

Marijuana: Clinical Considerations

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Disclosures

- ▶ I have no financial conflicts of interest
- ▶ I have significant concerns regarding the chronic use of many substances, and marijuana would be one of those.
- ▶ Discussions regarding the pro's and con's of marijuana use is something I do every day as it is one of the most misunderstood substances I deal with.




Objectives

After this Presentation You Should be able to:

- ▶ Be able to educate patients on the risk of dependence to marijuana with chronic use
- ▶ Discuss the medical issues which appear to benefit from cannabinoids.
- ▶ Educate patients on the medical conditions for which there is little evidence for effectiveness of cannabis products
- ▶ Discuss with patients potential adverse events with cannabinoids and possible drug interactions

General Information

- ▶ Marijuana is a Schedule 1 substance which implies high chance of addiction and abuse potential and “no currently accepted medical use”.
- ▶ Other Schedule 1 drugs include LSD, Heroin, and quaaludes
- ▶ Schedule 2 drugs have potential for abuse but also manifest medical benefits (opioids, cocaine and so on)

SCHEDULE	Medical use?	Potential for abuse	Potential for addiction
Schedule I			

Lifetime Dependence Risk in Users

- ▶ Marijuana 9%
- ▶ Heroin 23%
- ▶ Cocaine 17%
- ▶ Alcohol 15%



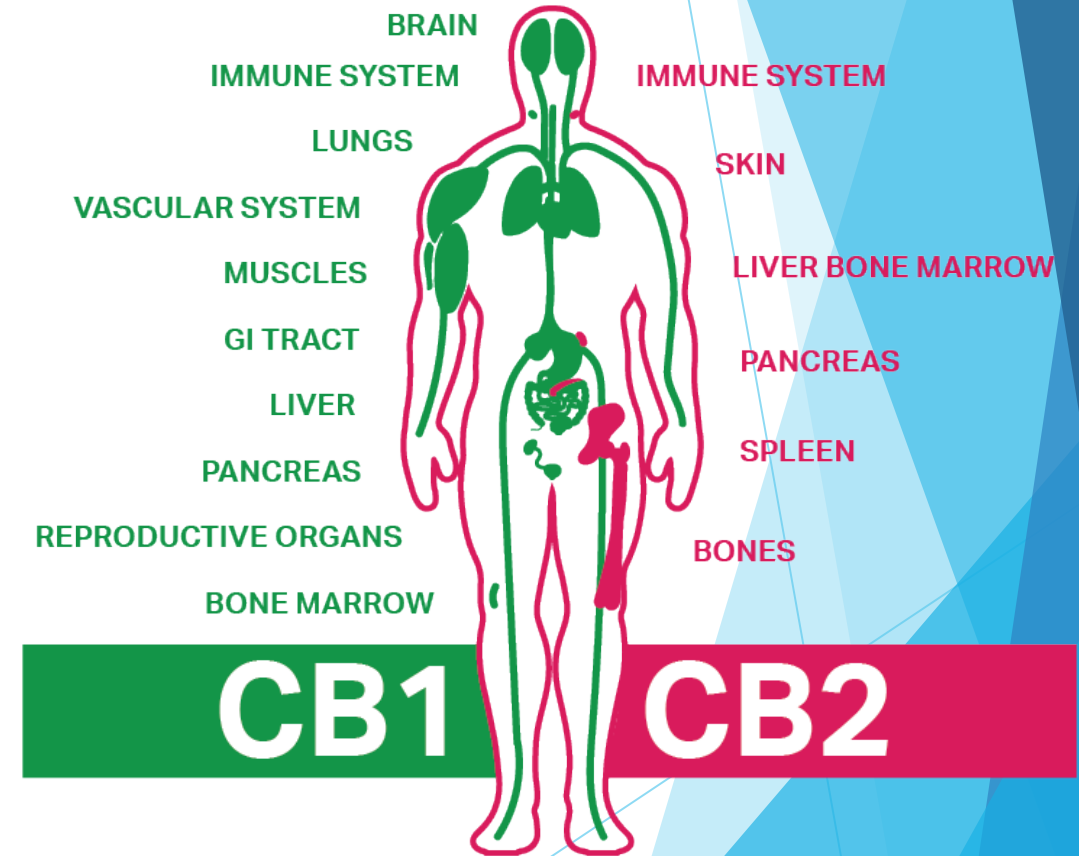
- ▶ *Marijuana dependence develops slowly, often is associated with younger initiation of use. Dependence in those initiating use after the age of 25 is minimal.

