Marijuana and Psychiatric Disorders

Chris Stewart, MD
Associate Professor of Psychiatry
University of Louisville School of Medicine
Department of Psychiatry

UofL Hospital

Presentation Objectives

- 1. Review current information on marijuana use in the United States.
- 2. Discuss mental illness, mental disorders and marijuana/cannabis use
- 3. Discuss and review current evidence for medical marijuana in the treatment of psychiatric disorders

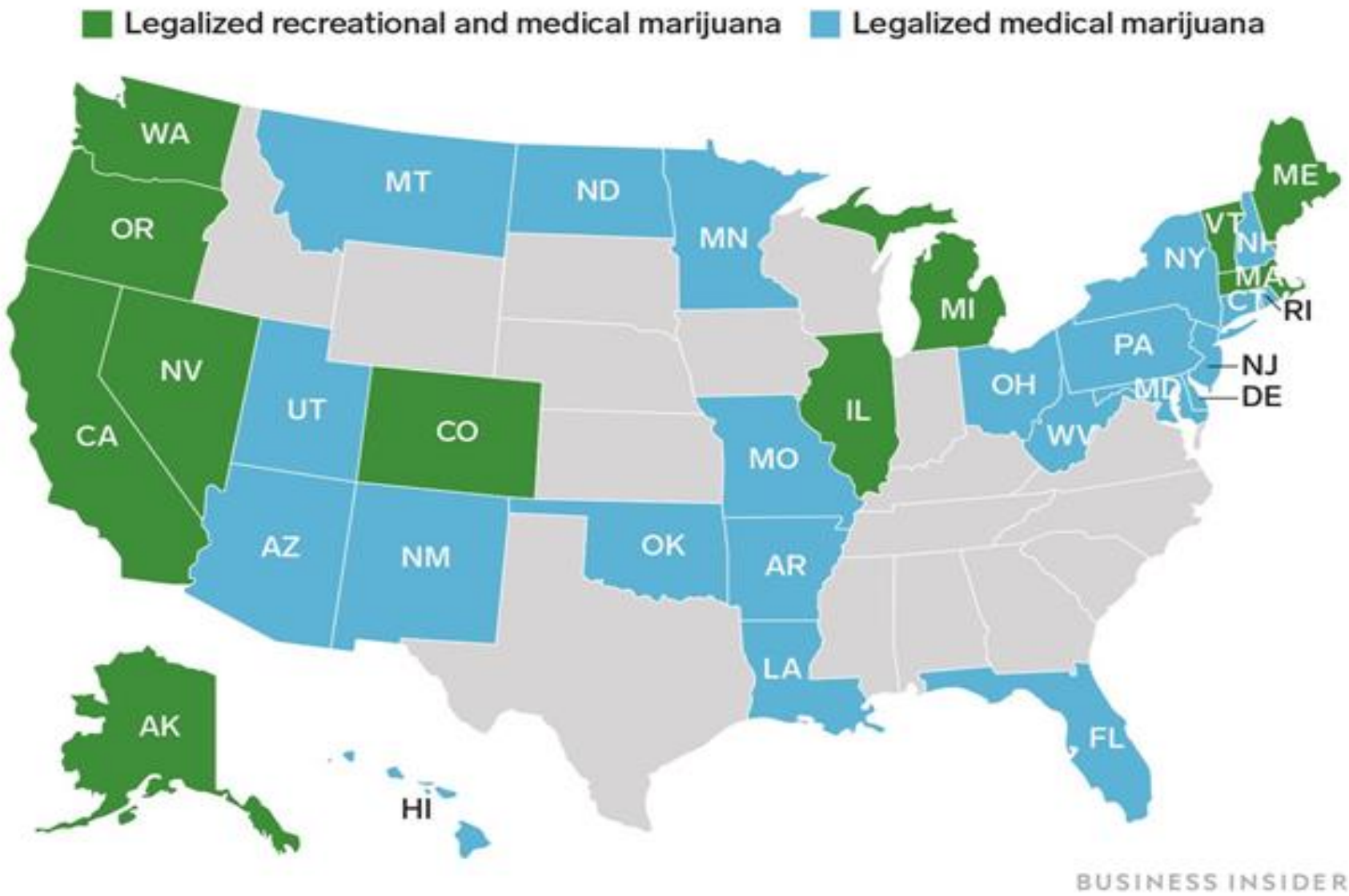
What is the scope of marijuana use in the United States?

Marijuana is the most used psychotropic drug in the United States, after alcohol. 45.3 million people reported past year use in 2018 .

Increased prevalence among men compared to women—a gender gap that widened in the years 2007 to 2014.

Widespread use among adolescents and young adults, 11.8 million ‘young’ users in 2018 according to NIDA.

