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CANNABIS: DOES IT HELP OR HURT ANXIETY?

BEVERLY SHIN, MD, DMA
ADDICTION PSYCHIATRY FELLOW
UNIVERSITY OF WASHINGTON



Cannabis: Does it Help or Hurt Anxiety?

Beverly Shin, MD, DMA
Addiction Psychiatry Fellow
University of Washington

DISCLOSURES

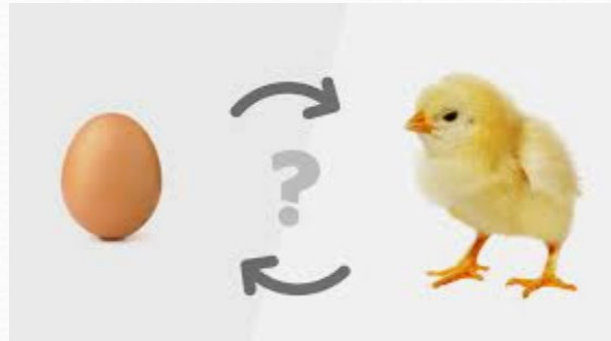
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OBJECTIVES

- Discuss complexities of cannabis plant, endocannabinoid system, and current regulatory hurdles in cannabis research to understand current dearth of clinically applicable studies of cannabis and anxiety
- Review the current epidemiologic and clinical evidence for anxiolytic and anxiogenic effects of cannabis, THC, and CBD
- Discuss cannabis withdrawal syndrome and anxiety
- Explore **ways to approach discussing cannabis** and anxiety with patients given discrepancy between widespread use and limited evidence

Cannabis Use Disorder and Anxiety Disorders Are Highly Co-Morbid

- Several studies have shown that **frequent cannabis users report higher levels of anxiety than non-users** and that as cannabis use increase, severity of anxiety symptoms reported increases
- As with other substance use disorders, individuals with anxiety disorder have a greater chance of presenting with cannabis use disorder, AND patients with cannabis use disorder are more likely to present with an anxiety disorder
- However, **causal relationship** between cannabis use disorder and anxiety (or vice versa) is **not clear**



Some hypotheses

- Cannabis may **cause anxiety** and lead to persisting anxiety disorders through disruption of endocannabinoid system or some other mechanism
- Cannabis may **alleviate anxiety**, and patients with anxiety disorders may be self-medicating with cannabis

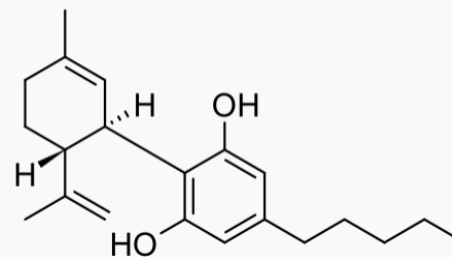
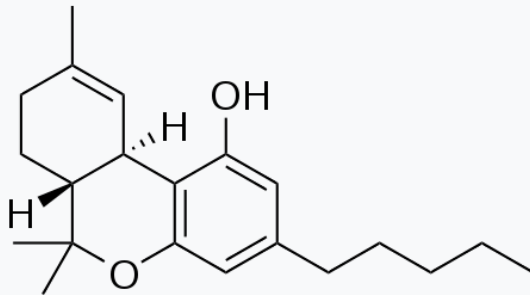


SO DOES CANNABIS HELP OR HURT ANXIETY?



Most Famous Cannabinoids

THC (Δ^9 -tetrahydrocannabinol)	CBD (Cannabidiol)
<ul style="list-style-type: none"> - Most psychoactive component of cannabis - Can cause or alleviate anxiety - Euphoria/intoxication - Cognitive impairment - Psychosis - Sedation 	<ul style="list-style-type: none"> - Less psychoactive - May alleviate anxiety
Thought to be addictive	NOT thought to be addictive



Cannabis is a complex substance with **MANY** potentially psychoactive components

- **>500 phytochemicals** (biologically active plant compounds)
- **>100 cannabinoids** (CBD and THC are only two of them)
- **>100 terpenes** (compounds that create the characteristic scent of many plants)





- Concentrations of THC, CBD, other cannabinoids, and terpenes may vary due to:
 - Type/species of cannabis
 - Harvesting/cultivation techniques
 - Environmental conditions
- Psychoactive effects of cannabis may be the result of **synergistic interactions** between many of these compounds
 - “**entourage**” theory of cannabinoids
 - Non-psychoactive cannabinoids or terpenes could modulate impact of psychoactive THC
 - Or may influence components of endocannabinoid system in ways that have not yet been characterized



Endocannabinoid system is also very complicated!