Brief but Interesting History

- ▶ Cannabis has been used for 5000 years medically, recreationally, and spiritually
- ▶ Dr. W.B. O'Shaughnessy wrote a paper in the 1830's in Calcutta about the uses of "Indian hemp" in the treatment of pain, vomiting, convulsions, and spasticity. This would generally mirror the conditions for which it has shown effectiveness today.
- ▶ As an aside, it has been reported the original draft of the Declaration of Independence was written on hemp paper...

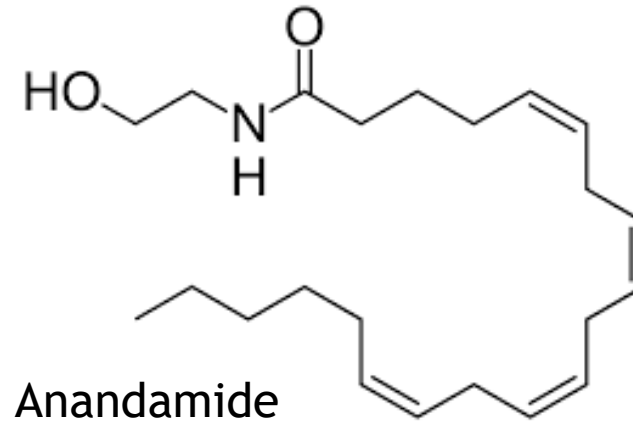
Endocannabinoid System

- ▶ Includes a network of CB1 and CB2 receptors throughout the body
- ▶ CB1 receptors are generally in the central and peripheral nervous system, with a lower concentration in the brainstem respiratory center
- ▶ CB2 are largely found in the immune and hematopoietic system
- ▶ Current understanding of this system is limited...



Cannabinoids

- ▶ Endocannabinoids- Anandamide
- ▶ Synthetic cannabinoids-Analogs of compounds found in cannabis plants such as Dronabinol and Nabilone
- ▶ Phytocannabinoids



Phytocannabinoids

- ▶ Psychoactive- Delta 9, Delta 8 and CBD which is weakly psychoactive
- ▶ Non-euphoric-CBD
- ▶ Others-which include 150 other less well described and lower concentration cannabinoids
- ▶ *remember there are also 500 other chemical compounds in the MJ plant

Phytocannabinoids

- ▶ CBD has two approved conditions for specific Cannabinoid-based medicine treatment:
 - 1) Lennox-Gastaut-Seizure disorder
 - 2) Dravet syndromes-myoclonic seizures

*some countries have other quality controlled products for specific medical conditions also

Synthetic Cannabinoids

- ▶ There are approved indications for these which include:
 - 1) Spasticity in MS-Nabilone
 - 2) AIDS/Cancer cachexia, nausea and vomiting- Nabilone or Dronabinol



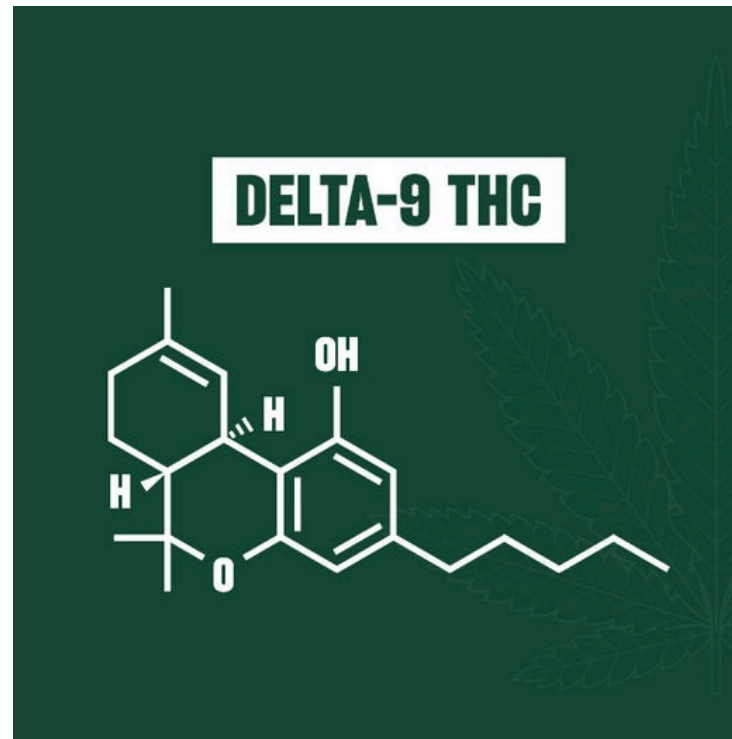
Marijuana and Safety

- ▶ In general, safety not well reported
- ▶ Assessments are difficult because:
 - 1) Differing study designs
 - 2) Indications for use vary
 - 3) No standardized dosing
 - 4) Administration routes differ



Most Studied Cannabinoids

- ▶ Delta 9
- ▶ Synthetic variants such as Dronabinol, Nabilone



If Used as a Medicine, How is it Best Dosed?