States where marijuana is legal

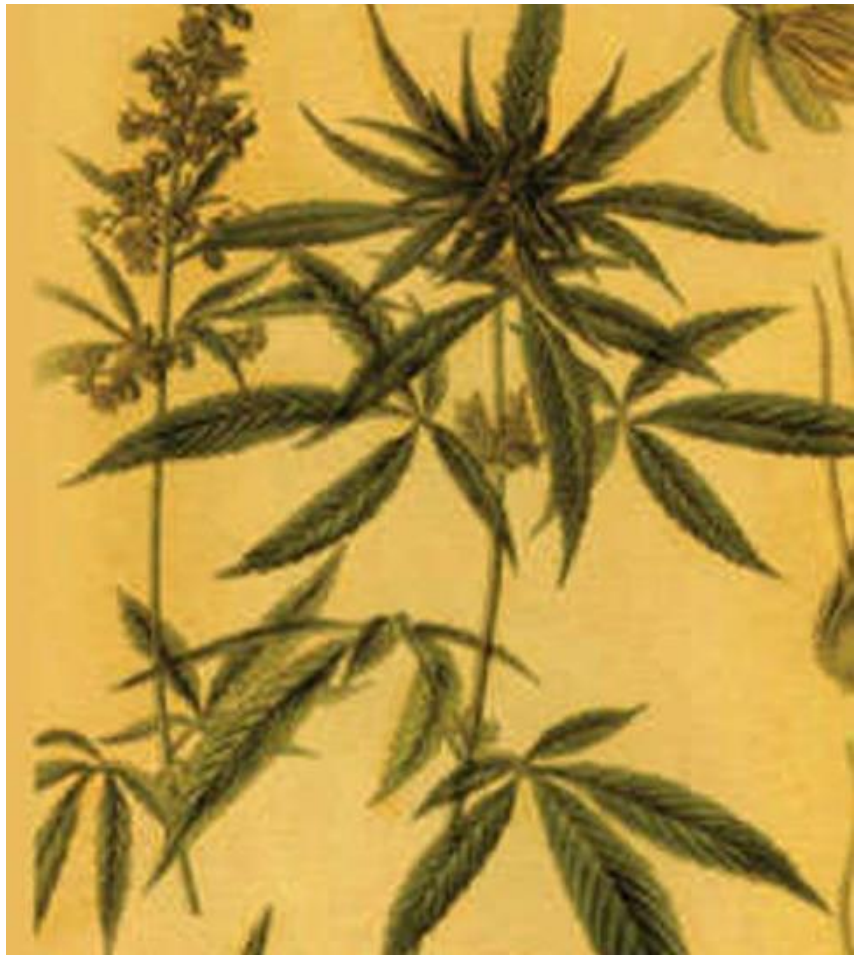


How do people use marijuana?

- People smoke marijuana in hand-rolled cigarettes **(joints)** or in pipes or water pipes **(bongs).** They also smoke it in **blunts**—emptied cigars that have been partly or completely refilled with marijuana. To avoid inhaling smoke, some people are using **vaporizers.**
- People can mix marijuana in **food (*edibles*)**, such as brownies, cookies, or candy, or brew it as a tea. A newly popular method of use is smoking or eating different forms of **THC-rich resins**

Delta-9-THC

- The main *psychoactive* (mind-altering) chemical in marijuana, responsible for most of the intoxicating effects that people seek, is *delta-9-tetrahydrocannabinol* (THC). The chemical is found in resin produced by the leaves and buds primarily of the female cannabis plant. The plant also contains more than 500 other chemicals, including more than 100 compounds that are chemically related to THC, called *cannabinoids*.



Acute Effects of Marijuana

- When marijuana is smoked, THC and other chemicals pass from the lungs into the bloodstream, which rapidly carries them throughout the body to the brain. The person begins to experience effects almost immediately.

- Many people experience a pleasant euphoria and sense of relaxation. Other common effects, which may vary dramatically among different people, include heightened sensory perception (e.g., brighter colors), laughter, altered perception of time, and increased appetite.

- If marijuana is consumed in foods or beverages, these effects are somewhat delayed—usually appearing after 30 minutes to 1 hour—because the drug must first pass through the digestive system. Eating or drinking marijuana delivers significantly less THC into the bloodstream than smoking an equivalent amount of the plant. Because of the delayed effects, people may inadvertently consume more THC than they intend to.

Somatic effects

- Some of the short-term physical effects of cannabis use include increased heart rate, dry mouth, reddening of the eyes, (congestion of the conjunctival blood vessels), a reduction in intra-ocular pressure, muscle relaxation and a sensation of cold or hot hands and feet and / or flushed face.

Adverse Consequences of Marijuana Use

Acute (present during intoxication)

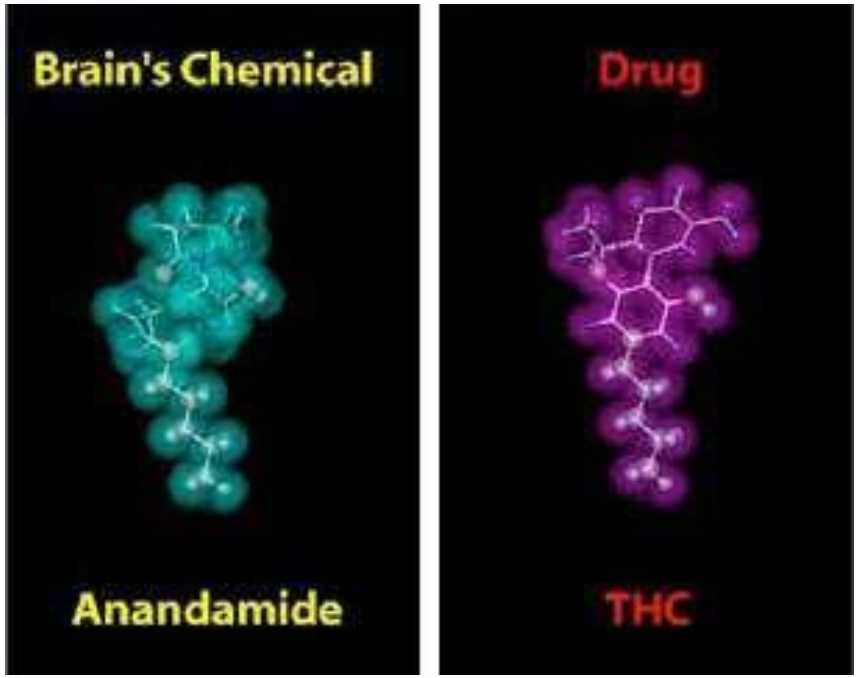
- Impaired short-term memory
- Impaired attention, judgment, and other cognitive functions
- Impaired coordination and balance
- Increased heart rate
- Anxiety, paranoia
- Psychosis (uncommon)

