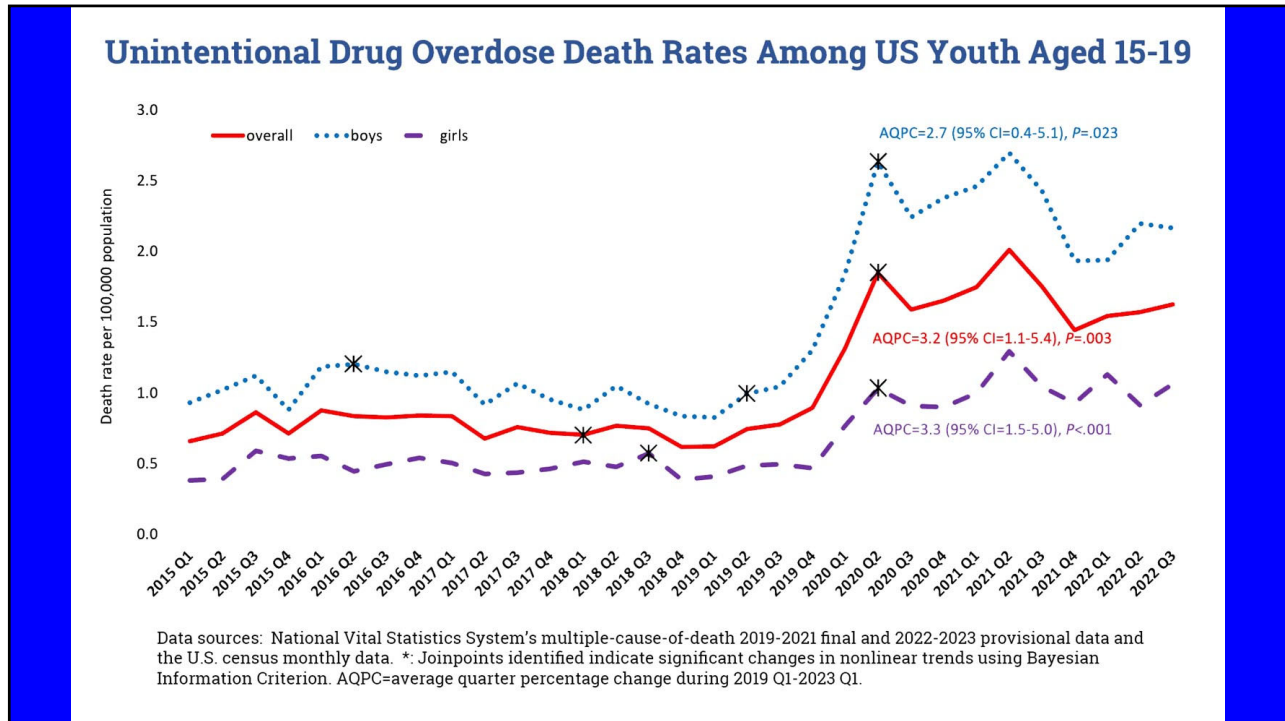
Adolescent and young adult substance use disorders, serious mental illness, and suicide risk

Duncan B. Clark MD PhD
University of Pittsburgh &
UPMC Addiction Medicine Services
STAR-Center Conference
May 10, 2024

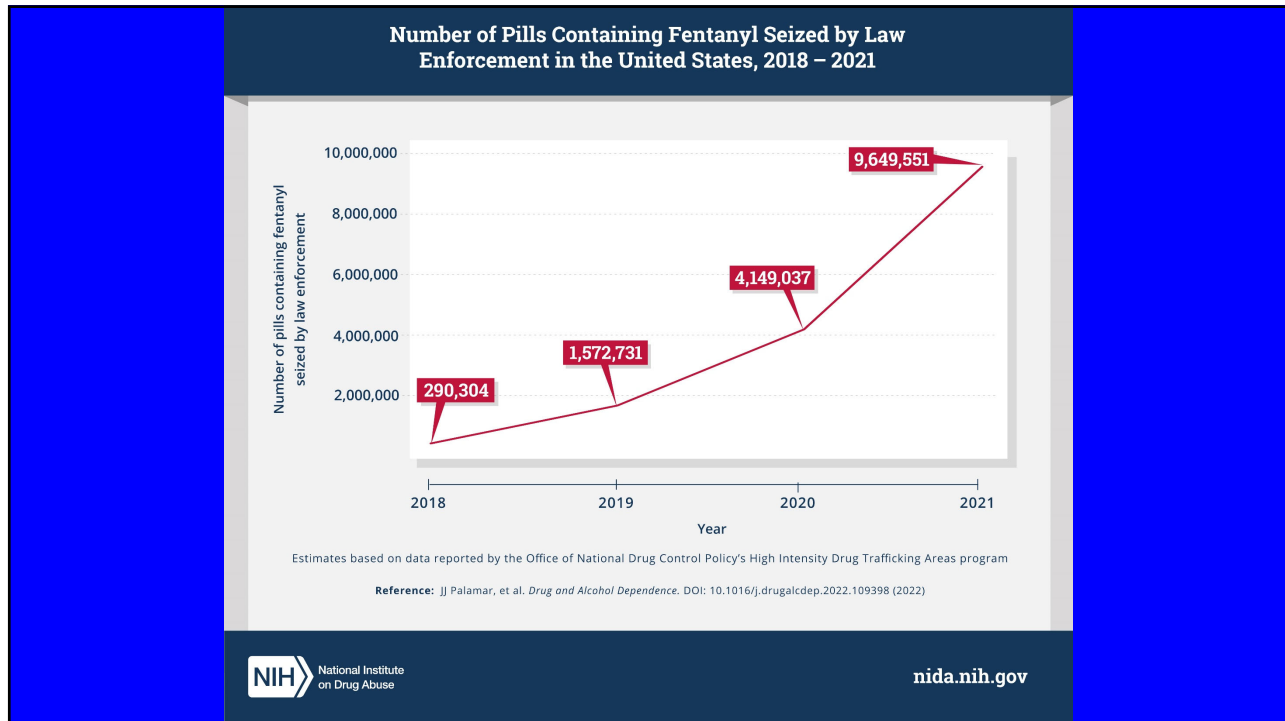
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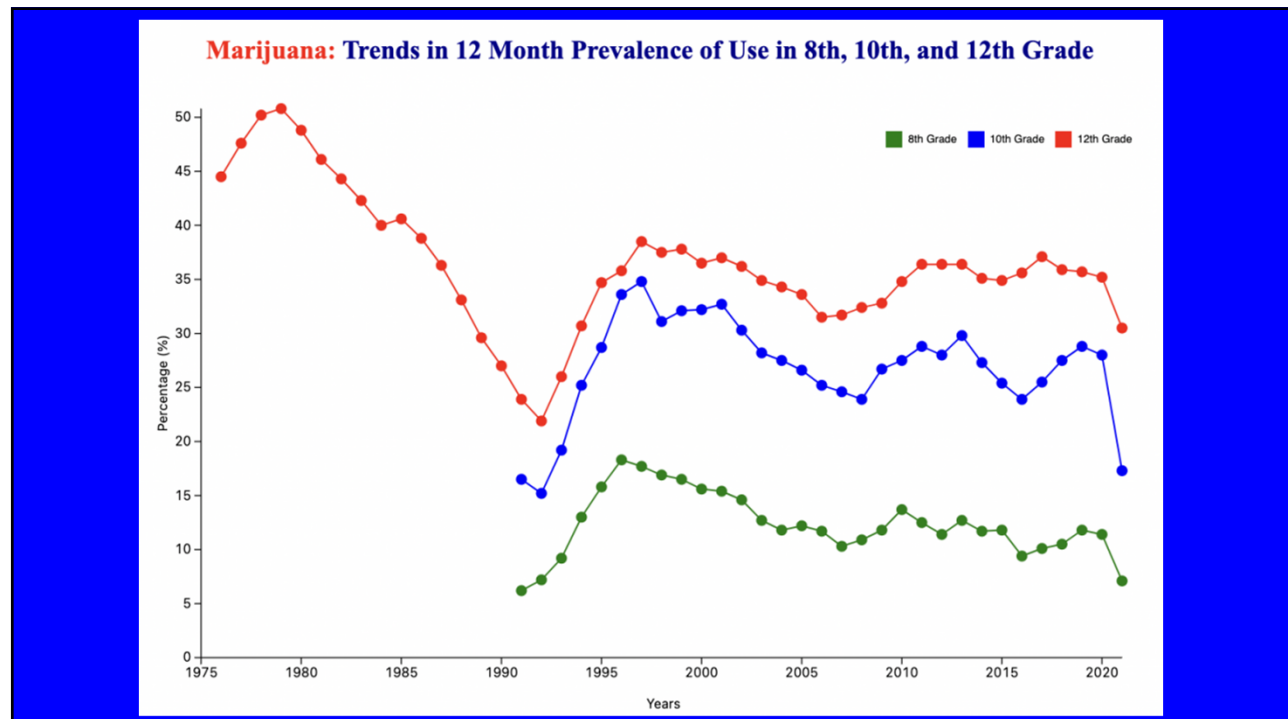