- ▶ Smoked-high bioavailability, rapid and predictable onset, “easy” titration (to maximize desired psychotropic effects and minimize negative ones)
- ▶ Oral forms-undergoes first pass hepatic metabolism so levels of active agents vary. Absorption is more erratic/peak concentrations are lower and harder to control.
- ▶ Vaporized method-avoids smoke and other toxins and may avoid pulmonary issues

Marijuana and Mental Health

- ▶ Recent Literature review by Hasin et al 2021
- ▶ Utilized Nesaric and NSDUH (National Epidemiologic Survey on Alcohol and Related Conditions and National Survey on Drug use and Health)
- ▶ Explored the comorbidity of Cannabis use and CUD with other substance use and psychiatric disorders.

Quick Definitions

- ▶ Causal: relating to or acting as a cause
- ▶ Association: the fact of occurring with something else: co-occurrence

Hasin et al. 2021

- ▶ There is strong evidence that past year CU and CUD are associated with Psychiatric Co-morbidities although the complexities are not totally understood
 - 1) Increased psychosis
 - 2) Mood disorders
 - 3) Anxiety
 - 4) Associated with personality disorders

CUD and Psychotic Disorders

Hasin et al. 2021

- ▶ Reviews and meta-analysis indicate cannabis is causal factor in both incidence and prognosis of psychosis
- ▶ THC is clearly the component that increases risk
- ▶ 6 country study confirmed that increased frequency of use and potency is associated with timing of first episode of psychosis

CUD and Psychotic Disorders

Hasin et al. 2021

- ▶ Reviews and meta-analysis also show even previous use of cannabis will predict/increase risk of first episodes of psychosis
- ▶ Continued use predicts severity of psychotic symptoms, worse overall functioning and relapse of SUD's

Cannabis and Psychosis

Swedish study Zammit et al

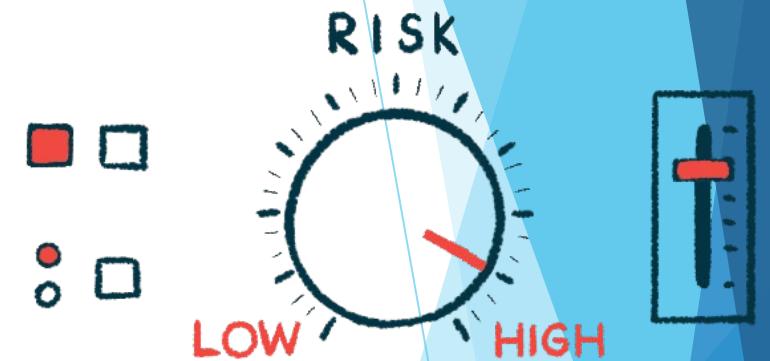
- ▶ 50,000 people in study
- ▶ Followed 27 years
- ▶ Adolescent use increased risk of psychosis
- ▶ Those who had used cannabis on more than 50 occasions had nearly a 7 times increase in diagnosis compared to those whom had never smoked.
- ▶ Association is clear, does it cause psychosis...not so much (Australian Study)

CUD and Mood Disorders

- ▶ People with MDD see Cannabis as less “risky” than those without MDD
- ▶ In those with past year or Lifetime history of CUD there is higher prevalence of Mood Disorders. OR of 1.9 for MDD and OR of 2.5 for Bipolar 1
- ▶ NSDUH data from 2002-2012 suggests daily and non daily use was 2x as prevalent in those with MDD compared to those without

Cannabis and Anxiety Disorders

- ▶ Some studies show worsening anxiety associated with higher dosing
- ▶ CBD in some studies showed improvement in anxiety
- ▶ Weekly cannabis use has been associated with nearly double the risk of patients later reporting anxiety or depression. Daily use carried nearly 5x the risk. No determination that cannabis was solely responsible for this effect.

