Cannabis Use Disorder

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I, Angela Patricia Sepulveda Velez, MD, have nothing to disclose.

I will discuss “off label” use of drugs for cannabis use disorder.

I will state that all drug treatments for cannabis use disorder are not FDA approved.

Objectives

- Familiarize with history and epidemiology
- Understand what it is, what it isn't, pharmacokinetics and pharmacodynamics
- Review clinical implications of cannabis use and some complications
- Familiarize with Substance Use Disorder Diagnosing Criteria
- Know of treatment and potential medications for treatment

Brief History of Cannabis

Asia 500 BC – herbal medicine use > textile (hemp) > recreational

Middle East and Asia 800 AD – popularity increased with spread of Islam

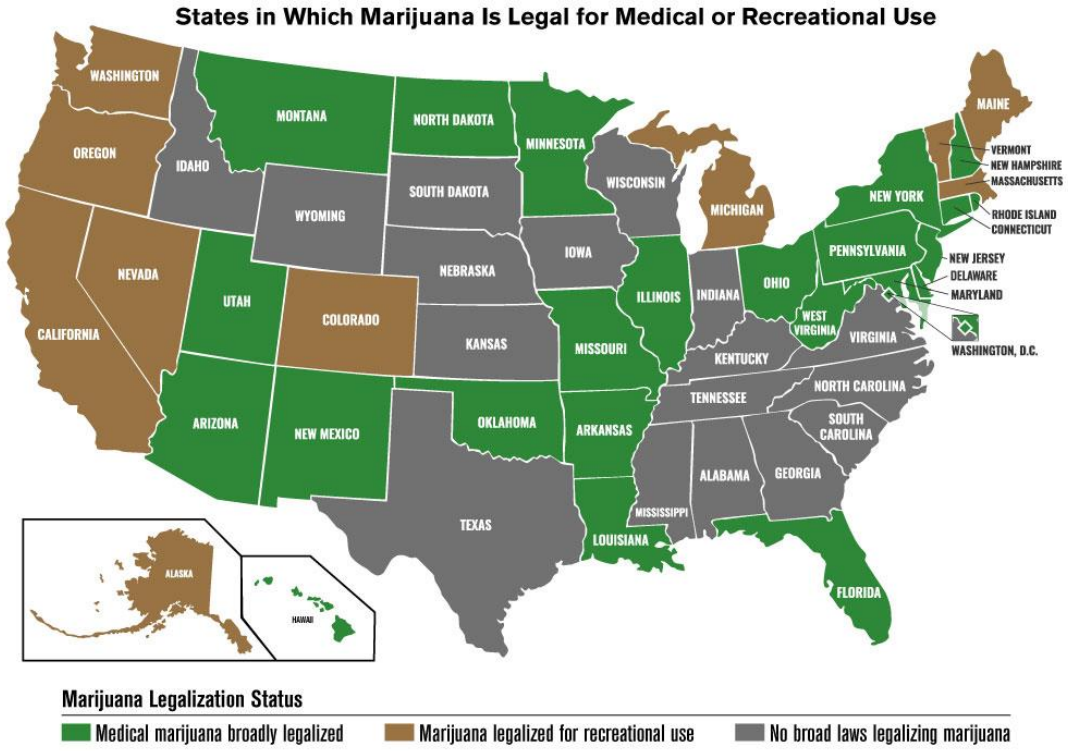
Colonies 1600s - required farmers to grow hemp

