

NORTH DAKOTA
ACADEMY OF FAMILY
PRACTICE: BIG SKY
CONFERENCE 2025

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MRO-C:
Cannabis Use
Disorder

1

Disclosures:

- I am paid presenter for Alkermes regarding their product Vivitrol. This will not be discussed in today presentation.

2

"Most middle- and high-income countries globally have become largely inured to the endemic premature mortalities related to more commonly used substances such as alcohol and tobacco. While these account for a much larger number of deaths and economic and social harms than opioids each year, the devastation wreaked by these substances, their casualties, and the associated blood and tears are all relatively willingly absorbed into the social fabric."

John F. Kelly and Sarah E. Wakeman, 2019

Perspective

3

Michigan Cannabis Laws

- Recreational Cannabis
 - Age requirements: Adults 21 and older can legally possess and use Marijuana.
 - Possession limits: up to 2.5 ounces of marijuana in public. Up to 10 ounces at home and must be stored securely.
 - Cultivation: Individuals can grow up to 12 plants per household for personal use.
 - Public Use: consumption is prohibited in public places and only allowed on private property with owners consent. No application or license is required for personal cultivation.
 - Sales and Licensing: Licensed business can cultivate process transport and sell marijuana. 10% excise tax and 6% sales tax.

4

Michigan Cannabis laws

- Medical Cannabis
 - Eligibility: Patients with qualifying medical conditions can obtain a medical card.
 - Possession limits: Patients can possess up to 2.5 oz of usable marijuana. Caregivers (registered to assist up to 5 patients) can grow up to 12 plants per patient.
 - Protections: Registered patients and caregivers are protected from arrest, prosecution, and penalty under state law.

5

Michigan Cannabis Laws

- Additional notes:
 - Driving under the influence is illegal. There is no set legal limit but law enforcement (Drug Recognition experts) considers behavior, driving patterns and physical signs. Public intoxication is illegal.
 - Workplace: Employers can still enforce drug free policies
 - Local authority: Municipalities can regulate or ban marijuana businesses with their jurisdiction.
 - Federal Law: Cannabis remains illegal federally which can create conflicts.

6

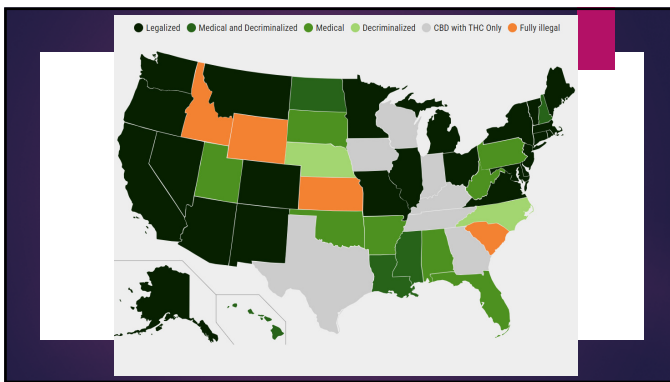
As of November 2024

- ▶ Recreational use: 24 states and the District of Columbia have legalized recreational cannabis for adults 21 and older
- ▶ Medical Use: 38 states permit for medical use
- ▶ Federal: Cannabis remains classified as Schedule 1 substance
- ▶ Recent: Florida rejected legalized recreational use
 - ▶ North and South Dakota rejected legalized recreational use
 - ▶ Nebraska legalized medical use

7

Nov election

8



9

Some Common Misconceptions

- Legal because it is safe
- Edibles and concentrates are safe
- Only adults are using as prescribed
- Everyone smoked weed back in the day
- Safe in pregnancy because it is "Natural"
- CBD is completely safe
- Marijuana is not addictive
- Legalization has reduced marijuana use
- Vaping is safe
- It is a solution to the opioid epidemic
- Benefits are scientifically proven

10

The Trends

- ▶ Increasing prevalence of use
- ▶ Use is starting earlier than early teen
- ▶ Decreased perception of risk
- ▶ Dangerously high concentration
- ▶ Fentanyl laced marijuana, Hallucinogen laced marijuana
- ▶ Lack of information on these risks
- ▶ Excessive marketing
- ▶ 10 -20 % (up to 30%) develop Cannabis use disorder

11

The Young Brain Is At Higher Risk

- ▶ In 2017, 22.9% of high school seniors used marijuana in the past 30 days compared with 9.7% who smoked cigarettes
- ▶ Among people aged 12 or older in 2021, 18.7% (or about 52.5 million people) reported using cannabis in the past 12 months.
- ▶ In 2022, an estimated 8.3% of 8th graders, 19.5% of 10th graders, and 30.7% of 12th graders reported using cannabis/hashish in the past 12 months.