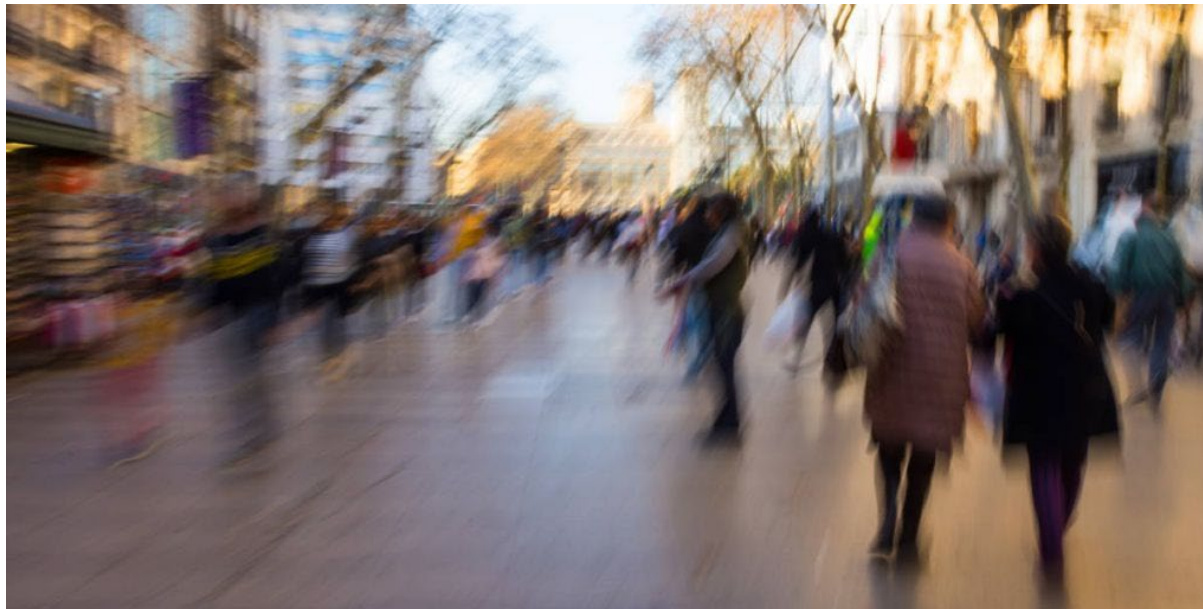


Cannabis and Anxiety Disorders

- ▶ There has been some evidence that cannabis may improve PTSD, although NESARC data showed 4x increased risk of development of CUD
- ▶ NESARC and NDSUH a comorbid relationship between CUD and Anxiety Disorders (agoraphobia, PTSD, GAD, Panic)

Cannabis and Anxiety Disorders

- ▶ The bottom line: The role of Cannabis in the etiology, prognosis and treatment of anxiety remain unclear.



Cannabis and Personality Disorders

- ▶ Past year CUD has association with all 10 personality disorders
- ▶ Antisocial and Dependent Personality disorders have the strongest associations
- ▶ Any cannabis use is associated with higher rates of other substance use disorders
- ▶ PD's are 4x more likely to have a past year CUD than controls

Cannabis and the Gateway Drug Theory

- ▶ Regular or heavy use is CLEARLY associated with increased risk for both misuse and dependence on other illicit substances.
*Neither causality nor directionality have been proven...
- ▶ A 25 year longitudinal study showed a strong association between adolescent use and later drug use, while also showing as cannabis use increased frequency of illicit drug use increased.

Cannabis and other SUD's-ETOH

- ▶ If your patient drinks alcohol and uses any other substances, MJ would be most likely
- ▶ If your patient developed a CUD in the last year, there is a 50% chance of AUD also
- ▶ Simultaneous use of cannabis and ETOH is associated with:
 - 1) Higher alcohol intake
 - 2) Higher likelihood of DUI
 - 3) Higher risk of self harm

Cannabis and other SUD's-Opioids

- ▶ Cannabis is associated with non-medical use of opioids in patients with pain and also in the general population
- ▶ In studies done in the VA system, CUD is associated with a higher number of opioid prescriptions filled

Cannabis and other SUD's

- ▶ CUD is associated with higher prevalence of other SUD's across all drug classes
- ▶ Past year CUD odds ratio of co-occurring use
 - 1) Cocaine 9.3
 - 2) Sedatives 5.1
 - 3) Opioids 4.6
 - 4) Stimulants 4.3
 - 5) Club drugs 16.1

Cannabis and Nicotine

- ▶ When talking with adolescents understand that it is more common to smoke cigarettes and cannabis (5.4%) than to smoke either substance alone (cigs 3.9%, MJ 2.2%)
- ▶ Please ask!