India 1830s – treatment for cholera symptoms

Scientists – THC discovery and use for nausea and anorexia

US and Mexico early 1900s – recreational use

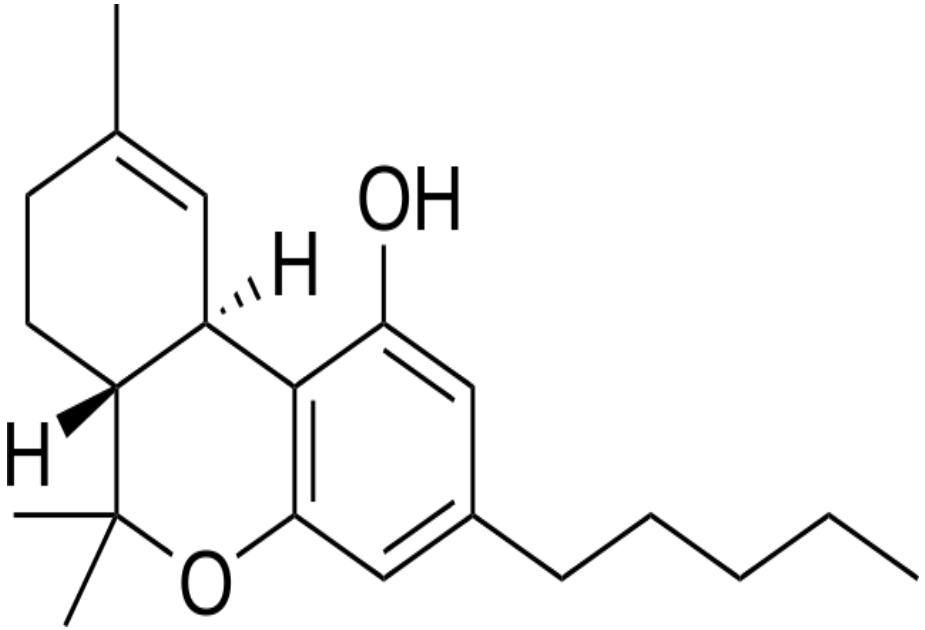
Great Depression - fear of the "evil weed" → 29 states outlawed cannabis by 1931



Highlights from 2020 National Survey on Drug Use and Health

- Illicit drug use - 49.6 million people used marijuana.
  - The percentage of people who used marijuana in the past year was highest among young adults aged 18 to 25 (34.5%) compared with 16.3% of adults aged 26 or older and 10.1% of adolescents aged 12 to 17.
- Initiation - 2.8 million initiated marijuana
- Perceived risk of SU
  - Only about one fourth of people aged 12 or older (27.4%) perceived great risk of harm from smoking marijuana once or twice a week.
  - Young adults aged 18 to 25 were less likely than adolescents aged 12 to 17 or adults aged 26 or older to perceive great risk of harm from smoking marijuana weekly.