12

Long-Term Cannabis Use and Cognitive Reserves and Hippocampal Volume in Midlife

Madeline H. Meier, Ph.D., Avshalom Caspi, Ph.D., Anichen R. Knodt, M.Sc., Wayne Hall, Ph.D., Antony Ambler, M.Sc., Honalae Harrington, B.A., Sean Hogans, B.A., Renate M. Houts, Ph.D., Richie Poulton, Ph.D., Sandhya Ramrakha, Ph.D., Ahmad R. Hariri, Ph.D., Terrie E. Moffitt, Ph.D.

Objective: Cannabis use is increasing among midlife and older adults. This study tested the hypotheses that long-term cannabis use is associated with cognitive deficits and smaller hippocampal volume in midlife, which is important because midlife cognitive deficits and smaller hippocampal volume are risk factors for dementia.

Methods: Participants are members of a representative cohort of 1,037 individuals born in Dunedin, New Zealand, in 1972–1973 and followed to age 45, with 94% retention. Cannabis use and dependence were assessed at ages 18, 21, 26, 32, 38, and 45. IQ was assessed at ages 7, 9, 11, and 45. Specific neuropsychological functions and hippocampal volume were assessed at age 45.

Results: Long-term cannabis users showed IQ decline from childhood to midlife (mean = -5.5 IQ points), poorer learning and processing speed relative to their childhood IQ, and informant-reported memory and attention problems. These deficits were specific to long-term cannabis users because they were either not present or were smaller among long-term tobacco users, long-term alcohol users, midlife recreational cannabis users, and cannabis quitters. Cognitive deficits among long-term cannabis users could not be explained by persistent tobacco, alcohol, or other illicit drug use, childhood socioeconomic status, low childhood self-control, or family history of substance dependence. Long-term cannabis users showed smaller hippocampal volume, but smaller hippocampal volume did not statistically mediate cannabis-related cognitive deficits.

Conclusions: Long-term cannabis users showed cognitive deficits and smaller hippocampal volume in midlife. Research is needed to ascertain whether long-term cannabis users show elevated rates of dementia in later life.

Am J Psychiatry 2022; 179:362–374; doi: 10.1176/appi.ap.2021.21060664

13

Driving While High

- ▶ 1 in 5 drivers are under the influence of marijuana, up from 1 in 10 prior to legalization (Washington Traffic Safety Commission)
- ▶ Since legalization in Colorado there has been a 66% increase in marijuana-related traffic deaths (Rocky Mountain HIDTA)
- ▶ Colorado saw a 33% and Nevada saw a 40% increase in average yearly premiums within the year prior and year after legalization passed.
- ▶ Liberty Mutual data report 1 in 5 teens have gotten behind the wheel after smoking marijuana.

14

What We Are Up Against

- ▶ This is a \$32 Billion industry in 2023
- ▶ Projected \$50bn by 2030
- ▶ Start up cost for a dispensary business \$150,000 to an average of \$750,000
- ▶ Generates a minimum \$1 million
- Average 3.1 to 4 million \$ annual revenue


15

1. An increasing number of jurisdictions are allowing cannabis supply for nonmedical purposes



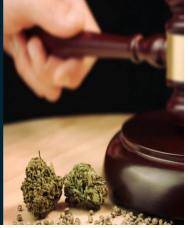
16

2. Cannabis prices are declining in places with commercial regimes. This affects several outcomes.



17

3. Caution is necessary when evaluating the evidence on legalization.



18



Illegal cannabis market

Largely function of prices & enforcement

- But quality and testing can matter, too

For residents in legal jurisdictions, increasing share getting cannabis from legal market