Cannabis and Cancer Risk

Few Studies-Poor Quality

- ▶ Lung Cancer-Studies often complicated by co-occurring tobacco use. Numerous studies have shown additive risk to varying degrees. A lung cancer study in Tunisia showed an 8-fold increase in lung cancer but there were concerns tobacco was mixed with the cannabis. No dose response data was collected. Callaghan et al. 2013 showed a 2 fold increase in “heavy” users (greater than 50 smoking episodes, 40 year follow up) and was controlled for tobacco use.

Cannabis and Cardiovascular Risk

- A fib incidence increases 30-50% with heavy cannabis use
- Prior research didn't show cannabis causes myocardial infarction
- Postoperative cardiac events increase 5X if cannabis used preop
- Recent cannabis decreases exertional capacity in angina by 50%

Cannabis and Cancer Risk

Few Studies-Poor Quality

- ▶ Cohort studies have show increased risks of prostate and cervical cancer in cannabis smokers who did not use tobacco
- ▶ Appears to be increased risk of adult gliomas regardless of tobacco use
- ▶ Parental use during pregnancy was associated with increased risk of childhood leukemia, astrocytoma, and rhabdomyosarcoma (no dose data available)

Cannabis and Sleep

- ▶ Common reason to use
- ▶ Few available studies
- ▶ Some studies have reported disruption in REM sleep with cannabis use
- ▶ Some studies have reported only subjective improved sleep quality
- ▶ Some studies have compared sleep quality in patients on smoking nights and non smoking nights, which are likely low quality studies as WD symptoms of not smoking could affect sleep

Cannabis and Cognition

- ▶ Becker et al. showed decreased white matter in specific areas of the brain. This correlated to diminished verbal learning and memory in users compared to non users
- ▶ Camchong et al. showed similar findings in CUD adolescents (compared to controls) with lower IQ scores and slower cognitive function

Cannabis and Cognition

- ▶ Frequency of use and also age of onset also effects cognitive outcomes such as executive controls and delayed recall times and difficulty in sustained attn.
- ▶ There have been many studies regarding cannabis use and academic performance. Often there are many confounding factors including other substance use. Over all most point toward poorer academic performance.

Cannabis and Cognition

- ▶ Regarding long term effect of chronic cannabis use...well there is not much to find
- ▶ Literature on adolescent cannabis use and neurologic functioning is limited and inconclusive.
- ▶ Most researchers believe the structural changes that occur in the brain over time must have significant effects over a life time but again, no data exists.

Cannabis and Prenatal Exposure

Nashed et al. 2021

- ▶ Preponderance of evidence suggests adverse outcomes, most notably FGR and Low Birth Weight. The physiologic mechanisms that underly these abnormalities may also be associated with other negative metabolic outcomes.
- ▶ There is also evidence that there is an association with deficits in memory, attention and learning

Cannabis and Prenatal Exposure

Nashed et al. 2021

- ▶ Prenatal exposure is predictive of increased depressive symptoms, prodromal symptoms of psychosis and sleep disturbances
- ▶ These cognitive and neuropsychiatric aberrations occur early in development and persist into adolescence and early adulthood

Cannabinoids and Drug Interactions

- ▶ Cannabinoids may effect both CYP and P450 metabolic pathways
- ▶ Drug-Drug interactions have not been well studied so much of present concerns are based on theoretical interactions
- ▶ Some clinical studies have been done on THC, but fewer than on CBD

Cannabinoids and Drug Interactions

- ▶ Many CYP substrate levels can be increased by THC including:
 - 1) CYP3A4 substrates-antidepressants, antipsychotics, opioids and benzos
 - 2) CYP2C9 substrates-PPI's, warfarin
 - 3) CYP2C19 substrates-phenytoin, montelukast, Buprenorphine

Cannabinoids and Drug Interactions

- ▶ Bottom line-if symptoms are occurring that could represent a DDI, you may need to look it up.



Final Thoughts

- ▶ Cannabis has over 500 compounds, and most (if not all) have been studied very little
- ▶ If you care for people who use Cannabis or you certify patients for medical Cannabis make sure you are able to discuss the many issues surrounding its use
- ▶ Most patients (and many providers) consider Cannabis safe, but adverse events occur when used with medications, and it is important to educate patients of those risks

Sources

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Want More Addiction Education?

- ▶ Join the SOAR ECHO each Wednesday at 12:15 to 1:15 facilitated by Kurt DeVine MD FASAM and Erin Foss RN CARN and hosted by Stratis Health.
- ▶ Both state and national speakers
- ▶ FREE CME
- ▶ Contact Kstangl@stratishealth.org or me at kurtdevine@centracare.com