Persistent (lasting longer than intoxication, but may not be permanent)

- Impaired learning and coordination
- Sleep problems

Categories of Cannabinoids

- Endocannabinoids
  - Anandamide
- Synthetic Cannabinoids
  - 'Spice' or 'K2'
- Phyto cannabinoids
  - Marijuana: THC, CBD
  - FDA approved purified Phyto cannabinoids



The Endocannabinoid System

1) G-protein coupled cannabinoid CB1 and CB2 receptors

2) Endogenous endocannabinoids that target these receptors, and possibly other receptors

3) Enzymes that catalyze endocannabinoid biosynthesis and metabolism

4) Mechanisms involved in cell accumulation of specific endocannabinoids

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THE ENDOCANNABINOID SYSTEM

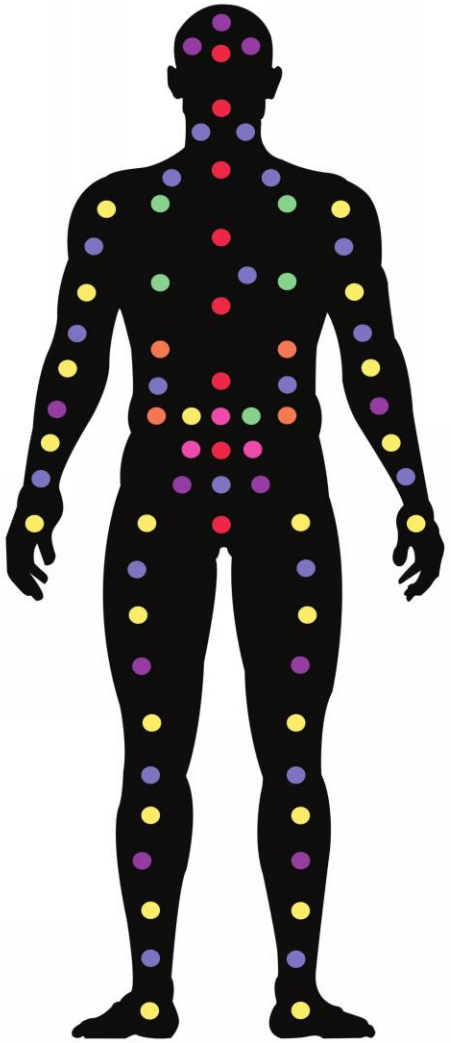
HUMAN CANNABINOID RECEPTORS

CB1
Receptors are concentrated in the brain & the central nervous system but are also present in some nerves and organs.

CB2
Receptors are mostly in peripheral organs, especially cells associated with the immune system.

TRVP1
Receptors are concentrated in the blood, bone, marrow, tongue, kidney, liver, stomach & overies.

TRPV2
Receptors are concentrated in the skin, muscle, kidney, stomach & lungs.



GPR 18
Receptors can be found primarily in bone marrow, the spleen and lymph nodes, and to a lesser extend the testes

GPR55
Receptors are found in the bones, the brain, particularly the cerebellum, and the Jejunum and Ileum.

GPR 119
Receptors are found predominantly in the Pancreas and the intestinal tract, in small amounts

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Is marijuana addictive?

- Recent data suggest that 30 percent of those who use marijuana may have some degree of marijuana use disorder., with 9 percent of users being at risk for becoming addicted
- People who begin using marijuana before the age of 18 are four to seven times more likely to develop a marijuana use disorder than adults.
- Marijuana use disorders are often associated with *dependence*—in which a person feels withdrawal symptoms when not taking the drug.

Table 2.
Cannabis withdrawal syndrome
THC indicates delta-9-tetrahydrocannabinol.