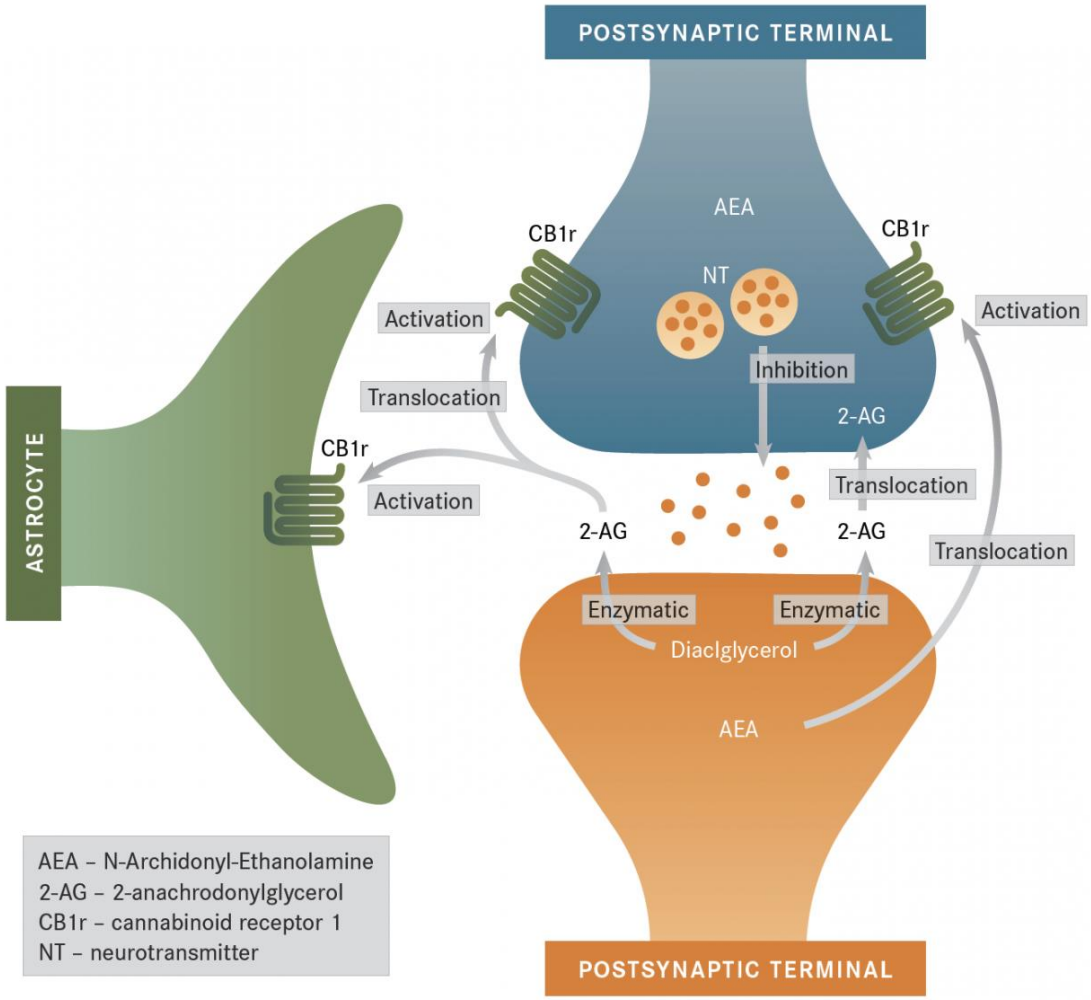
What is Cannabis?

