Cannabis and Synthetic Cannabinoids an Addiction Psychiatrist's Friend or Foe?

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Objectives

- History of cannabis
- Neurobiology
- Medical Cannabis
- Applications in Addiction psychiatry
- Case example

Cannabis: history and overview

- Plant Cannabis sativa, flowers and leaves contain THC
- Has been used for thousands of years (since 4000 B.C.)
- Documented in 19th and early 20th century as analgesic, hypnotic and anticonvulsant
- Has been used for many years in US to treat glaucoma, nausea, chronic pain and muscle spasticity

Marijuana Preparations

- In US: most frequently smoked in a pipe, bong or joint
- Δ^9-THC highly lipid soluble, dried leaves are heated and mixed with butter/milk to make edible
- Dose of THC is highly variable
  - “Bhang”/”grass”: rough mixture of flowers, leaves, stems and seeds 1-3% THC
  - “ganja”/”sinsemilla”: unfertilized female flowers 3-8%THC
  - “charas”/”hashish”: collection of resin beads from sterile buds 10-15%
  - “hash oil”/”dabs”/ “shatter”: extraxction of cannabis preparations with organic solvent 30%-35% THC
- Studies show increase in potency of cannabis preparations across US

Epidemiology of Cannabis

- Most widely used **illicit** drug in US
- Cannabis Use disorders (CUD) tend to begin late adolescence to early adulthood
- 30% college students used cannabis is previous year, 25% of these had CUD
- In 1996 Thomas reported 15% cannabis users reported acute psychotic symptoms
- Several studies have shown a risk around 6.0 for cannabis users to development schizophrenia

Epidemiology continued

- Increase in cannabis use does not produce corresponding increase in schizophrenia
- Greater risk of developing psychotic illness if used earlier in adolescence
- Cannabis use was significantly associated with a decrease in age of onset of schizophrenia
- Zammit et al 17 reported a 27-year follow-up of the Swedish cohort that also found a dose-response relationship between frequency of cannabis use at baseline and risk of schizophrenia during the follow-up
- Moore et al 23 found an increased risk (odds ratio, OR=1.4; 95% confidence interval, CI: 1.20, 1.65) of psychotic disorder if someone ever used cannabis

Highlights from 2020 National Survey on Drug Use and Health

- 2020: 17.9% (49.6 million of those surveyed) used marijuana
- Percentage of people who used marijuana in past year was highest among 18-25 (34.5%) compared to 16.3% of adults >26 yrs old and 10.1% of adolescents 12 to 17.
- 2.8 million initiated marijuana use in patients >12 years old
- Only 1 in 4 people >12 years old perceived great risk of harm from smoking marijuana 1-2x/ week
- Young adults (18-25 yrs) less likely to perceive risk than other age groups

Neurobiology: Receptors

- Two known cannabinoid receptors: CB1 and CB2
- CB1 found in high concentration in the hippocampus, neocortex, basal ganglia and cerebellum
  - Modulates pain, mediates motivation, mood and cognition

- CB2 primarily in peripheral tissues
  - Abundantly expressed on immune cells and modulate immunity and inflammatory responses
  - Also identified on microglial cells in brain and spinal cord (exist in increased quantities when there is injury or cell damage)
- Δ^9-THC is CB1 and CB2 **partial** agonist (presynaptic receptor, activation triggers NT release)
- Cannabidiol CB1 and CB2 **antagonist**
- Synthetic cannabinoids are **FULL** agonists

Neurochemical Actions Mediating reward for Cannabis use

- Potency: amount of Δ^9-THC
- HOWEVER, psychoactive and addictive properties also mediated by endogenous cannabinoids, other exogenous cannabinoids from marijuana besides Δ^9-THC or interactions at these receptors
- High dose cannabidiol potentiates effects of Δ^9-THC via CB1 receptor dependent mechanism

Neurochemical actions (cont'd)

- Cannabis use corresponds to dopamine release in the ventral striatum, increased extracellular dopamine in nucleus accumbens and increased activity of dopamine neurons in VTA
- Δ^9-THC blocks plasticity in the nucleus accumbens

*generates reinforcing effects via dopaminergic systems

Neurobiological effects of Chronic Cannabis Use

- Withdrawal: increased anger/aggression, anxiety, depressed mood, irritability, restlessness, sleep difficulty, strange dreams, decreased appetite and weight loss
- Budney et al. 2007 cited the cessation of withdrawal syndrome with administration of marijuana or dronabinol
- Likely due to down regulation of endocannabinoid systems

Chronic Cannabis use (cont'd)

- CB1 co-expressed with serotonin and dopamine
- Δ^9-THC decreases sensitivity to opioids as well as cannabinoids at GABAergic and glutamategric synapses
- Chronic cognitive deficits improve with cessation of use

Marijuana Potency

Today's marijuana is stronger.