Variable	Description
Signs and symptoms	Irritability/anger Anxiety/depressed mood Insomnia Altered dreams Anorexia Abdominal cramping Headaches Tremors Fevers/chills
Onset	<1 day for high-dose, chronic users
Duration	Up to several weeks
Treatment	Symptomatic therapy, synthetic THC

Addiction Liability

10% who ever use marijuana become daily users

Conditional dependence – risk of dependence of those who ever use substance

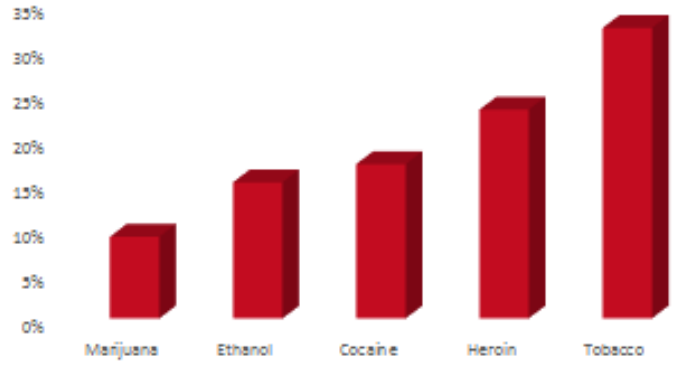
Marijuana 9%

Ethanol 15%

Cocaine 17%

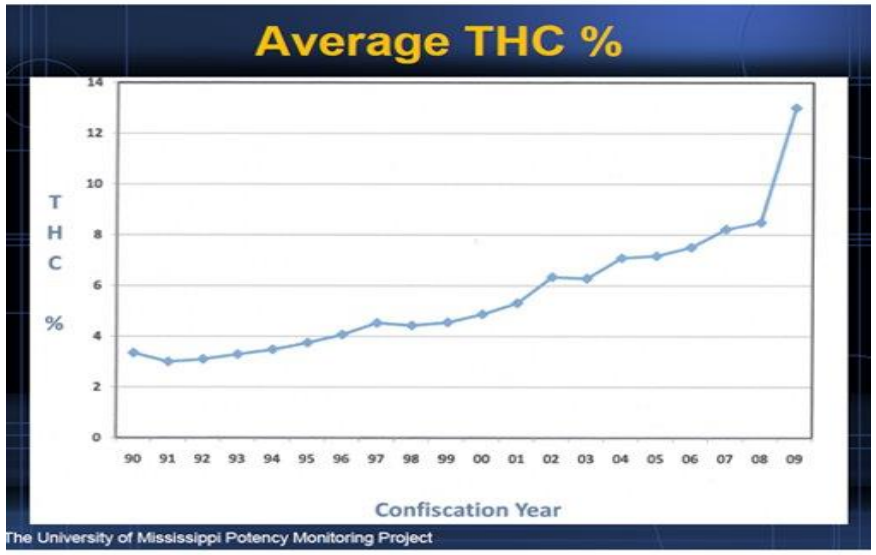
Heroin 23%

Tobacco 32%



Rising potency

- **Marijuana potency, as detected in confiscated samples, has steadily increased over the past few decades.**
- **In the early 1990s, the average THC content in confiscated marijuana samples was roughly 3.8 percent. In 2014, it was 12.2 percent. The average marijuana extract contains more than 50 percent THC, with some samples exceeding 80 percent.**



Cannabinoid-based medications

- Purified Phyto cannabinoids:
- *Sativex*, mix of THC/CBD, approved for treatment of chronic pain in MS;
- *Epidolex,* purified cannabidiol (CB D) approved for pediatric seizure disorder
- Synthetic FDA approved:
- *Nabilone*, synthetic THC, approved for anti-emesis in cancer
- *Dronabinol,* synthetic THC, FDA ap proved as anti-emetic, AIDS wasting syndrome

	CANNABINOID-BASED MEDICATIONS		
	Substance	**Route of Administration**	**Description**
Natural Product Derived Compounds	**Cannabidiol (CBD)**	Oral capsule Oromucosal spray	Cannabinoid extracted from *Cannabis* plant
	Cannabis	Multiple	Multiple active cannabinoids
	Cannador	Oral capsule	THC and CBD from *Cannabis* extract
	Epidiolex® **(FDA Fast Track)**	Oil	Concentrated CBD from *Cannabis* extract
	Nabiximol (Sativex®) **(FDA Fast Track)**	Oromucosal spray	THC and CBD extract from two *Cannabis* plant varieties
	Tetrahydrocannabinol (THC)	Oral capsule Smoked Oromucosal spray	Active cannabinoid of *Cannabis* plant
	THC/CBD	Oral capsule	Combination of cannabinoids
Synthetic Compounds			
	Ajulemic acid (AjA) (FDA PHASE II Active)	Oral capsule	Synthetic nonpsychoactive cannabinoid
	Dronabinol (Marinol®; Syndros®) (FDA approved)	Oral capsule	Synthetic THC
	Nabilone (Cesamet®) (FDA approved)	Oral capsule	Synthetic cannabinoid—THC analogue

Synthetic Cannabinoid Toxic Effects

- Illicit Designer Drugs:

- 'K-2'
- 'Spice'
- JWH-018 (full CB agonist)
- APICA

System	Synthetic Cannabinoid Intoxication Effects
Cardiac	Tachycardia, supraventricular tachycardia, ventricular fibrillation, myocardial infarction, sudden cardiac death, coronary arterial thrombosis
Hematological	Immune thrombocytopenia, intracranial hemorrhage, coagulopathy
Neurological	Dizziness, drowsiness, tremor, altered mental status, seizure, acute ischemic infarction
Psychiatric	Agitation, anxiety, paranoia, psychosis, suicidal ideation, delirium, dissociation, depersonalization, hallucinations, disorganized behavior
Renal	Acute kidney injury, acute tubular necrosis
Other	Nausea, vomiting, rhabdomyolysis, hyperthermia

Challenges and Barriers

There are several challenges and barriers in conduction cannabis and cannabinoid research, including:

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trails and observations studies) are needed