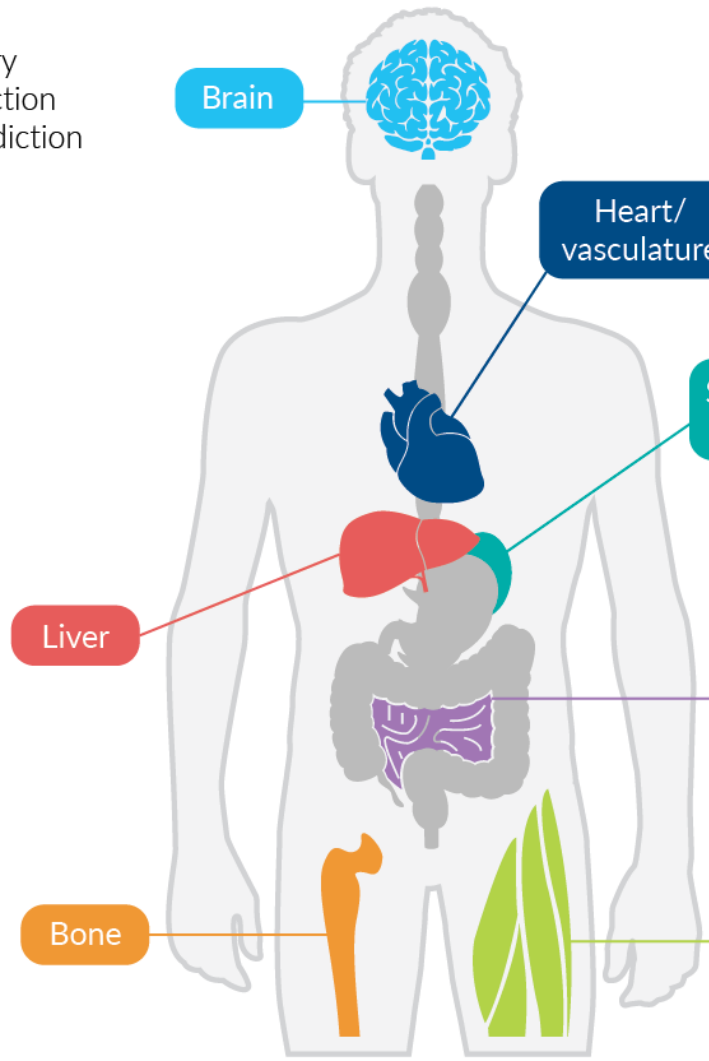


Endocannabinoid System/Signaling

- Mediated by endocannabinoid AEA and 2-AG interactions with 2 G-protein coupled receptors: cannabinoid receptor 1 (CB1) and cannabinoid receptor 2.
- AEA is a strong partial agonist to CB1 and a very weak agonist to CB2, whereas 2-AG exhibits moderate to weak affinity for both receptors.
- NT modulation
  - Dopamine (DA) - euphoria, reward, pleasure
  - GABA - muscle relaxation, sleepiness
  - ↓ Glutamate - relaxation, ↓ memory

FIGURE. Cannabinoid Actions in CB1, CB2 Receptors.





CB_1
- Neurotransmission
- Cognition and memory
- Control of motor function
- Reward pathways/addiction
- Nociception

CB_2
- Nociception
- Neuroinflammation
- Neuroprotection

CB_1
- Steatosis
- Fibrinogenesis
- Insulin resistance

CB_2
- Antifibrinogenic
- Hepatoprotection

CB_2
- Bone formation and turnover

CB_1
- Heart rate
- Hypotension
- Cardiac dysfunction
- Weakened myocardial contractility

CB_2
- Cardioprotective

CB_1 & CB_2
- Immunomodulation

CB_1
- Gut motility
- Appetite

CB_2
- Gut motility
- Inflammation

CB_1
- Energy metabolism
- Insulin resistance

Cannabis Effects

- Respiratory – carcinogen
- Immune - In preclinical tests, the effects of CB_2 receptor activation extend to modulate systems involved in neuropathic pain and autoimmune disorders.
- Cardiovascular – Multiple
- GI – CHS
- Liver – alters metabolism of endo and exogenous compounds
- Renal – ATN
- Endocrine – contribute to DM
- Reproduction – decreased fertility. The lipid solubility of THC allows for its rapid transfer to the fetus through the placenta as well as rapid transfer into breast milk.

Synthetic Cannabinoid Receptor Agonist (SCRA)

- Commonly known as Synthetic Cannabis
- Is not synthetic THC and has a different chemical structure than THC
- It does active endogenous cannabinoid receptors
- THC is a partial (or low efficacy) agonist of CB1, meaning that it is incapable of exerting full activation of the receptor at the highest concentrations. SCRAs, by contrast, are generally characterized as full (or high efficacy) CB1 agonists, eliciting maximal activation of the receptor beyond what is achievable with THC.
- SCRAs also increase extracellular dopamine levels in the nucleus accumbens shell in rodents (a common property of rewarding drugs) with much greater potency than THC, suggesting a potentially greater abuse liability.
- Compared to cannabis, SCRA use is associated with a more rapid development of dependence and a more complex and severe withdrawal syndrome

Table 1
Acute physiological effects of synthetic cannabinoid receptor agonists.