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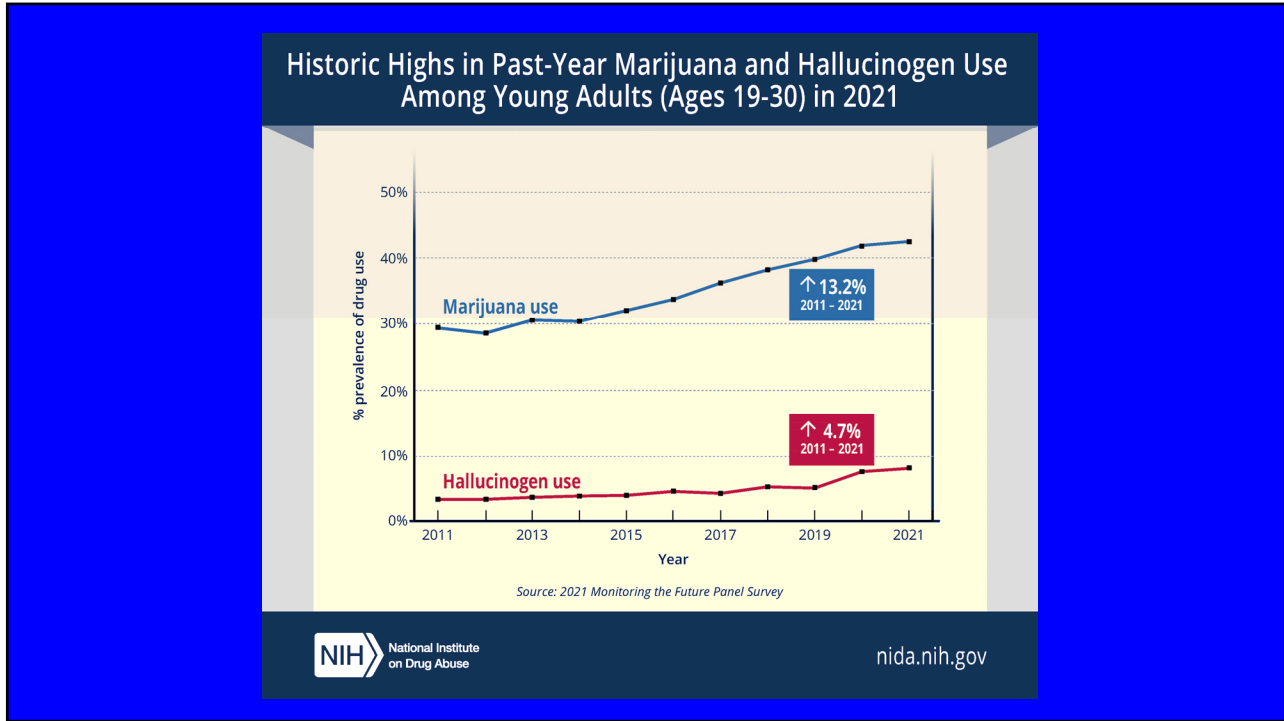
Common cannabis questions

Has cannabis or other substance use increased?
 Has cannabis potency changed?
 What are the adverse health effects of cannabis?
 Is cannabis addictive? Does discontinuation cause withdrawal?
 Why do people use “medical marijuana”?
 Does cannabis cause or treat anxiety?
 Does cannabis help or impede learning?
 Does cannabis improve or impair sleep?
 Which medications help with cannabis and comorbid disorders?
 Does cannabis reduction or discontinuation improve outcomes?