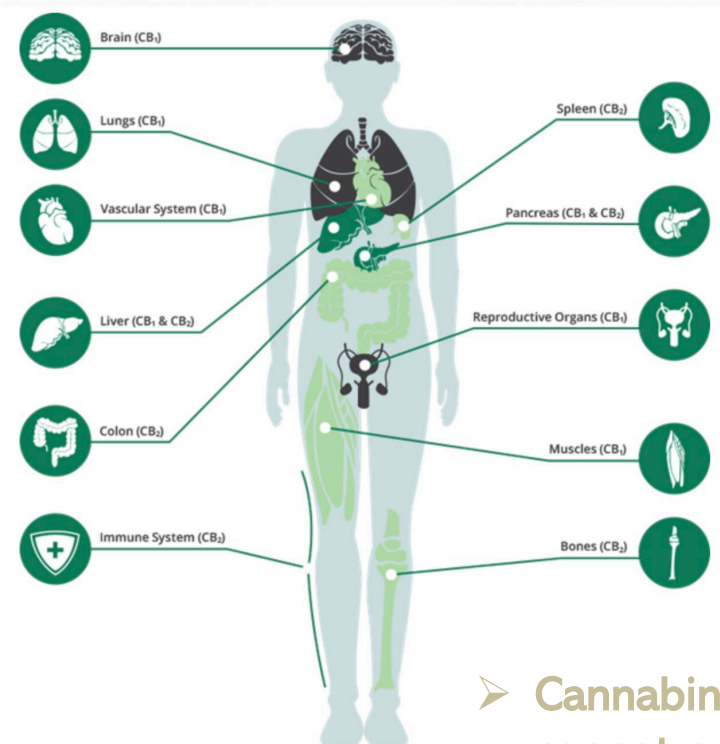
CB1 Receptor

- Mainly in the **brain**
- Peripheral nervous system, liver, thyroid, uterus, bones, and testicular tissue
 - Learning and memory
 - Executive function
 - Sensory/motor responsiveness
 - Emotional reactions
 - Feeding
 - Homeostasis

CB2 Receptor

- **Immune cells**, spleen, and gastrointestinal system, (though some present in brain and peripheral nervous system)

- Cannabinoid receptors are all over the brain and body, so we cannot make simple generalizations about what happens when CB1/CB2 receptors are globally turned on/off



Getting back to the question at hand...

What do your patients/clients tell you about cannabis and anxiety?



What Epidemiological Studies Tell Us About Cannabis and Anxiety

Many of our patients are using cannabis to treat their anxiety

- Top two target symptoms reported by medical marijuana users are **pain and anxiety**
- Three large cross-sectional studies (N = 9,842 total) found that **over half** of participants surveyed used medical cannabis for anxiety

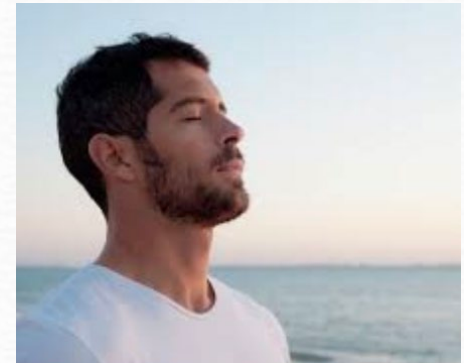


Many of our patients are replacing prescription medications for anxiety with cannabis

- Two large survey studies (N=3,545 total) indicated that **nearly half** of respondents had substituted an anxiety medication prescribed to them for anxiety with medical cannabis
- In one study, 61% of participants had **completely replaced** prescription medications for anxiety with cannabis

Many people report that cannabis helps with their anxiety, with few adverse effects

- In a 2019 survey study of 2032 medicinal cannabis users 92% of respondents reported that cannabis had improved their anxiety symptoms
- The Strainprint Cannabis Tracker is a smart-phone app designed for medical cannabis users to track symptom changes as a function of cannabis
 - It can track dose and THC:CBD ratio
 - In 5085 tracking sessions:
 - 93.5% reported improvement in anxiety after using cannabis
 - only 2.1% reported worsened anxiety
 - 4.4% experienced no change in anxiety after using cannabis



So what does clinical research tell us about cannabis and anxiety?