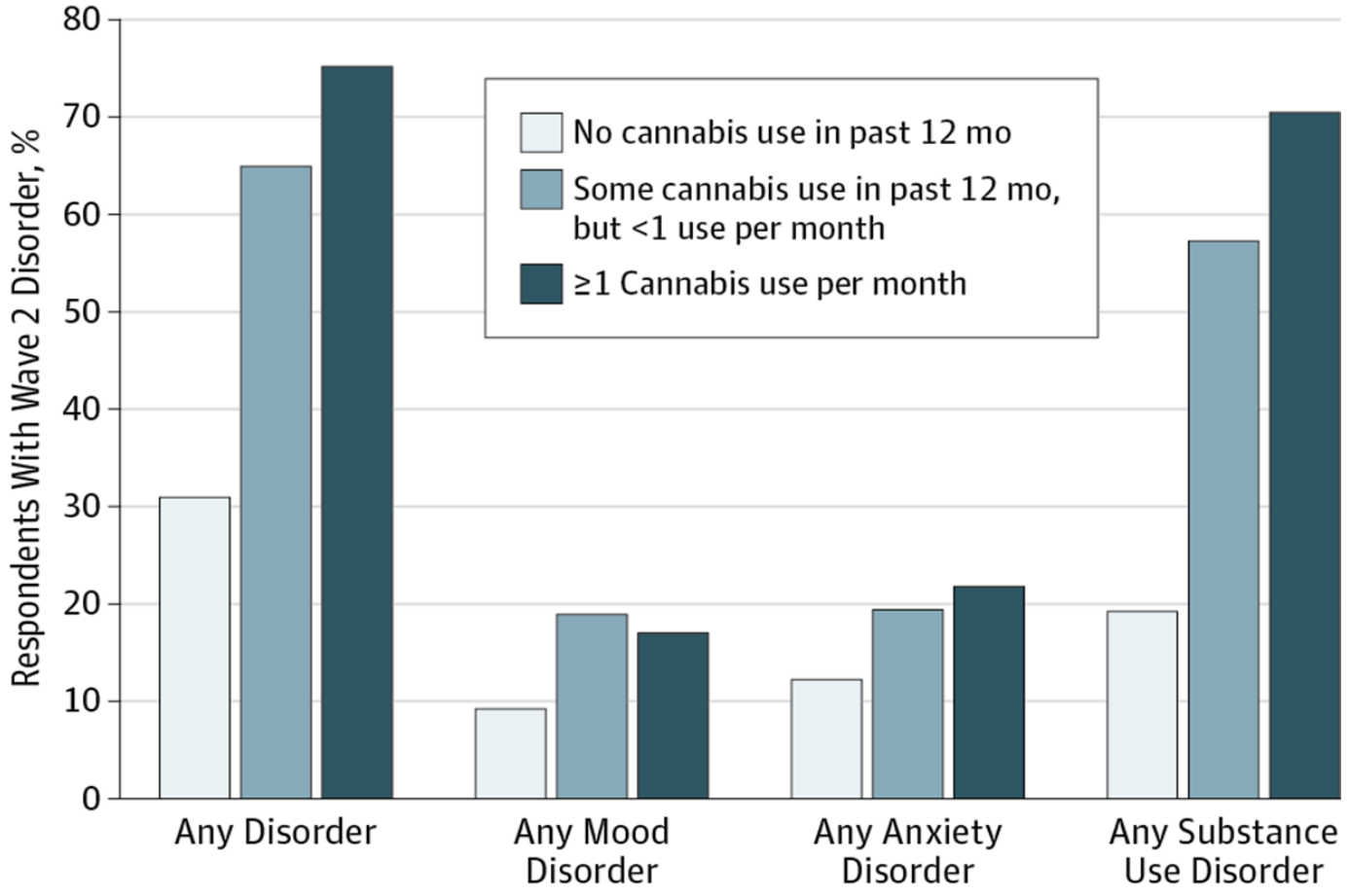
Is there a link between marijuana use and psychiatric disorders?

- Several studies have linked marijuana use to increased risk for psychiatric disorders, including psychosis (schizophrenia), depression, anxiety, and substance use disorders, but whether and to what extent it actually causes these conditions is not always easy to determine.
- Recent research suggests that smoking high-potency marijuana every day could increase the chances of developing psychosis by nearly five times compared to people who have never used marijuana.
- The amount of drug used, the age at first use, and genetic vulnerability have all been shown to influence this relationship. The strongest evidence to date concerns links between marijuana use and psychiatric disorders in those with a preexisting genetic or other vulnerability.

Is there a link? - continued

- Research using longitudinal data from the National Epidemiological Survey on Alcohol and Related Conditions examined associations between marijuana use, mood and anxiety disorders, and substance use disorders. After adjusting for various confounding factors, ***no association between marijuana use and mood and anxiety disorders was found.*** The only significant associations were increased risk of alcohol use disorders, nicotine dependence, marijuana use disorder, and other drug use disorders.

From: Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence From a US National Longitudinal Study



Long-term (cumulative effects of repeated use)

- Potential for marijuana addiction
- Impairments in learning and memory with potential loss of IQ*
- Increased risk of chronic cough, bronchitis
- Increased risk of other drug and alcohol use disorders
- Increased risk of schizophrenia in people with genetic vulnerability**
- *Loss of IQ among individuals with persistent marijuana use disorder who began using heavily during adolescence

- **These are often reported co-occurring symptoms/disorders with chronic marijuana use. However, research has not yet determined whether marijuana is causal or just associated with these mental problems.