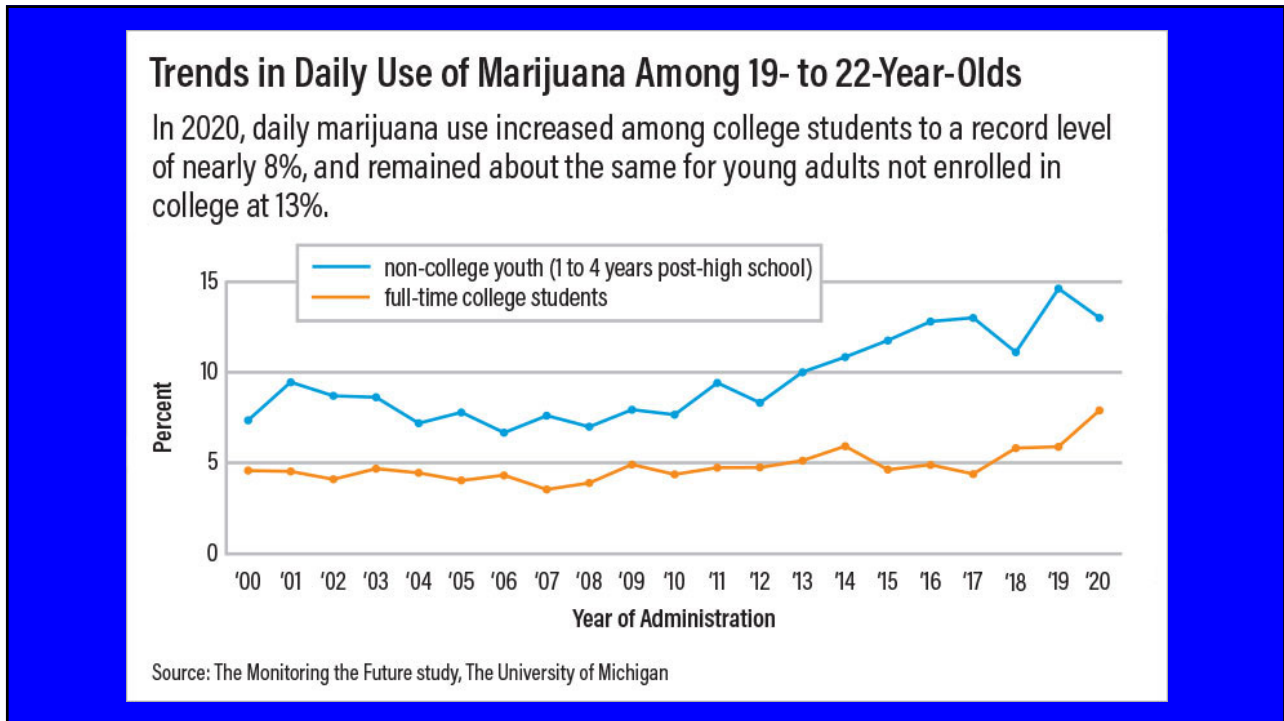
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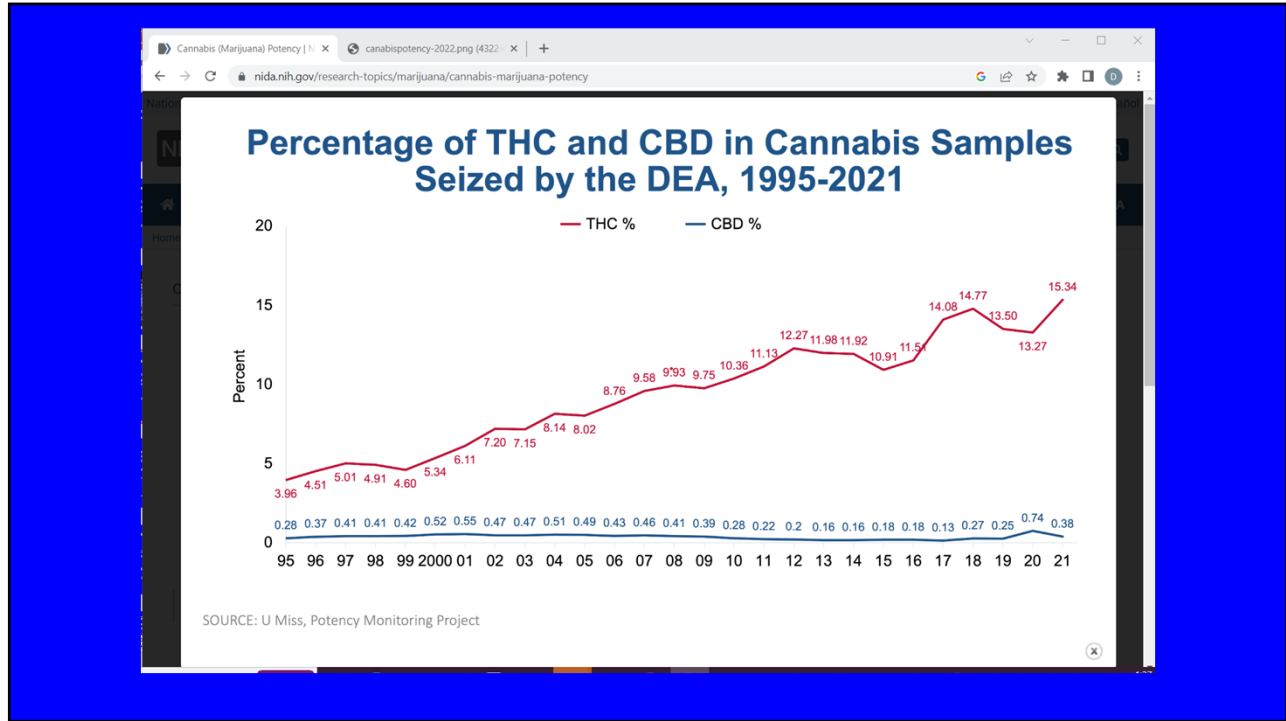
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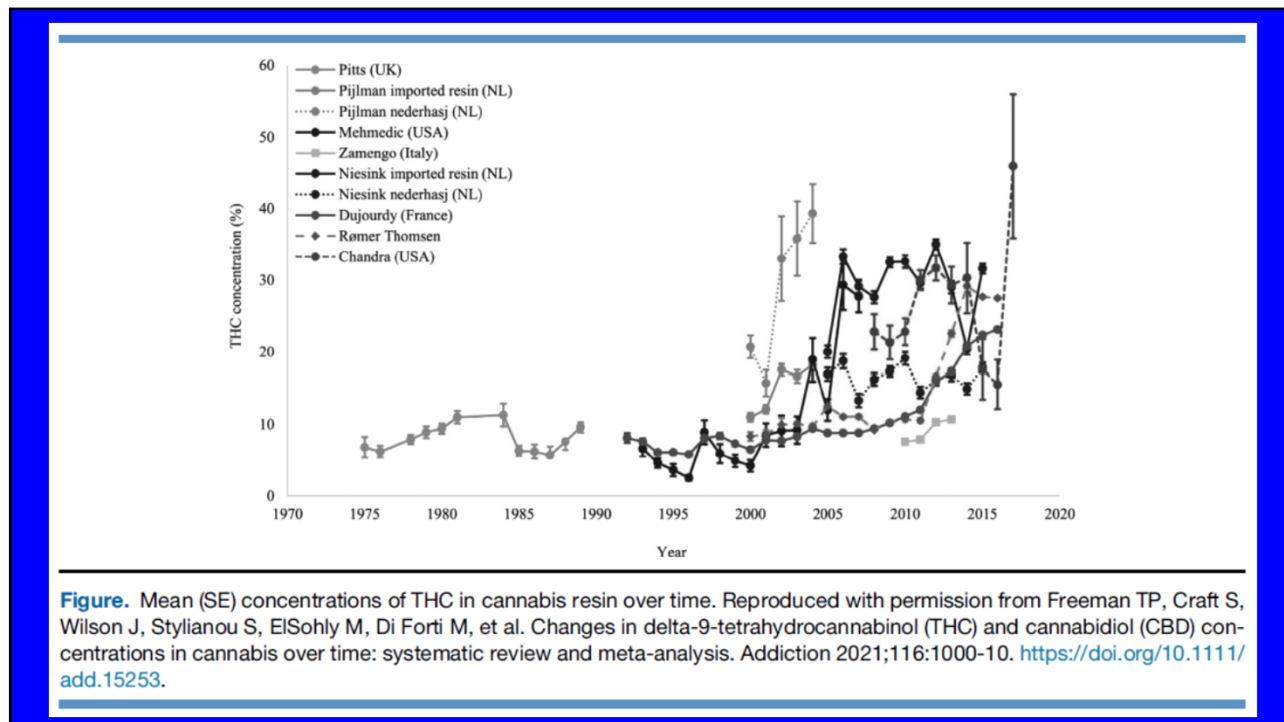
TABLE 1

Common Types of Commercial Cannabis Products and Methods of Use

Form	Other names	Methods of use	Comments
Concentrate (high THC)	Wax, shatter, dab, butane hash oil	Dabbing (inhale)	Dab (< 1 cm) placed on hot metal rod; THC concentration may be up to 90%; may cause explosion
Edibles (THC and CBD)	Gummies, teas, brownies, candies, infused drinks	Oral consumption	Butter/oils used to extract cannabinoids; many possible formulations
Marijuana	Bud, flower	Smoking, vaping	Often purchased as an eighth (3.5 g), with a typical joint containing 0.5 g to 1 g; THC concentration is 5% to 20%
Oils (THC and CBD)	Hash oil, honey oil, cannabis oil, CBD oil	Topical	Alcohols and other solvents used for extraction; dangerous if inhaled; THC concentration is 15% to 50%
Resin	Hash, dry sift	Smoking, vaping	Concentrate is made from trichomes (flower protrusions); THC concentration is 2% to 8%
Tincture (THC and CBD)	Tincture of cannabis, green dragon, CBD tincture	Oral consumption, sublingual, topical	Ethanol used for extraction
Vape pen	Vape juice, e-juice, e-liquid	Vaping	Similar to electronic cigarettes except contains THC concentrate, tinctures, or oils

CBD = cannabidiol; THC = tetrahydrocannabinol.
 Information from references 10 and 11.