Today's marijuana has more than **3 times** the concentration of THC than marijuana from 25 years ago. More THC — the mind-altering chemical in marijuana — may lead to an increase in dependency and addiction.

MARIJUANA
THE RISKS ARE REAL

Risks of Marijuana

MARIJUANA
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Risks of Marijuana

Lowers brain power.

Marijuana affects your brain development. Use by adolescents has been linked to a decline in IQ scores — up to 8 points! Those are points you don't get back, even if you stop using.

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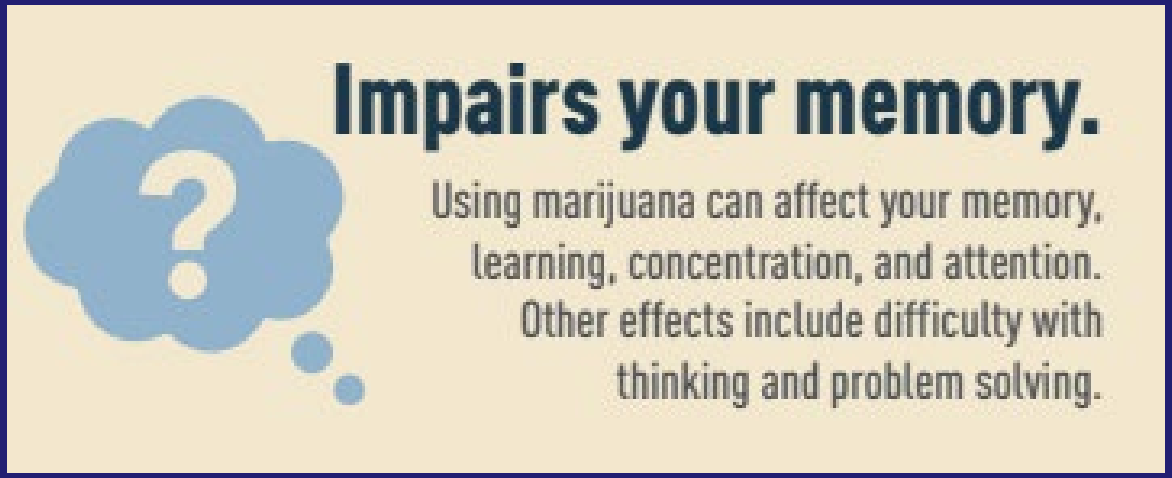
THE RISKS ARE REAL

Risks of Marijuana



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THE RISKS ARE REAL

Risks of Marijuana

Affects your performance.

Using marijuana can lead to worse educational outcomes. Compared with teens who don't use, students who use marijuana are more likely not to finish high school or get a college degree.

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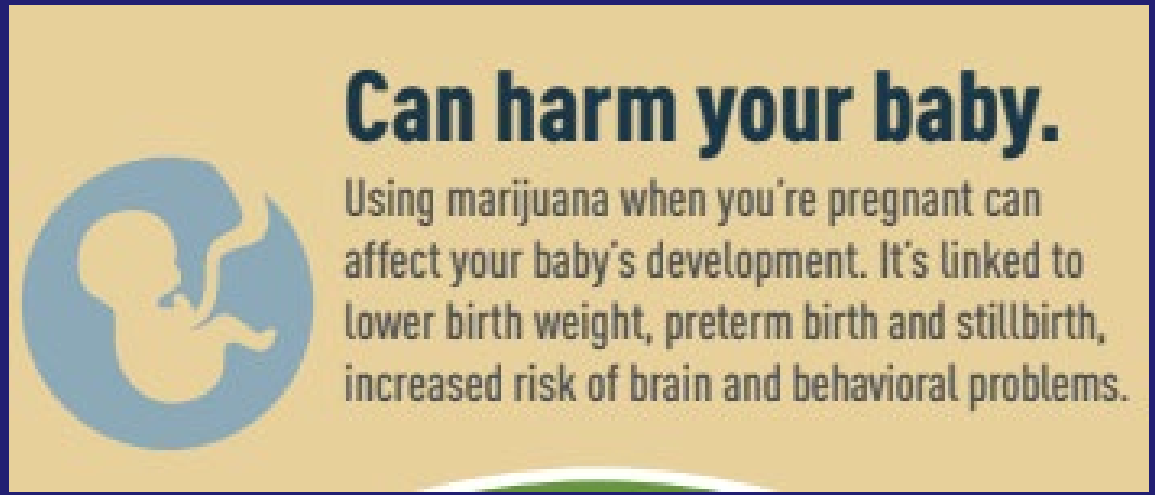
THE RISKS ARE REAL