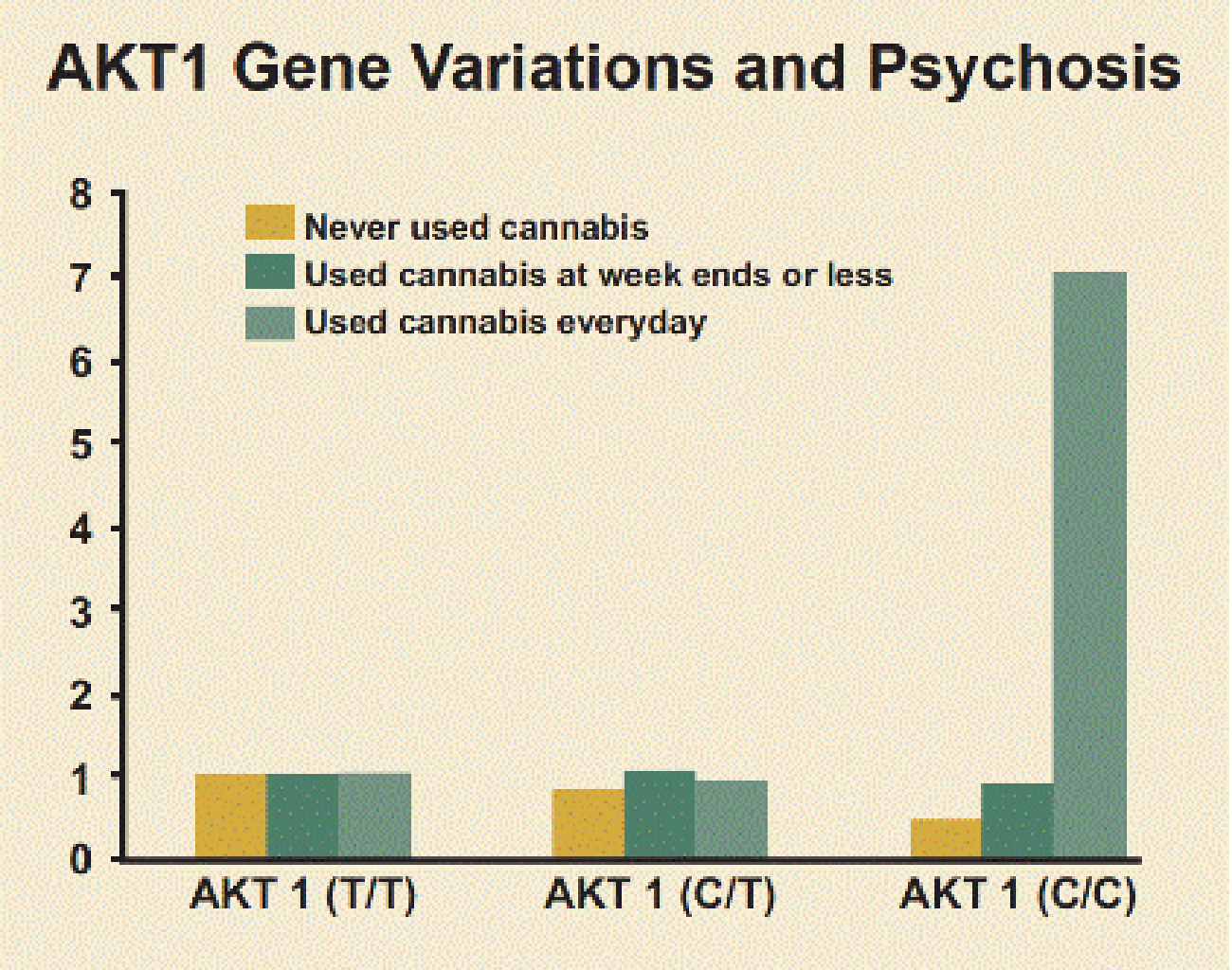
Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis.

JAMA Psychiatry. 2019 Apr 1;76(4):426-434. doi: 10.1001/jamapsychiatry.2018.4500
.

Low to Moderate Increased risk among Adolescent Cannabis Users for depressed mood, suicidal ideation and suicide attempts. No statistical relationship to anxiety.

Whether adolescent marijuana use can contribute to developing psychosis later in adulthood appears to depend on whether a person already has a genetically based vulnerability to the disorder. The AKT1 gene governs an enzyme that affects brain signaling involving the neurotransmitter dopamine. Altered dopamine signaling is known to be involved in schizophrenia. AKT1 can take one of three forms in a specific region of the gene implicated in susceptibility to schizophrenia: T/T, C/T, and C/C. Those who use marijuana daily (green bars) with the C/C variant have a seven times higher risk of developing psychosis than those who use it infrequently or use none at all. The risk for psychosis among those with the T/T variant was unaffected by whether they used marijuana.

Source: Di Forti et al. *Biol Psychiatry*. 2012.



The influence of adolescent marijuana use on adult psychosis is affected by genetic variables. This figure shows that variations in a gene can affect the likelihood of developing psychosis in adulthood following exposure to cannabis in adolescence. The COMT gene governs an enzyme that breaks down dopamine, a brain chemical involved in schizophrenia. It comes in two forms: "Met" and "Val." Individuals with one or two copies of the Val variant have a higher risk of developing schizophrenic-type disorders if they used cannabis during adolescence (dark bars). Those with only the Met variant were unaffected by cannabis use.