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11

High potency cannabis use in adolescents

Daily cannabis use rates increasing [7% high school seniors]
 Among 12th grade cannabis users: 40% edibles; 34% vaped; 30% dabbed
 THC concentrates for vaping: up to 95% THC

Daily users vs. non-users: 5x odds of psychotic disorders

High-potency vs. low-potency users

- 2x odds of anxiety disorders
- 2x risk of psychosis
- more memory problems

THC toxicity: Colorado ER visits: 2009: 1.8/1000 visits; 2015: 4.9/1000

Vargas et al. High-potency cannabis use in adolescence. *J Pediatrics* 252, 191-197, 2023

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DSM-5 CUD Symptoms

<u>Rate</u>	<u>Brief Identifier</u>	<u>DSM-5 Definition</u>
78%	Much time	A great deal of time using, obtaining, recovering
73%	Tolerance	Need to consume more for same effect; decreased effect
66%*	Craving	Strong desire or urge to use
66%	Social Problems	Continued use despite interpersonal problems
65%	Role Obligations	Failure to fulfill obligations school/home
63%	Quit/Cut Down	Repeated unsuccessful attempts to quit
51%	Hazardous Use	Recurrent use when physically hazardous (driving)
37%*	Withdrawal	Three or more withdrawal symptoms
32%	Reduced activities	Important activities reduced or given up
22%	More/Longer	Using more or for longer than intended
13%	Psycho/Physical	Psychological or physical problems

[14-18 y.o.; n=214; out-pt treatment; cannabis users; * added in DSM-5; *based on two symptoms: Chung et al. 2008: Drug and Alcohol Dependence]

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Health Effects of Cannabis

- During adolescence
 - impaired academic and work achievement
 - increased likelihood of problem use
- Functional effects
 - cannabis DUI increases MVAs
 - impaired attention, memory, learning
- Mental disorders
 - increased risk of psychoses
 - exacerbates bipolar disorder
 - increased risk of other SUDs

National Academy of Sciences: January 2017;
Volkow: NEJM, 2014

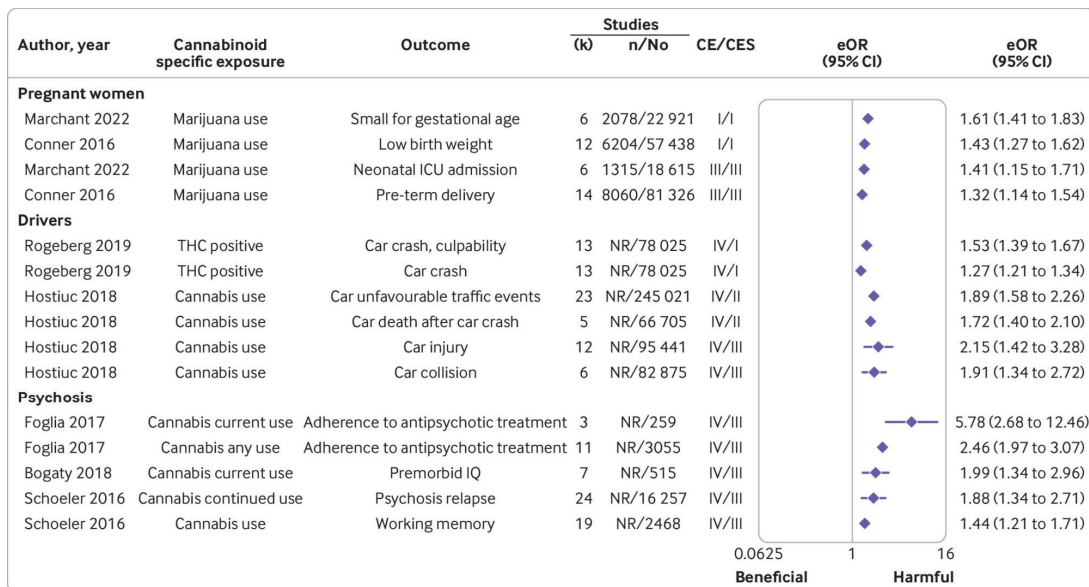
14

Balancing risks and benefits of cannabis use: umbrella meta-analyses of randomized controlled trials and observational studies. Solmi et al. British Journal of Medicine 2023; 382: e072348

Systematic reviews with meta-analyses of observational studies and RTCs that have reported on the efficacy and safety of cannabis, cannabinoids, or cannabis-based medicines were included.

Convincing or converging evidence recommends avoiding cannabis during adolescence and early adulthood in people prone to have or have mental health disorder, who are pregnant, and while driving.

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Author, year	Cannabinoid specific exposure	Outcome	Studies		CE/CES	eOR (95% CI)	eOR (95% CI)
			(k)	n/No			
General population							
Kiburi 2021	Cannabis	Psychosis	18	2512/67 684	II/II		1.71 (1.47 to 2.00)
Borges 2016	Cannabis heavy use	Suicide attempt	12	1066/21 956	III/III		3.20 (1.72 to 5.94)
Moore 2007	Cannabis most frequent use	Psychotic symptoms	6	1465/59 671	III/III		2.18 (1.45 to 3.27)
Gibbs 2015	Cannabis use	Mania symptoms	2	NR/5520	IV/III		3.00 (1.73 to 5.23)
Gurney 2015	Cannabis weekly use	Testicular cancer non-seminoma	3	719/2138	IV/III		2.82 (1.77 to 4.48)
Gurney 2015	Cannabis >10 years use	Testicular cancer non-seminoma	3	719/2138	IV/III		2.39 (1.47 to 3.86)
Gurney 2015	Cannabis current use	Testicular cancer non-seminoma	2	532/1803	IV/III		2.20 (1.57 to 3.07)
Lorenzetti 2019	Cannabis regular use	Medial orbitofrontal cortex volume	6	NR/356	IV/III		1.72 (1.29 to 2.30)
Lorenzetti 2019	Cannabis regular use	Total orbitofrontal cortex volume	7	NR/472	IV/III		1.63 (1.31 to 2.03)
Johnson 2017	Cannabis use	Physical dating violence perpetuation	13	NR/17 356	IV/III		1.45 (1.19 to 1.77)
Moore 2007	Cannabis use	Depression	11	NR/17 628	IV/III		1.21 (1.11 to 1.31)
Healthy people							
Schoeler 2016	Cannabis use	Visual immediate recall	2	NR/89	IV/II		3.76 (2.64 to 5.34)
Schoeler 2016	Cannabis use	Prospective memory	5	NR/294	IV/II		3.43 (2.23 to 5.28)
Schoeler 2016	Cannabis use	Verbal learning	41	NR/3085	IV/II		2.03 (1.72 to 2.39)
Schoeler 2016	Cannabis use	Verbal delayed recall	38	NR/3368	IV/II		1.95 (1.63 to 2.34)
Schoeler 2016	Cannabis use	Verbal immediate recall	40	NR/3169	IV/III		2.10 (1.52 to 2.97)
Schoeler 2016	Cannabis use	Verbal recognition	21	NR/1485	IV/III		1.69 (1.36 to 2.07)
Schoeler 2016	Cannabis use	Working memory	39	NR/4550	IV/III		1.29 (1.14 to 1.46)