- Washington (through 2017): 40-60% of THC (Kilmer et al., 2019)
- Oregon (through 2018): 55% of adult market (OLCC, 2019)
- Colorado: Over 90% (Barcott & Whitney, 2022)*

Roll out in NY has been a mess

Still have illegal export markets in legal states

19



Traffic crashes and fatalities

No evidence that leg improved traffic outcomes

Early US studies didn't find an effect, but some, not all, recent studies find legalization is positively associated with motor-vehicle fatalities

Study of UY finds increase in traffic injuries associated with home grow registrations, but not pharmacies

Evidence from Canada generally finds no effect

20

Cannabis-related treatment, hospitalizations, & poisoning calls

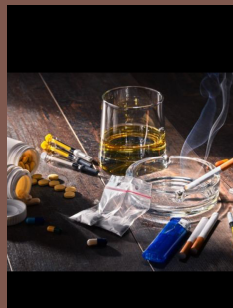
Theoretical effect of leg on cannabis treatment admissions is ambiguous

- Trend data suggest declines in CO & WA, but WA decline started before legalization (WSIPP, 2017; RMHITDA, 2019)
- Youth cannabis admissions down, especially in legalized states (CDC, 2020), but rigorous studies are not conclusive

Seeing increases in cannabis-related ER visits, hospitalizations, & poison calls

- Many pre-post (notable exceptions e.g., Shi & Liang, 2019; Dilley et al., 2021)
- Increasing number of studies based on Canada
- How much can be attributed to a change in stigma?

21



Use of other drugs

Evidence of decrease in opioid prescriptions, but no consensus on overdose deaths

Evidence for alcohol & tobacco mixed

- Different metrics and populations
- A few studies examining co-use of cannabis & either alcohol or tobacco, finding either an increase in co-use or no change depending on the substance and socio-demographic characteristics
- Be skeptical of those who claim they know answer with certainty

22

History of Cannabis

- ▶ Subspecies of Hemp
- ▶ Marijuana
- ▶ Hashish Resin, Hash Oils, edibles
- ▶ Genetically engineered under optimal conditions for greater potency
- ▶ BC 2727: Medicinal properties described
- ▶ Removal in US 1947, made schedule 1 drug 1970
- ▶ Dronabinol approved FDA 1970
- ▶ Delta 9 isolated 1965
- ▶ Endocannabinoid receptors cloned

23

Cannabis legalized

- ▶ Legalized for recreational use in 2012: Colorado



24

Canabis is getting more potent

- ▶ **THC concentration:** The potency (concentration or strength) of THC in cannabis is often shown as a percentage of THC by weight (or by volume of an oil). THC potency in dried cannabis has increased from an average of 3% in the 1980s to around 20% today. Some strains can have an average as high as 30% THC. Oils and dried products maybe up to 70%.

25

Canabis Hyperemesis Syndrome

- ▶ **What is cannabis hyperemesis syndrome (CHS)?** CHS is a condition first identified in 2009 and associated with long-term, regular cannabis use. Symptoms include nausea and recurring vomiting that is not linked to other symptoms, such as fever; although weight loss and dehydration may result. Because of how rare CHS was in the past, it may go unrecognized, undiagnosed, or misdiagnosed (frequently as cyclical vomiting disorder). Temporary relief is often found with hot showers combined with the topical application of capsaicin oil. Symptoms will go away with complete abstinence from cannabis use. A return to cannabis use may result in the return of CHS.

26

Canabinoid Receptors:

- ▶ Most widely located G protein receptor
- ▶ Endogenous Canabinoids: 5 classes of molecules
- ▶ Exogenous Canabinoids
 - ▶ Phytocannabinoids
 - ▶ Synthetic cannabinoids

27

Exogenous Canabinoids

- ▶ **Phytocannabinoids:**
 - ▶ Greater 140 in Cannabis plants
 - ▶ Delta 9 tetrahydrocannabinol: hashish, oils, extracts
 - ▶ Cannabidiol: CBD
 - ▶ FDA Approvals:
 - ▶ Cannabidiol: Epidiolex solution: Lennox Gastro and Drexel Syndrome: \$32,000 per year
 - ▶ THC: Marinol and Nabilone (Cesamet): Chemo nausea and HIV wasting
 - ▶ Nabiximols: Sativex Spastichy, 1:1 CBD:THC. Not in US
 - ▶ Evidence for chronic pain: no FDA approvals yet

28

Endogenous Canabinoids

Arachidonyl ethanolamide	2-Arachidonyl-glycerol	2-Arachidonyl-glycerol - ether
2-Arachidonyl-Dopamine	Virodlimine	widespread neuromodulatory system that plays important roles in central nervous system (CNS) development, synaptic plasticity, and the response to endogenous and environmental insults.