Risks of Marijuana



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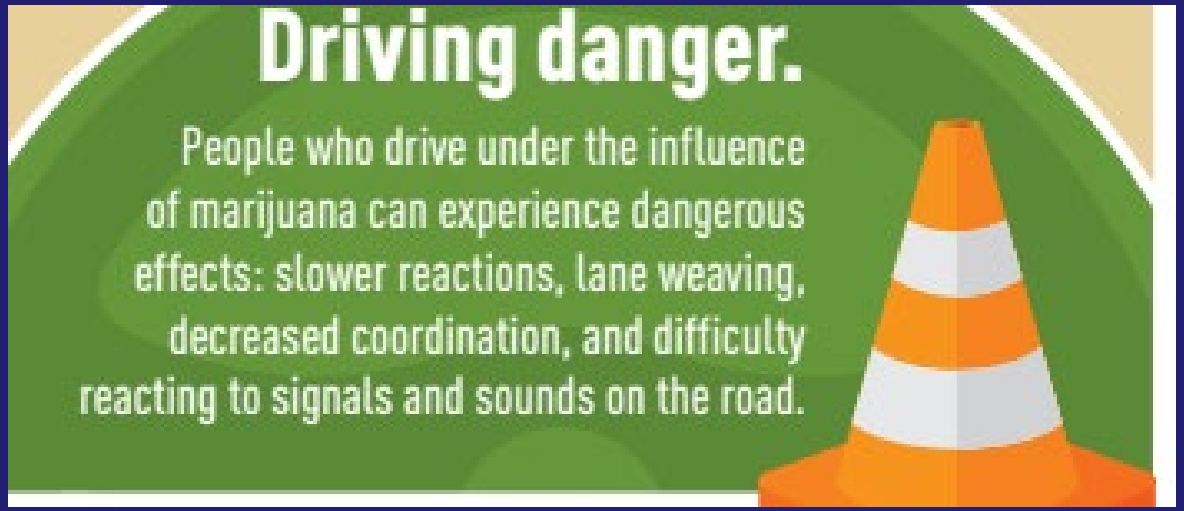

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THE RISKS ARE REAL

Cannabis Intoxication

- “pleasurable high”: euphoria
- Other effects: anxiety, paranoia, distorted sense of time, associative thinking, short term memory loss
- Physical effects: sedation, increased heart rate/BP/RR, dry mouth, injected conjunctiva, increased appetite, slowed reaction time
- Heavy marijuana use lowers testosterone levels and sperm count and quality

Prescription Synthetic Cannabinoids

- Dronabinol:
  - chemically identical to Δ^9-THC
  - Schedule III
  - Treatment of anorexia associated with weight loss in AIDS and nausea and vomiting due to chemotherapy not responsive to standard treatments
- Nabilone:
  - partial agonist
  - Schedule II
  - Nausea and vomiting in chemotherapy
- Rimonabant
  - Synthetic cannabinoid with inverse agonist properties at CB1 receptors
  - Supposed to be antiobesity drug but not available in US bc of adverse psychiatric symptoms

Medical Marijuana

Definition: derivatives of the Cannabis sativa plant that are used to ease symptoms caused by certain medical conditions

U.S. **federal law** prohibits the use of whole plant Cannabis sativa or its derivatives for any purpose.

Conditions Medical Marijuana suggested for:

From ny.gov:

“You may be eligible for medical cannabis if you have one or more of the following conditions: cancer, HIV infection or AIDS, amyotrophic lateral sclerosis (ALS), Parkinson's disease, multiple sclerosis, spinal cord injury with spasticity, epilepsy, inflammatory bowel disease, neuropathy, Huntington's disease, post-traumatic stress disorder, **pain that degrades health and functional capability as an alternative to opioid use, substance use disorder**, Alzheimer’s, muscular dystrophy, dystonia, rheumatoid arthritis, autism, or **any other condition**, at the discretion of your health care provider.”