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Pharmacokinetics and pharmacodynamics

Cannabis sativa characteristics

- THC potency: <2% in 1970s to 15% - 34% today
- Smoked marijuana bioavailability: 2% to 50%
- >1000 est. chemicals in smoked marijuana
 - >100 cannabinoids
 - >400 other chemicals have been isolated

Cannabinoid receptors

- CB1: brain, downregulated by THC
- CB2: other organs

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Pharmacokinetics

Absorption	THC bioavailability
inhaled	10% - 35%
ingested	04% - 12%

Distribution: THC is highly lipophilic: stores in fat

Metabolism: Liver metabolism: THC to 11-OH-THC to THC-COOH

Elimination: 20% elimination in urine; 65% feces; saliva; sweat; hair

Plasma half-life: occasional users: 1-3 days; chronic users: 5-13 days

Huestis. Human Cannabinoid Pharmacokinetics. Chem Bio 2007: 4(8), 1770-1804;
Chayasirisobhon. Mechanisms of action and pharmacokinetics of cannabis. Perm. J. 25(19),
200, 2021; Hunt & Jones. Pharm Exp Ther 1980: 215: 135-144

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Elimination

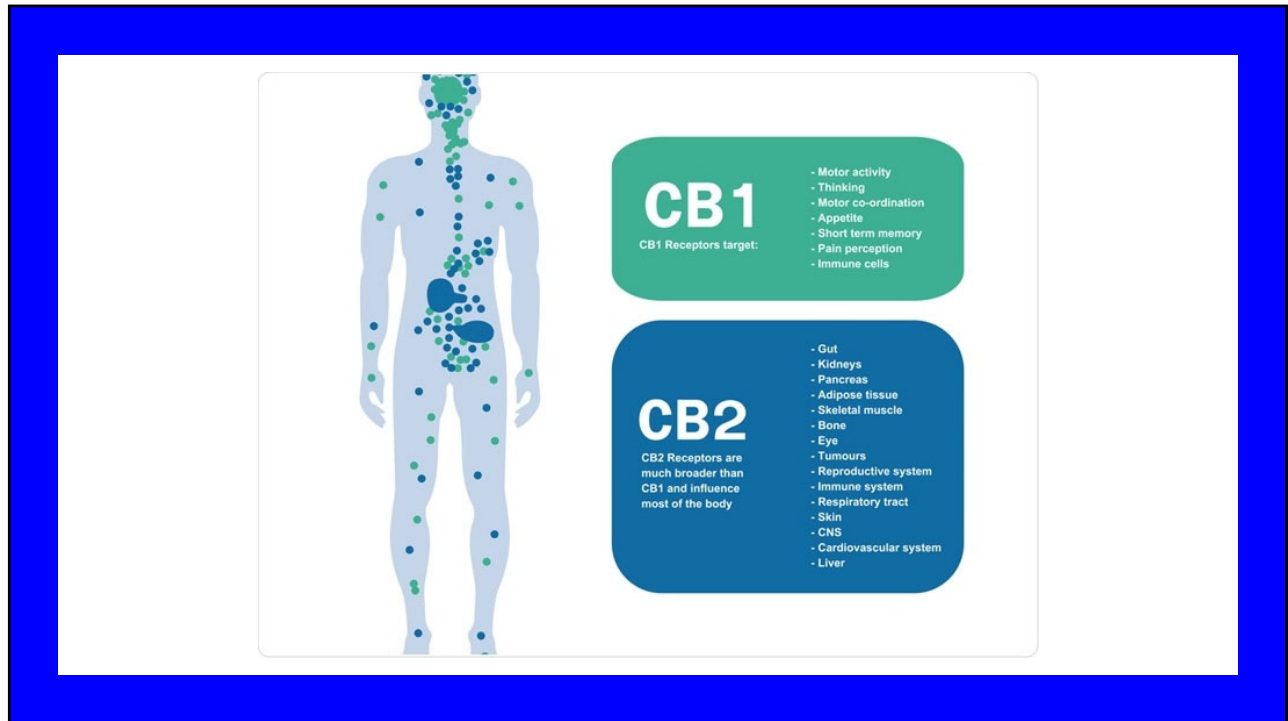
Chronic, frequent cannabis use
Admission THC-COOH >150 ng/mg

	half life	effective elimination
THC	4 days	20 days
THC-COOH	12 days	60 days

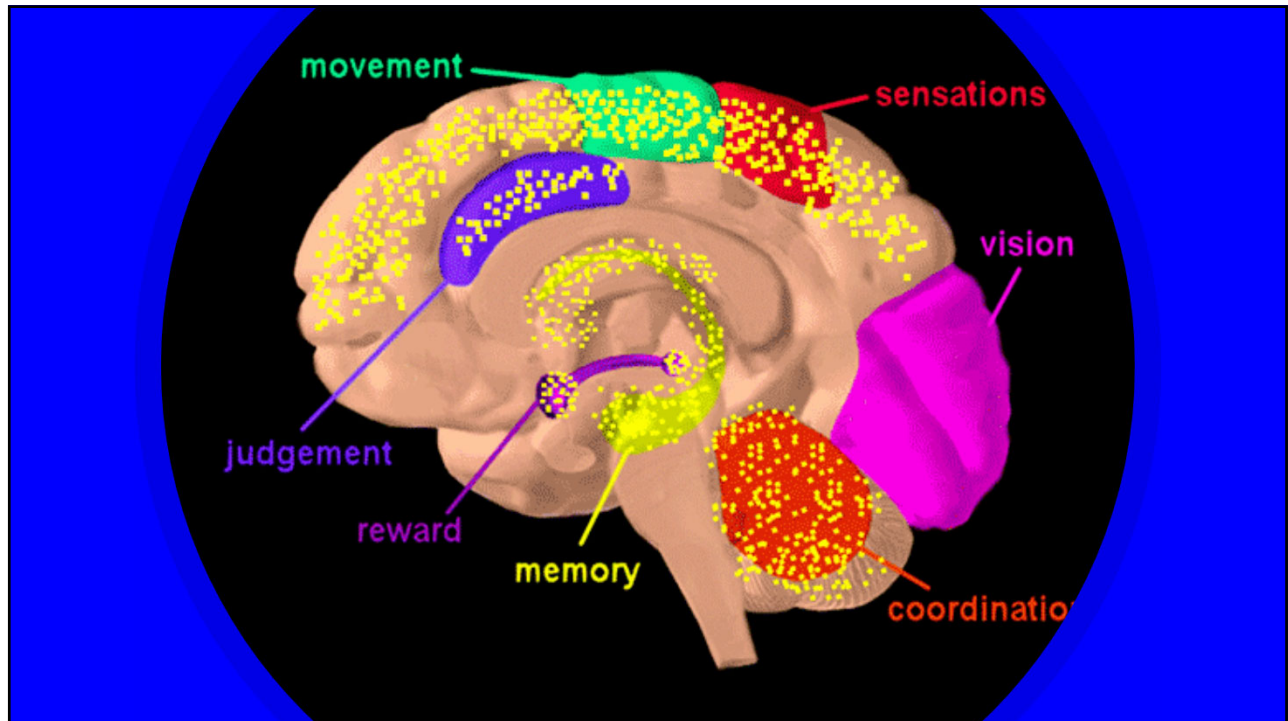
[Goodwin et al. J Analy Toxicol 2008, 32(8)]