29

Cannabinoid receptors

- ▶ **CB1:** hippocampus (memory learning), basal ganglia (motor function), cortex (executive functions), cerebellum (balance), amygdala (novelty, emotion), nucleus accumbens (reward)
- ▶ Endogenous Canabinoid receptor activation decrease cAMP and decreases neuronal excitability; tonically active; endogenous off regulates
- ▶ **CB2:** Immune function, spleen, tonsils, lower CNS neurons

30

CBD: whats the big deal

- Widely available: topical, fabric, edible, liquid, food, beverage
- 2018 federal restrictions removed: now concerns with purity and potency
- May show positive for THC
- Sedation, GI side effects

31

Neuromodulator

The role of the endocannabinoid system is to regulate other neurotransmitters: inhibit GABA and glutamate

Endocannabinoids:

- Pain threshold
- Working memory, creative memory
- Novelty of experience
- Focus attention, fear, anxiety stress response
- Appetite, global characteristics of consciousness

32

CBD

Major non-psychoactive component of Cannabis

- Endocannabinoid System Modulation: CB1 And CB2: CBD has low affinity for CB1 (negative allosteric modulator: reducing psychoactive affects) and CB2
- Enhances Endocannabinoid Levels: Inhibits the breakdown of anandamide: regulates mood, pain and inflammation.
- Serotonin Receptors (5-HT): CBD acts as an agonist of the 5-HT1A receptor, anxiolytic, antidepressants, reduction in nausea and vomiting, neuroprotection
- Transient Receptor Potential (TRP) Channels: TRPV1 Vanilloid Receptor 1: Pain Modulation, body temp, inflammation

33

CBD

- GABA-A positive allosteric modulator: reduce anxiety, promotes relaxation
- Adenosine Receptors: inhibits reuptake enhancing signaling: anti-inflammatory and neuroprotection
- PPARs (Peroxisome Proliferation Activation Receptors) Activates PPAR gamma receptors: regulate lipids and insulin sensitivity, anti-inflammatory and anticancer effects.
- Pharmacokinetics: 19% bioavailability, lipophilic, hepatic metabolism CYP450 and fe. Antifolate elimination, anxiolytic, anti-inflammatory, neuroprotective, antipsychotic, cardioprotective.
- Side effects: fatigue, diarrhea, weight gain, dry mouth

34

Incidence and Prevalence

- 228 million worldwide use 4% of global population
- US: lifetime, past year, past month: 47.1%, 21.8 and 15.4 %
- 30% of users meet criteria for Cannabis Use disorder
- Cannabis users: increase, alcohol, tobacco use, opioid use, stimulant use, benzodiazepine use, club drug use
- Psychiatric disorder: increased depression, anxiety, PTSD, ADHD, schizophrenia. ? Bipolar

35

Synthetic Cannabinoids

Over 180 known compounds manufactured in illicit drug labs

- Sprayed onto herbs and smoked, insufflated, orally ingested
- K2, Spice, various names/brands
- "Herbal incense" or "fragrant potpourri"

Potent full CB1 agonists (2-800x more potent than THC)

Generally decreasing rates: adolescents (1.6% of high school students in 2021), forensic settings, military

NPR

36

Synthetic Cannabinoids



K2 and Spice

Significant increase in neuropsychiatric symptoms: psychosis, delirium, seizure, coma

37

Synthetic Cannabinoids

- Intoxication similar to cannabis, e.g., tachycardia, conjunctival injection, increased appetite, ataxia
- Higher risk of serious neuropsychiatric toxicity: agitation, delirium, hallucinations, psychosis, seizures, coma
- Diagnosis
 - Not on standard UDS, typically not cross reactive with THC
 - Can get confirmatory testing
- Treatment largely supportive: IV fluids (high risk of rhabdo), quiet room
 - Sedatives, antipsychotics for severe anxiety or agitation