Spoiler Alert

There are **NO** prospective studies examining the effect of whole plant cannabis on participants with anxiety disorders

- There are a few very small randomized controlled trials looking at **cannabis constituents** (i.e. THC or CBD) and anxiety disorders
- We know **some** things about THC and CBD and anxiety from animal and **healthy** human studies
- But again, given potentially synergistic activity between hundreds of compounds in whole plant cannabis,
studying THC or CBD in isolation \neq studying whole plant cannabis



Cannabis and anxiety in anxiety disordered patients: Randomized placebo-controlled studies

Nabilone (synthetic THC) and anxiety disorders

- 8 participants with generalized anxiety disorder received a single dose of nabilone 2mg (synthetic THC) or placebo, then once weekly dosing of nabilone of various doses of nabilone or placebo over 5 weeks
 - **Anxiety symptoms not improved** in nabilone group compared with placebo
- 20 participants with diagnosed anxiety disorders received nabilone 1mg three times daily vs. placebo over the course of 1 month
 - **Anxiety symptoms improved** in the nabilone compared with placebo group
 - But total scores on Hamilton Anxiety Rating Scale were very low to begin with
- **Conflicting results**



Cannabis and anxiety in anxiety disordered patients: Randomized placebo-controlled studies

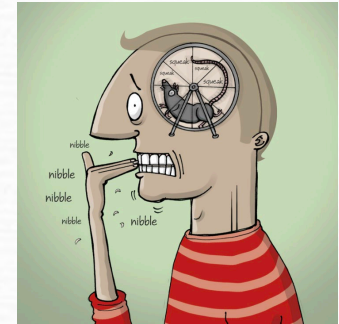
CBD and Social Anxiety Disorder

- 10 men treatment-naïve men with diagnosis of social anxiety disorder given a single dose of 400mg oral CBD or placebo, then exposed to an anxiety-provoking stimulus
 - CBD-pretreated subjects had a **significant decrease in anxiety** compared with placebo with no appreciable adverse effects
- 24 treatment-naïve undergraduates with a diagnosis of social anxiety disorder given either a single dose of 600mg oral CBD or placebo 90 minutes prior to a simulated public speaking test
 - Compared with placebo, CBD-pre-treated group had
 - **Decreased anxiety** during public speaking test
 - Less cognitive impairment and discomfort



Cannabis and anxiety: Animal studies and clinical studies on healthy subjects

- Some conflicting results, but current evidence suggests the following about THC and CBD
 - **THC** appears to be **anxiogenic** in a dose-dependent way
 - Low doses in some studies have been found to be anxiolytic
 - At very high doses, can cause extreme anxiety and panic attacks
 - The higher the dose of THC, the more anxiety was reported/observed
 - **CBD** appears to be **anxiolytic**
 - Most studies show anxiolytic effect at moderate doses, though recent studies suggest higher doses needed
 - Unlike THC, higher doses have not been shown to cause anxiety



Cannabis and anxiety: Animal studies and clinical studies on healthy subjects

- THC acts differently when given by itself vs. with other cannabinoids or terpenes
 - Multiple animal and human studies suggest that CBD (most often in high doses) may decrease anxiogenic effect of THC when co-administered
 - “entourage” theory of cannabinoids
- Several clinical studies demonstrated that anxiogenic effects of THC are greater among infrequent or non-users relative to frequent users



Factors that may influence anxiolytic/anxiogenic response to cannabis:

- Isolated cannabinoids vs. whole plant cannabis
- Dose
- Duration of use
- Method of consumption
- THC-CBD ratio
- Prior exposure
- Individual and genetic vulnerability
- Gender
- Baseline anxiety level

What can we conclude about cannabis and anxiety from all of this?

- **We urgently need more studies!** Currently lacking large, adequately-powered, longitudinal studies of cannabis in patients with anxiety disorders
- Most studies use isolated cannabinoids, but many of our patients are using whole plant cannabis



Why are epidemiological data and clinical data conflicting??

- Vast majority of people surveyed say cannabis decreases anxiety, but most were using whole cannabis products, which has more THC than is used in studies
 - Between 1995 and 2015, there has been an estimated 212% increase in THC content in marijuana flower
- Animal/clinical data suggests that higher doses of THC should cause **more** anxiety, not less
 - Could be sampling bias in epidemiological studies
 - Or could be that because of entourage theory, whole plant cannabis and isolated cannabinoids have very different effects on anxiety
 - Or...???



CANNABIS IS THE MOST WIDELY USED ILLICIT DRUG IN THE WORLD

Anxiety is the most prevalent mental disorder in the world

Cannabis use disorder and anxiety disorders highly co-comorbid

So why so few studies??