[Lowe et al. Drug Alcohol Depend 2009, 105]

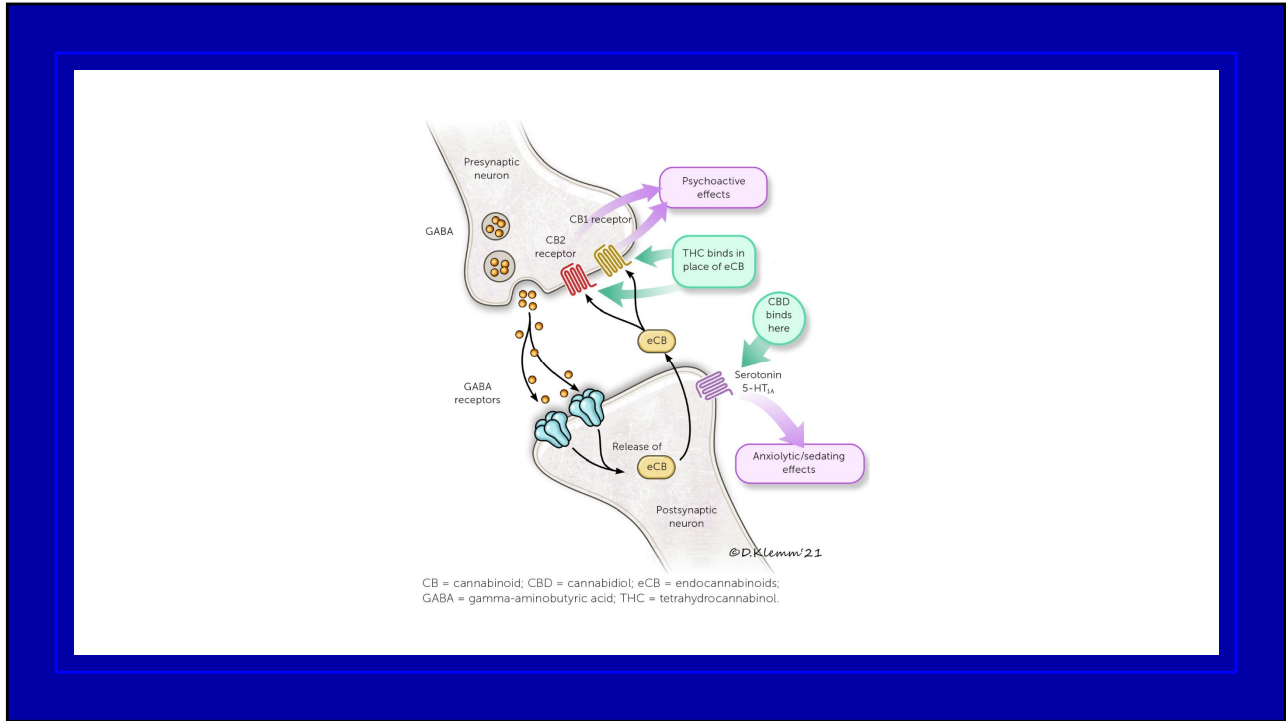
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Cannabis Withdrawal Symptoms

<u>Rate</u>	<u>Identifier</u>
66%	Craving
46%	Irritable
38%	Trouble concentrating
34%	Trouble sleeping
33%	Restless
28%	Angry, violent
28%	Change in appetite
26%	Anxious
26%	Headache
25%	Depressed
23%	Fatigue

[14-18 y.o.; n=214; out-pt treatment;
Chung et al. 2008: Drug and Alcohol Dependence]

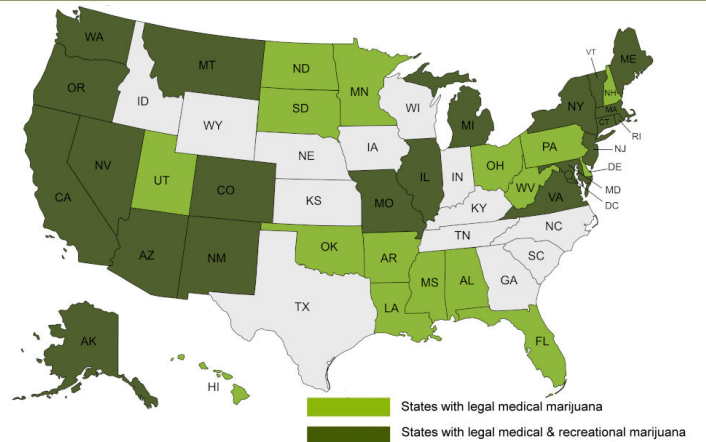
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Legal History of Cannabis in USA

Late 1800s	cannabis used in pharmaceuticals
1900 – 1930	some state marijuana laws
1930	Federal Bureau of Narcotics: Harry Anslinger claimed cannabis caused violence; advocated criminalization
1937	Marijuana Tax Act: effectively made possession illegal If not 'registered,' tax \$100/ounce [\$2200 today] 1969: unconstitutional: 5 th Amendment self-incrimination
1952	Boggs Act: 1 st possession: 2-10 years; \$20,000 fine
1970	Controlled Substances Act: marijuana Schedule 1: illegal for any purpose
1973	Drug Enforcement Administration created
1986	Federal Analogue Act: Schedule I if "substantially similar" for human consumption
1990	Solomon – Lautenberg: "smoke a joint, lose your license" Opt out provision: 2021 all states except Alabama, Arkansas, Florida
1998	California legalizes medical cannabis; U.S. House opposed
2000	Conant vs McCaffrey: 1 st Amendment physician right to recommend [not prescribe] Clinton administration threatened to arrest prescribing physicians
December 2022	Medical Marijuana and Cannabidiol Research Expansion Act "shall not be a violation...physician to discuss...harms and benefits of marijuana..."
February 2023	DEA confirms Δ ⁸ THC-O & Δ ⁹ THC-O are Schedule I

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Legal Medical & Recreational Marijuana States



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Pennsylvania Qualifying Medical Conditions



- Amyotrophic Lateral Sclerosis (ALS)
- Anxiety disorders
- Autism
- Cancer, including remission therapy
- Crohn's disease
- Damage to the nervous tissue of the central nervous system (brain-spinal cord) with objective neurological indication of intractable spasticity and other associated neuropathies
- Dyskinetic and spastic movement disorders
- Epilepsy
- Glaucoma
- HIV/AIDS
- Huntington disease
- Inflammatory bowel disease (IBD)
- Intractable seizures
- Multiple Sclerosis (MS)
- Neurodegenerative diseases
- Neuropathies
- Opioid Use Disorder
- Parkinson's disease
- Post-Traumatic Stress Disorder (PTSD)
- Severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain
- Sickle Cell Anemia
- Terminal Illness
- Tourette syndrome

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Medical Reasons for Marijuana Use [Azcarte et al., 2020]

Of U.S. adults [n=9,003], report medical marijuana use [n=591]

Most common reasons	%
Anxiety	49%
Insomnia	47%
Chronic pain	42%
Depression	39%
Mood stabilization	32%
PTSD	15%

Azcarate et al. J Gen Intern Med 2020 35(7): 13, 1979-1986

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PA Indications for Medical Marijuana Use [Kimless et al., 2022]

Survey administered in 2021 at individual dispensary [n=207]

Primary condition for certification	%
Anxiety disorders	50%
Severe chronic or intractable pain	22%
PTSD	08%
Inflammatory bowel disease	03%
All others (each)	≤2%

Kimless et al. An observational cross-sectional survey exploring the indications for and responses to medical marijuana use in certified patients in Pennsylvania. J Primary Care Comm Health 13, 1-10, 2022

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Cannabis and Anxiety

Cannabis, a cause for anxiety? A critical appraisal of the angiogenic and anxiolytic properties. Sharpe et al. J Transl Med 2020, 18: 374

Surveys: >90% report improved anxiety symptoms BUT remission higher in NONusers

Rodent studies: THC dose-dependent effect: higher dose – angiogenic

Acute dose human trials: angiogenic response “firmly established”

“...no human studies provided any evidence of anxiolytic effects.”

frequent cannabis users: smaller increases in anxiety

“THC was found to have a profound angiogenic effect” at doses up to 30 mg.