System	Pathology
Mortality	• Acute toxicity the most common cause of death • Cardiac arrhythmia • Acute kidney failure • Traumatic injury
Heart	• Hypertension • Tachycardia • Arrhythmia • Chest pain • Acute myocardial infarction
Brain	• Seizure • Haemorrhagic stroke • Ischaemic stroke
Kidneys	• Acute kidney injury
Lungs	• Acute respiratory failure • Dyspnoea
Liver	• No evidence of acute hepatotoxicity or chronic liver disease
Other	• Hyperthermia • Rhabdomyolysis • Psychiatric: Excited delirium syndrome/acute behavioural disturbance, psychosis, hallucinations, paranoia, acute anxiety

SCRAs

- Documented toxic effects are more severe and extensive
- SCRA-related modulation of T-type calcium channels having been suggested recently as a potential mechanism for acute cardiovascular effects
- May cause central and peripheral respiratory depression with need for intubation
- Associated with a range of acute psychiatric sequelae, including excited delirium syndrome delirium and acute psychosis > "zombie outbreaks"

SCRAs

- There are no documented deaths from THC toxicity, while drug toxicity is the most common diagnosis for SCRA-related death.
- Clinically significant adverse events are not the typical case presentation for cannabis intoxication, but rather for psychostimulants.

Table 2
Comparative acute physiological effects of synthetic cannabinoid receptor agonists (SCRAs), cannabis and psychostimulants.

System	SCRAs	Cannabis	Psychostimulants
Mortality			
• Documented death due to acute toxicity	√		√
Heart			
• Hypertension	√	√	√
• Hypotension	√	√	√
• Tachycardia	√	√	√
• Arrhythmia	√	√	√
• Chest pain common clinical presentation	√		√
• Acute myocardial infarction			
Brain			
• Seizure	√	√	√
• Haemorrhagic stroke	√		√
• Ischaemic stroke	√		√
Kidneys			
• Acute kidney injury	√		√
Lungs			
• Acute respiratory failure	√		
• Dyspnoea	√		
Liver			
• Hepatotoxicity			√
Psychiatric			
• Agitated delirium	√	√	√
• Psychosis	√	√	√
• Hallucinations	√	√	√
• Paranoia	√		√
• Acute anxiety	√		
Other			
• Hyperthermia	√		√
• Rhabdomyolysis	√		√

Screening

- The urine test is based on detection of a THC metabolite, 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (9-carboxy-THC).
- Studies indicate that 80%-90% of the total dose of delta-9-THC is excreted within 5 days, ~20% in urine and 65% in feces.
- Plasma concentrations of delta-9-THC peak by the time a smoked dose is completed and usually fall to approximately 2 ng/ml within 4-6 hours.
  - 9-carboxy-THC is detectable in plasma within minutes after a dose is smoked and remains in plasma considerably longer than THC itself.
- Urine samples containing at least the stated detection level of 9-carboxy-THC will test positive at least 95% of the time.
- Only blood-sample measurements are likely to correlate with a person's degree of exposure.
  - A positive result by the urine cannabinoid test indicates only the likelihood of prior use.
- THC can accumulate in body fat, creating higher excretion concentrations and longer detectability.
- If an affect on performance is the main reason for screening, the urine cannabinoid test result alone cannot indicate performance impairment or assess the degree of risk associated with the person's continuing to perform tasks.
- If a history of marijuana use is the major reason for screening, the urine test for cannabinoids should be able to detect prior use for up to 2 weeks in the casual user and possibly longer in the chronic user.

Cannabinoid Hyperemesis Syndrome (CHS)

- Repeated and severe bouts of vomiting
- Pathophysiology still unclear > theory:
  - CB receptors in brain and GI tract > brain has opposite symptoms of CHS, but GI tract with tendency for nausea/emesis
  - Initial cannabis use: brain overpowers GI, but with continuous use, brain receptors stop responding and GI overcomes
- Phases:
  - Prodromal – morning nausea/emesis and fear of the latter, usual no change in eating habits, tendency to use more cannabis thinking it will help (m – yrs)
  - Hyperemesis – N/V, DHT, hot showers (hypothalamus Temp/N regulator)
  - Recovery phase – after consumptions stops (d – m), can return with use

> Am J Psychiatry. 2018 Apr 1;175(4):343-350. doi: 10.1176/appi.ajp.2017.17020223. Epub 2017 Nov 28.

Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis

Marie Stefanie Kejser Starzer [1], Merete Nordentoft [1], Carsten Hjorthøj [1]

- All patient information was extracted from the Danish Civil Registration System and the Psychiatric Central Research Register. The study population included all persons who received a diagnosis of substance-induced psychosis between 1994 and 2014 (N=6,788); patients were followed until first occurrence of schizophrenia or bipolar disorder or until death, emigration, or August 2014. The Kaplan-Meier method was used to obtain cumulative probabilities for the conversion from a
- **Results:** Overall, 32.2% (95% CI=29.7-34.9) of patients with a substance-induced psychosis converted to either bipolar or schizophrenia-spectrum disorders. The highest conversion rate was found for cannabis-induced psychosis, with 47.4% (95% CI=42.7-52.3) converting to either schizophrenia or bipolar disorder. Young age was associated with a higher risk of converting to schizophrenia. Self-harm after a substance-induced psychosis was significantly linked to a higher risk of converting to both schizophrenia and bipolar disorder. Half the cases of conversion to schizophrenia occurred within 3.1 years after a substance-induced psychosis, and half the cases of conversion to bipolar disorder occurred within 4.4 years.

Diagnosis

- The patient exhibits the following related to substance use in the past 12 months:

- During the times when you drank/used, did you end up drinking/using more than you planned when you started? {yes no:314532}
- Did you repeatedly want to, or tried to cut down on your drinking/use? {yes no:314532}
- On the days that you drank/used, did you spend substantial time obtaining, using, or recovering from its effects? {yes no:314532}
- Did you crave or have a strong desire or urge to drink/use? {yes no:314532}
- Did you spend less time meeting your responsibilities at work, at school, or at home, because of your drinking/use? {yes no:314532}
- If your drinking/use caused problems with your family or other people, did you still keep on drinking/using? {yes no:314532}
- Did you drink/use more than once in any situation where you or others were physically at risk, for example, driving a car, riding a motorbike, using machinery, etc? {yes no:314532}
- Did you continue to drink/use even though it was clear that it had caused or worsened psychological or physical problems? {yes no:314532}
- Did you give you important work, social, or recreational activities because of your use? {yes no:314532}
- Did you need to drink/use a lot more in order to get the same effect that you got when you first started drinking/using? Or did you get much less effect when drinking/using the same amount? {yes no:314532}
- When you cut down on heavy or prolonged drinking/use, did you have any withdrawal symptoms? {yes no:314532}

- The patient {does/does not:200015} meet DSM-5 Criteria for *** Use Disorder in the past 12 months and the severity (2-3 = mild, 4-5 = moderate, 6 or more = severe) is assessed as {Desc; none/mild/moderate/severe:140030}.

Treatment

- Stopping, MA, CBT, Contingency Management
- No FDA approved medications
- NAC, gabapentin – potentially helpful

Non-FDA Approved Treatments

- N-acetylcysteine (NAC)
  - Helps regulate glutamate
  - Used in cocaine, gambling, skin picking and OCD
  - Gray 2012
    - 15 – 21 yo
    - NAC 2400mg/day vs placebo
    - Urine drug screen (UDS) negative for THC
    - 2 weeks after treatment, abstinence 36.2 vs 20.7%, respectively
  - Decrease drug seeking behavior
  - Increase time of clean UDS
  - Risks: N/V, drowsiness, insomnia, vivid dreams, anaphylaxis if IV (not PO)
- Gabapentin
  - Blocks alpha-2d subunit of the voltage-gated calcium channel which modulates GABA in the amygdala
  - Goal of ~1200mg/day
  - Mason (2012)
    - 18 - 65yo
    - Gabapentin 1200mg vs placebo for 12 weeks
  - Increase in negative UDS
  - Decrease self-reported cannabis use
  - Reduction in withdrawal symptoms (mood disturbance, craving, and sleep disturbances)
  - Risks: HA, N, insomnia, depression

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