So what does the research show?

- After chronic non-cancer pain, *mental health* is cited as most common reason for medicinal marijuana
- However, Black et al. showed in a systemic review and meta-analysis that there is **scarce evidence** to suggest cannabinoids improve depressive, anxiety, ADHD, PTSD or psychotic symptoms.
- Reinarman et al. cited that the patient reported use of medical cannabis was nearly threefold greater for pain (82.6%) and **five times greater** for anxiety or depression (63.9%)

How should the Addiction Psychiatrist Provide Guidance on this?

- For some patients cannabis has no negative effects, for others it can significantly impact mental health
- The Lactose analogy
- Always part of the discussion, regardless of the origin of the cannabis (prescribed or not) the effects are the same and the potential for withdrawal exists
- There is no evidence to support medicinal cannabis as a treatment for cannabis use disorder

What are the treatments? Pharmacotherapy

- No FDA approved medications
- Medications under consideration
  - NAC: modulatory effects of on glutamergic transmission. Some effectiveness in adolescents
  - Gabapentin- 1200 mg /day reduced marijuana use, sleep problems and depression
  - Cannabidiol proved better than placebo in phase 2a double blind RCT
- No effect: buspirone, dronabinol, nefazodone, buproprion SR and depakote

Why not agonist therapy?

- Levin (2011) tried to give 20 mg dronabinol twice daily, weekly MI and CM strategies
- No reduction in marijuana use, but decreased withdrawal symptoms and therefore positive effect in retention
- Authors postulated needing higher dose and longer treatment
- However when dronabinal + α2 agonist lofexidine in lab, participants had less withdrawal and less self administered cannabis

Treatment of Cannabis Use Disorder: Psychotherapy

- 12 Step Facilitation (TSF) Counseling
- Motivational Interviewing
- CBT
- Contingency Management

12 Step Facilitation Counseling

- Designed to increase the likelihood that the individual will engage and actively participate in 12 step self help group and become abstinent
- 3 major tenets
  - Acceptance of chronic nature of drug addiction as an illness that no one has control over and abstinence as the only option
  - Surrender to a higher power/ acceptance of the fellowship
  - Active involvement in 12-step program activities
- No known efficacy trials for TSF counseling for marijuana dependence

Motivational Interviewing

- Non-confrontational counseling style that focuses on exploring and resolving ambivalence and strengthen motivation to change
- Motivational enhancement therapy (MET): 4 sessions adaptation of MI
- Validated in in marijuana treatment trials

Cognitive Behavioral Therapy

- Focused on learning process involved in behavior
- Exploring positive and negative consequences of continued use, self monitoring to recognize cravings and high risk situations and develop coping strategies
- Has been validated in the treatment of marijuana dependence

Contingency Management

- Allowing individuals to earn vouchers for abstinence
- Proven successful in helping individuals maintain abstinence in clinical trials
- Works in achieving abstinence during trial period but when combined with other therapies, higher percentage of patients abstinent at follow up
- Suggests CM effective strategy to help initiate abstinence and boost effects of other strategies

Brief Intervention vs. Longer treatment

- Trials comparing brief vs. longer treatment groups reduced marijuana use more than control groups, no difference based on length of treatment
- May be most effective in a primary care setting

Adolescent Psychotherapy Approach: Special Consideration

- Addition of family approaches
- Cannabis Youth Treatment Study
  - MET-CBT
  - Family Support Network Therapy
  - Adolescent Community Reinforcement Approach (ACRA)
  - Blend of CBT, MET, family therapy and systems based approached
  - Multidimensional family therapy (added case management)
- Amount of days abstinent increased by 24%
- Most cost effective approaches were 5 sessions of MET-CBT and ACRA
- Findings of this trial did not prove longer/ more resource intensive therapy are superior for adolescents

CIRCLE study

- RCT for contingency management for cannabis use in young people with recent history of psychosis
- Primary outcome: difference in time to acute psychiatric care
- Looked at cost effectiveness analysis
- Results showed that CM is not an effective intervention for improving the time to acute psychiatric admission or reducing cannabis use in psychosis, at least at the level of voucher reward offered.

Additional Clinical Considerations for the Addiction Psychiatrist

- Many of our patients are seeking services for other substances, however use cannabis daily
- We should be mindful to provide psychoeducation to patients about how cannabis abstinence might impact recovery
- As patients become abstinent from one substance it may impact their pattern of use of cannabis, discuss and monitor this

Questions?