Summary: “...the available human clinical studies demonstrate a common angiogenic response to THC (especially at higher doses.)”

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THC Acute Effects: Subjective

<u>Effect</u>	<u>Dose [mg of THC] & administration</u>			<u>peak time</u>
Pleasant	0	<	10 ^s 10 ^v 25 ^s 25 ^v	10 min
Sleepy	0	<	10 ^s 10 ^v 25 ^s 25 ^v	2 hour
Hungry	0	<	10 ^s 10 ^v 25 ^s 25 ^v	3 hour
Unpleasant	0 10 ^s 10 ^v	<	25 ^s 25 ^v	1 hour
Anxious	0 10 ^s 10 ^v	<	25 ^s 25 ^v	30 min
Paranoid	0 10 ^s 10 ^v 25 ^s	<	25 ^v	30 min
Memory impaired	0 10 ^s 10 ^v	<	25 ^s 25 ^v	1 hour
Difficulty performing routine tasks	0 10 ^s	<	10 ^v 25 ^s 25 ^v	30 min

mg THC; s=smoked; v=vaporized. THC concentrations: 10^s 10^v 25^s 25^v

n.b., cannabis had lower THC than typically available

[n=17 healthy adults; within-subject double-blind crossover design. Spindle et al. 2018: JAMA Network Open]

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Cannabis Withdrawal

- ages 18-65; n=29; daily marijuana users
- In-patient research unit; abstinence up to 30 days

Results

Cannabis Withdrawal Syndrome: criteria met by 56%

Cannabis craving: 49%; gradually diminished throughout

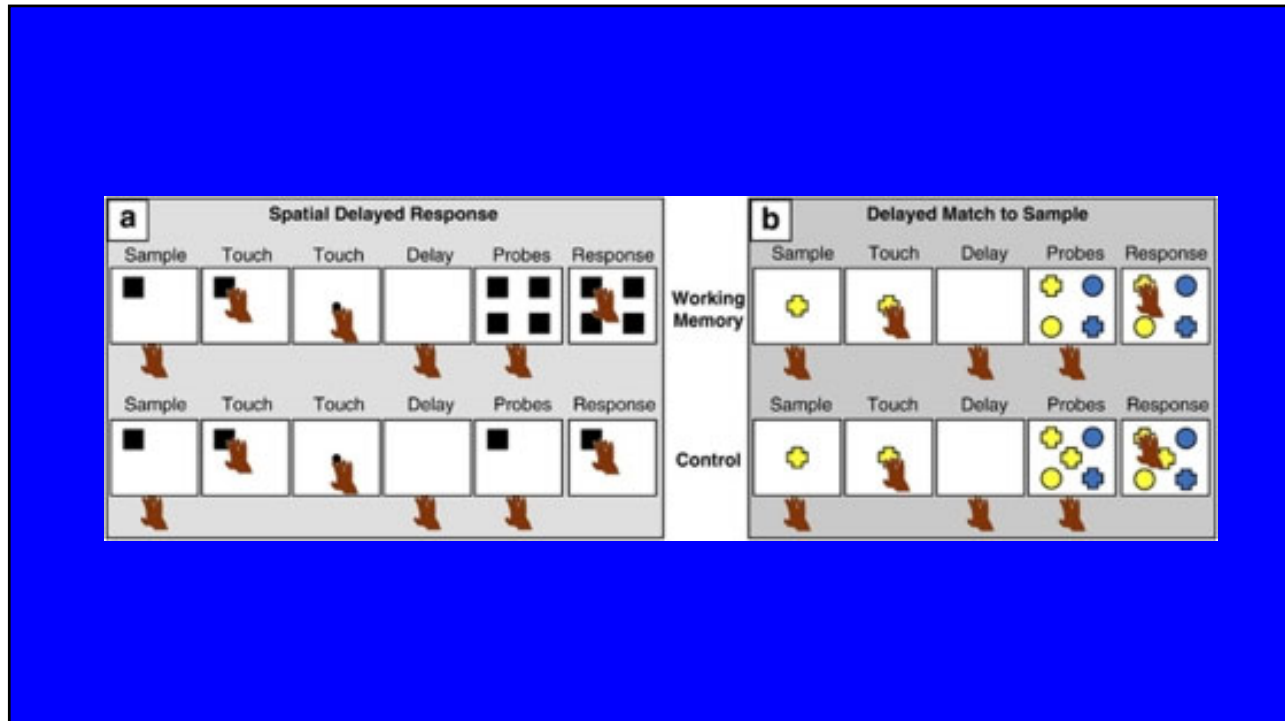
Irritability: 37%; peaked Day 13, resolved Day 23

Anxious: 29%; peaked Day 7, resolved Day 20

Sleep: less deep sleep, more waking, vivid dreams

Lee et al (2001) Am J Addictions 23: 234-242

32



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THC effects on working memory

Animals: male rhesus monkeys [n=14]; THC group [7]; Vehicle group [7]

Spatial delayed response task: location-recall WM test
 form, maintain, recall spatial location-matching rule
 delay periods: 1, 4, 8, 16 seconds

THC doses: 30, 60, 120, 180 micrograms/kg

Results: "THC administration impaired accuracy on the spatial WM task in a delay- and dose-dependent manner; Importantly, the THC-induced spatial WM deficits were not because of motor or motivational impairments."

Verrico et al. Delay- and dose-dependent effects of delta-9 -THC administration on spatial and object working memory tasks in adolescent rhesus monkeys. *Neuropsychopharmacology* 37, 1357-1366, 2012

34

THC Acute Effects: Cognitive tests

Tasks representative of workplace performance or motor vehicle operation

DAT: Divided Attention Task: divided attention
DSST: Digit Symbol Substitution Task: memory, information processing
PASAT: Paced Auditory Serial Attention Task: sustained & divided attention

<u>Effect</u>	<u>Dose [mg of THC] & administration</u>			<u>peak time</u>
DAT	0 10^s	<	10^v 25^s 25^v	1 hour
DSST	0 10^s 25^s	<	10^v 25^v	1 hour
PASAT	0 10^s 10^v 25^s	<	25^v	30 min

[n=17 healthy adults; within-subject double-blind crossover design]
 Spindle et al. 2018: JAMA Network Open]

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Cannabis and Cognition: Acute & Residual effects

Cannabis, and Cognitive Functioning: Bourque & Potvin: Frontiers in Psychiatry 2021

Influences: abstinence duration; use frequency, comorbidity, age of initiation, domains

Acute effects	# studies	decrements	
		Acute	Residual (abstinence)
Cognitive domain			
Attention	30	small	small
Verbal learning	14	moderate	small
Verbal memory	12	moderate	small
Working memory	23	moderate	---
Executive function	13	moderate	small
Processing speed	38	moderate	small
Impulsivity	14	small	

Summary: "...residual effects...12 hours to more prolonged...abstinence...small deficits in attention, executive functioning, and processing speed...more negatively affected in acute phases of intoxication..."