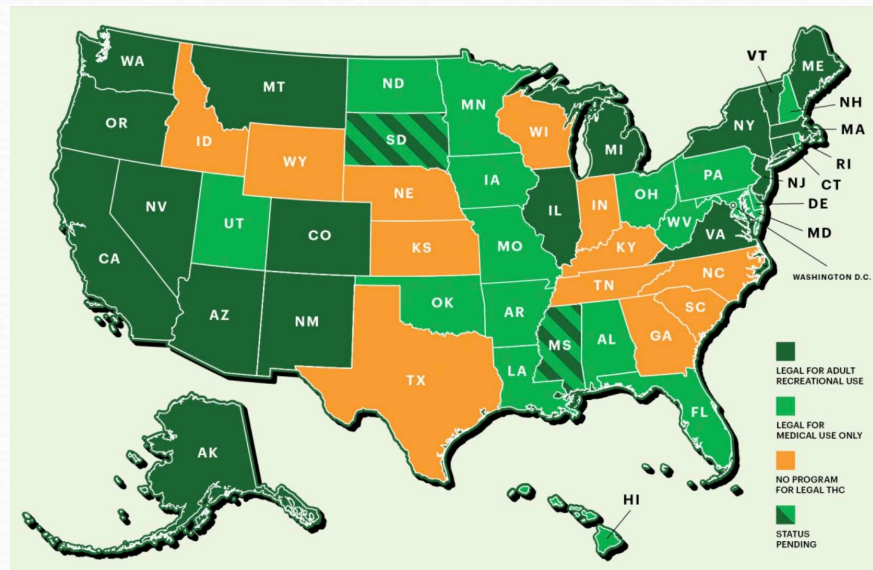


Conducting cannabis research is a HUGE PAIN for researchers because of current laws

- In the Controlled Substances Act of 1970, the DEA categorized cannabis as a Schedule I substance
- Schedule I includes substances with “no medical value and high potential for abuse” and includes heroin, LSD, MDMA, and peyote

DEA Schedule	Abuse Potential	Example of Drugs	Medicinal Use
Schedule I	Highest	Heroin, LSD, Marijuana, Psilocybin	No accepted use; limited use for research purposes
Schedule II	High	Morphine, PCP, Cocaine	Accepted use with restrictions
Schedule III	Medium	Selected Amphetamines, Anabolic Steroids, Codeine with aspirin	Accepted use
Schedule IV	Low	Diazepam, Ambien, Xanax	Accepted use
Schedule V	Lowest	Over the counter prescription drugs containing codeine	Accepted use

- Cannabis remains a Schedule I (i.e. illegal) substance on federal level
- 36 states and the District of Columbia have legalized cannabis for **medical use**
- Of these states, 18 have also legalized adult use of **recreational** cannabis



Discrepancy between state and federal cannabis policies has made things very difficult for researchers interested in studying cannabis

- MANY very cumbersome federal and state regulatory hurdles, including obtaining DEA schedule 1 registration
- National Institute on Drug Abuse (NIDA) is the **ONLY** legal supplier of cannabis for research
 - Stringent storage and security requirements and more regulatory hurdles!
 - Lacks a range of different formulations and potencies and may not be representative of what people are actually using
- Regulatory hurdles cost time and money; virtually impossible without strong institutional support; Funding especially difficult for cannabis research
- Given cost and regulatory knowledge base required, especially difficult for new researchers



Anxiety from Cannabis Withdrawal

- Cannabis Withdrawal Syndrome now a DSM-V diagnosis
- In a study of 496 people with chronic daily cannabis use trying to quit; 95% reported at least one withdrawal symptom
- Most commonly reported withdrawal symptoms include:
 - **Anxiety/restlessness**
 - Hostility/agitation
 - Insomnia
 - Depressed mood



Potential Pharmacologic treatments for anxiety 2/2 cannabis withdrawal:

- **More studies needed**
- Small studies showed some promise for
 - Gabapentin
 - Nabilone (synthetic THC)
 - Nabiximols (synthetic THC/CBD)
- Venlafaxine thought to **worsen cannabis** withdrawal syndrome in small studies
- Fluoxetine, bupropion, buspirone, lithium, atomoxetine, and divalproex had **no relevant effect** in small studies



So how do we talk to our patients about cannabis and anxiety?

- Partnership with our patients is especially important
- Be transparent about what we do/don't know
- Ongoing discussions of risk vs. benefit given unknowns
- THC:CBD ratio may be more helpful than strain/brand
- Try to track THC:CBD content and and track symptoms



THANKS!

What questions do you have?

shinbev@uw.edu

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