38

Acute THC intoxication

- ▶ Alteration in mood
- ▶ Decrease anxiety
- ▶ Cognitive impairment: memory, processing speed: may last up to 72 hours
- ▶ Sedation or changes in consciousness
- ▶ Sensory intensification
- ▶ Psychosis

39

Cannabis use disorder Criteria

- ▶ Problematic cannabis use with impairment and distress and 2 of the following:
 - ▶ Larger amount used than intended
 - ▶ Desire or unsuccessful attempts to cut back on use
 - ▶ Craving
 - ▶ Failure with work home and other obligations
 - ▶ Social or interpersonal problems
 - ▶ Reduced social recreational activities
 - ▶ Hazardous use
 - ▶ Tolerance
 - ▶ Withdrawal

Mild, moderate or severe

20-30% of past year users meet criteria.

40

Cannabis Withdrawal Syndrome

- ▶ 3 of the following:
 - ▶ Irritability, anger or aggression
 - ▶ Worsening anxiety
 - ▶ Insomnia
 - ▶ Appetite decrease and weight loss
 - ▶ Restlessness
 - ▶ Worsening depression
- ▶ Somatic: abdominal pain, sweating, fatigue, fevers, chills

41

Cannabis and education

- ▶ Lower GPA, less satisfaction and engagement in school and school activities, increase expulsions and dropout
- ▶ Absenteeism, unemployment
- ▶ Persistent adolescent related cognitive decline

42

Reasons to seek treatment

- Loss of control or impairment
- Academic or occupational failure concerns
- Worsening mood
- Hyperemesis
- Family and social dynamic conflicts

43

Pharmacotherapy for Cannabis Use disorder

- ▶ N-acetylcysteine: The antioxidant n-acetylcysteine (NAC), an N-acetyl prodrug of the naturally occurring amino acid cysteine, has been tested in the treatment of cannabis use disorder. Evidence of efficacy is not consistent among trials. It is available as an over-the-counter supplement. May decrease cravings. Glutamate modulator
- ▶ Gabapentin: Voltage gated calcium channels. 1200 mg daily: reduced cannabis use verified by cannabinoid-negative urine tests and self-reported cannabis use, decreased cannabis withdrawal symptoms (Marijuana Withdrawal Checklist), and greater improvement on cognitive tests of executive function as compared with placebo

44

Pharmacotherapy

- ▶ Nabiximols: Sativex: MS spasticity, chronic pain. mixed clinically evidence
- ▶ Canabidiol: CBD no evidence of improvement or decrease use
- ▶ Topiramate: Inhibits voltage-gated sodium channels, enhances gaba activity, glutamate inhibition Less use with higher dosing 200 mg.
- ▶ Varenicline: Partial Agonist at alpha-4beta-2 nicotinic acetylcholine receptors evidence points to decrease use while taking
- ▶ No evidence for Antidepressants (ie, bupropion, fluoxetine, venlafaxine, and vilazodone), atomoxetine, divalproex, lithium, buspirone, and cannabinoid receptor agonists (synthetic THC (ie, dranabinol), nabilone)
- ▶ No evidence with neuromodulation

45

Behavioral therapies

- ▶ Motivational Interviewing: change the maladaptive behavior. Expressing empathy Helping the patient identify discrepancies between their problematic behaviors and broader, personal values Accepting the patient's resistance to change Enhancing the patient's self-efficacy (ie, confidence in their capability to surmount obstacles and successfully change)
- ▶ Motivational enhancement therapy: Improve patient motivation to change, ambivalent patient
- ▶ Cognitive Behavioral therapy: education, relaxation exercises, exposure, coping skills training, stress management, or assertiveness training
- ▶ Contingency Management: reward
- ▶ Family Based Therapies

46

Summary

- ▶ Reviewed:
 - ▶ Cannabis laws
 - ▶ Cannabis perception
 - ▶ Cannabinoid receptors
 - ▶ Exogenous and Endogenous Cannabinoids
 - ▶ Criteria for use disorder
 - ▶ Pharmacological and Behavioral treatments

47