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Cannabis and Cognition: Acute and Residual effects [Bourque & Potvin, 2021]

Δ^9 -THC Content: "...higher dosage...induced significantly more detrimental effects on verbal learning and memory, reaction times, and response inhibition..."

Frequent cannabis use: "...following Δ^9 -THC exposure... blunted perceptual alterations, psychotomimetic effects, anxiety, and increases in cortisol relative to occasional users...smaller...impairments in immediate and delayed verbal memory tasks, while performing worse during the placebo condition..."

Comorbidity with psychosis–spectrum disorders: "...enhanced sensitivity to the cognitive impairing effect of Δ^9 -THC in psychosis..."

Deficits increase with greater use: "...research showed a dose-response effect ...on the amplitude of associated cognitive deficits..."

Abstinence duration: "...residual effects have a short-term duration...they are reversible..."

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Cannabis and Amotivational Syndrome

Observational study: two assessments

Subjects: college students [n=505]

Measures: marijuana use [#days past 30 days], other substance use
demographics, personality,
general self-efficacy [initiative, effort, persistence]

Analyses: 13 pertinent baseline covariates included

Results: "...only marijuana (but not alcohol or tobacco) intake significantly and longitudinally prompted lower initiative and persistence...Findings provide partial support for the marijuana amotivational syndrome, underscore marijuana as a risk factor in decreased general self-efficacy..."

Lac & Luk. Testing the Amotivational Syndrome... Prev Sci 19(2), 117-126, 2018

38

Cannabis and Sleep: cannabis as sleep aid: a diary study

217 college students with cannabis and/or alcohol use

30% used cannabis as a sleep aid; completed 14-day diary

Nights with cannabis as sleep aid: longer sleep duration
 less wake time after onset
 more next-day fatigue

Goodhines et al. Cannabis and alcohol use for sleep aid Health Psychology 2019; 38: 1036-1047]

39

Cannabis Abstinence Effects

- ages 18-50; n=12
- daily marijuana users
- On 5 days – off 3 days – on 5 days – off 3 days

Results

large change	moderate change
Withdrawal Discomfort	aggression
craving	irritability, anger
decreased appetite	restlessness
sleep difficulty	strange dreams

Budney et al (2001) Arch General Psychiatry 58: 917-924

40

Cannabis Withdrawal

- **ages 18-65; n=29; daily marijuana users**
- **In-patient research unit; abstinence up to 30 days**

Results

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Anxious: 29%; peaked Day 7, resolved Day 20

Sleep: less deep sleep, more waking, vivid dreams

Lee et al (2001) Am J Addictions 23: 234-242

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Cannabis use disorder and comorbid depression in adolescents & YA

Subjects: n=70; ages 15- 25 years old

Design: double-blind, placebo controlled

Medication: fluoxetine [Prozac]: 20 mg. or placebo x 12 weeks

Behavioral: CBT and Motivational Enhancement Therapy x 9 sessions

Results: Substantial improvement was noted in both groups.

“...fluoxetine did not demonstrate greater efficacy than placebo for treatment either the depressive symptoms or the cannabis-related symptoms...”

Cornelius et al. Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. Drug and Alcohol Dependence 112, 39-45, 2010.

42

Cannabis use disorder and comorbid depression in adults

[Levin et al., 2010]

Subjects: n=103; ages 35 ± 10; 18 - 60 years old

Design: double-blind, placebo controlled

Medication: venlafaxine [Effexor] XR: 225 mg. or placebo x 12 weeks

Behavioral: Weekly CBT

Results: “The proportion of patients achieving a clinically significant mood improvement...was high and did not differ between groups...The proportion of patients achieving abstinence was low overall, but was significantly worse on VEN-XT=R (11.8%) compared to placebo (36.5%)...Mood improvement was associated with reduction in marijuana use in the placebo group...”

Levin et al. A randomized double-blind, placebo controlled trial of venlafaxine-extended release for co-occurring cannabis dependence and depressive disorders. *Addiction* 108(6), 1084-1094, 2013.

43

SSRIs for Cannabis Use Disorder: Depression, Anxiety, PTSD

64 randomized controlled trials with 6128 participants

Systematic review: 8 randomized clinical trials [Sharma et al., 2022]

“SSRIs reduced depressive symptoms in...cannabis...use disorder...”

“...generalized anxiety symptoms in...marijuana use disorder...”

“Evidence for PTSD was inconclusive.”

“SSRIs facilitated abstinence for...cannabis use...”

Fluoxetine showed the highest antidepressant effect.”

“Conclusions: Results support the use of SSRIs to treat substance use, depression, and anxiety in individuals with addiction.”

Fluyau et al. Selective serotonin reuptake inhibitors in the treatment of depression, anxiety, and post-traumatic stress disorder in substance use disorders: a Bayesian meta-analysis. *European J clin Pharmaco* 78(6): 931-942, 2022

44

N-acetyl cysteine [NAC] for Cannabis Use Disorder

NAC: antioxidant derived from amino acid cysteine

Systematic review: 8 randomized clinical trials [Sharma et al., 2022]

Conclusions: "NAC has shown to be effective in promoting abstinence, medication adherence and reducing cannabis use and cravings among cannabis dependent users."

Dose: 2400 mg/day; OTC cost: 50 cents per day; side effects: "unusual" include GI: N/V/D/C

Sharma et al. N-acetyl cysteine in the treatment of cannabis use disorder: A systematic review of clinical trials. Addictive Behaviors 129, 107283, 2022

45

Reducing or increasing cannabis use over 12 weeks

Baseline characteristics	reduction	increase
N	152	150
Age	31 yrs	30 yrs
Cannabis days/30	27	25
Anxiety above average	37%	34%
Depression above norm	14%	17%
Poor sleep quality	69%	69%

Cannabis reduction associated with: reduced anxiety
reduced depression
improved sleep

Cannabis reduction effects on sleep [J Substance Abuse Treatment 2017: 81: 53-58]

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Common cannabis questions

Has cannabis use increased? Rates lower in high school ages, but rates of daily use have increased in teens & young adults and THC doses have dramatically increased to unprecedented levels.

Is cannabis addictive...withdrawal? THC discontinuation causes withdrawal symptoms, including anxiety and insomnia, that diminish over days or weeks.

Why do people use “medical marijuana”? Most common uses are for anxiety and sleep.

Does cannabis cause or treat anxiety? THC intoxication & withdrawal cause anxiety.

Does cannabis help or impede learning? THC intoxication impairs memory.

Does cannabis improve or impair sleep? At low doses, THC intoxication reduces sleep onset time and increases time sleeping. At high doses, sleep onset time increases and sleep quality is impaired. Cannabis withdrawal causes insomnia.

Which medications help with cannabis and comorbid disorders? Medications for comorbid symptoms less effective and difficult to evaluate. Consider NAD for craving.

Does cannabis reduction or discontinuation improve outcomes? With cannabis reduction or discontinuation, THC-related anxiety, depression, memory problems, and sleep difficulties improve over hours, days, or weeks.