Source: Caspi et al. *Biol Psychiatry*. 2005.

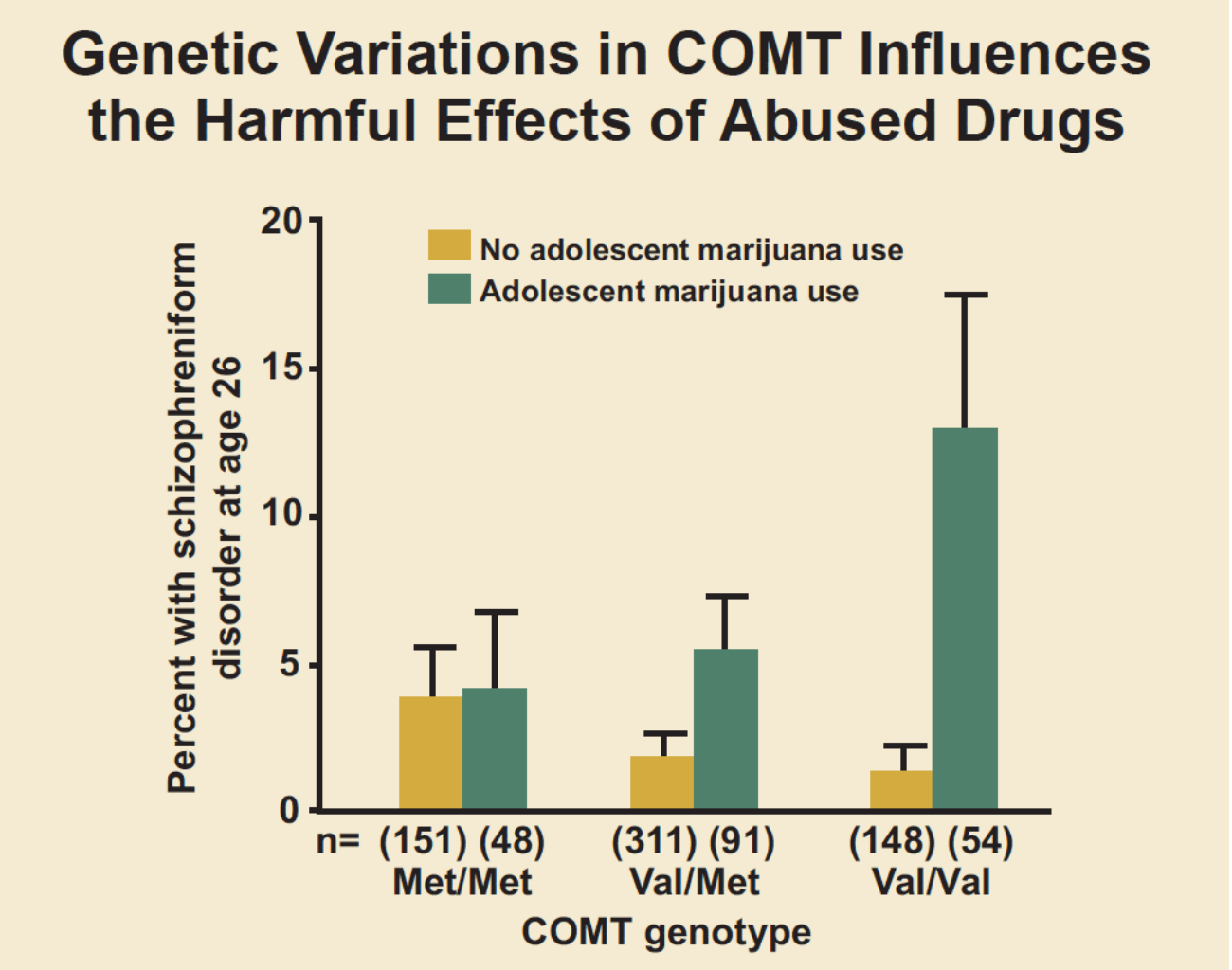


TABLE. Studies on the clinical administration of CBD to treat psychosis in individuals with schizophrenia or non-affective psychosis

Study	N	Dose of CBD	Assessments of symptoms	Findings
Zuardi et al.[8]	1	Up to 1500 mg/d in 2 divided doses for 26 days	BPRS	Improvement of symptoms, no adverse effects
Zuardi et al.[9]	3	Up to 1280 mg/d for 4 weeks	BPRS	Mild improvement only in one subject, no adverse effects
Zuardi et al.[10]	6	Up to 600 mg/d for 4 weeks	BPRS, PPQ, CGI	Improvement of symptoms, no adverse effects
Leweke et al.[11]	42	Up to 800 mg/d for 4 weeks in 3-4 divided doses	BPRS, PANSS	CBD was as effective as amisulpride for improvement of symptoms; CBD had superior adverse effect profile
McGuiare et al.[12]	88	1000 mg/d in 2 divided doses for 6 weeks	PANSS, BACS, GAF, CGI-I, CGI-S	CBD group had lower levels of positive psychotic symptoms and subjects were more likely to have been rated as improved and as not severely unwell by their clinician; they also showed greater improvements in their cognitive processing speed and in overall functioning; the rate of adverse events was not significantly different with placebo
Boggs et	36	600 mg/day in 2 divided	PANSS, MCCB	There was no significant effect of CBD on interaction in either

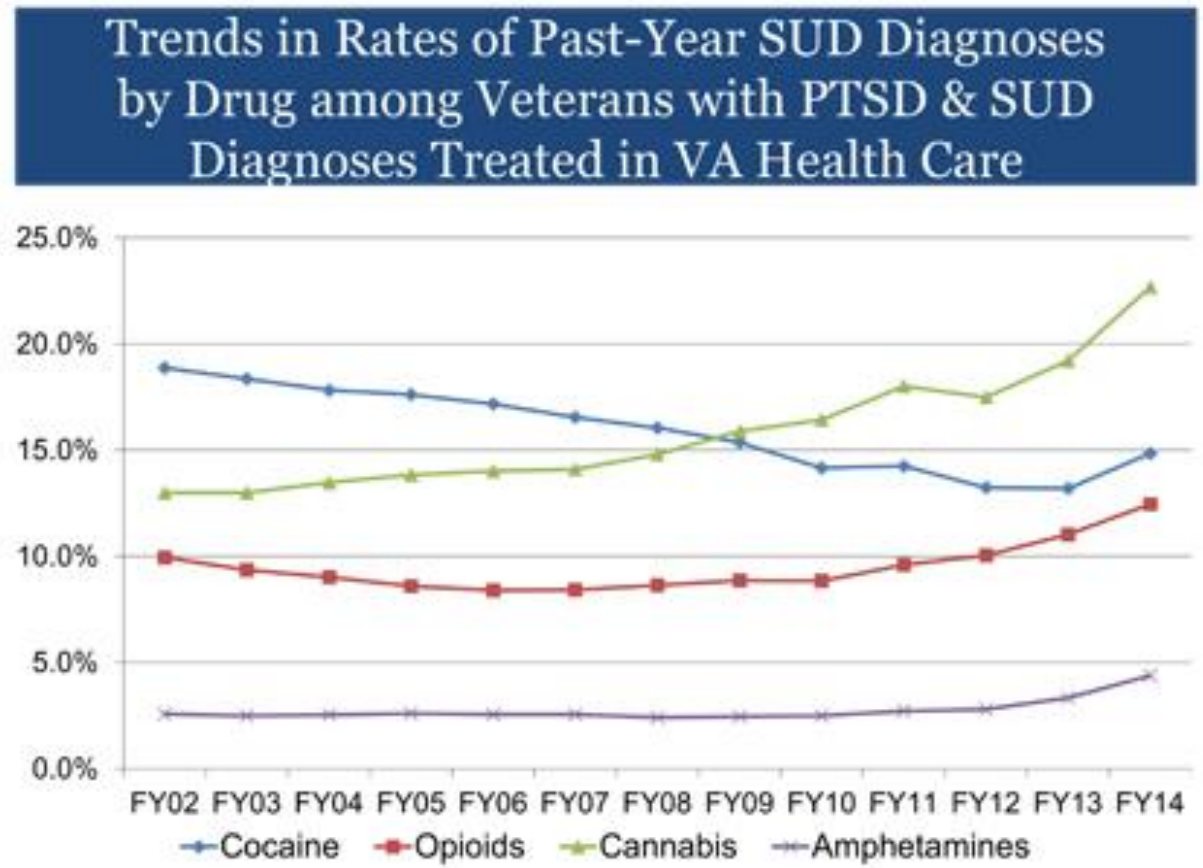
Bipolar Disorder and Cannabis

- Cannabis use among patients with Bipolar Disorder predicts worse course of the illness, poorer compliance with treatment
- Cannabis is the most used/abused drug among patients with diagnosis
- Like schizophrenia, increased risk of psychosis with cannabis use
- Increased risk of mania/hypomania
- Increased association of suicidal ideation and behavior
- Increased risk for co-occurring substance use, especially alcohol, but also any addiction

Post Traumatic Stress Disorder and Cannabis

Marijuana Use and PTSD among Veterans

Marcel O. Bonn-Miller, Ph.D. and Glenna S. Rousseau, Ph.D. 2015.



- The percentage of Veterans in VA with PTSD and SUD who were diagnosed with cannabis use disorder increased from 13.0% in fiscal year (FY) 2002 to 22.7% in FY 2014. As of FY 2014, there are more than 40,000 Veterans with PTSD and SUD seen in VA diagnosed with cannabis use disorder (6).

- “Marijuana Use Is Associated With Worse Outcomes in Symptom Severity and Violent Behavior in Patients With Posttraumatic Stress Disorder” Samuel T. Wilkinson, MD; Elina Stefanovics, PhD; and Robert A. Rosenheck, MD. J Clin Psychiatry. 2015 Sep; 76(9): 1174–1180.

- From 1992 to 2011, veterans with DSM-III/-IV PTSD (N = 2,276) were admitted to specialized Veterans Affairs treatment programs, with assessments conducted at intake and 4 months after discharge.
- Subjects were classified into 4 groups according to marijuana use: those with no use at admission or after discharge (“never-users”), those who used at admission but not after discharge (“stoppers”), those who used at admission and after discharge (“continuing users”), and those using after discharge but not at admission (“starters”).

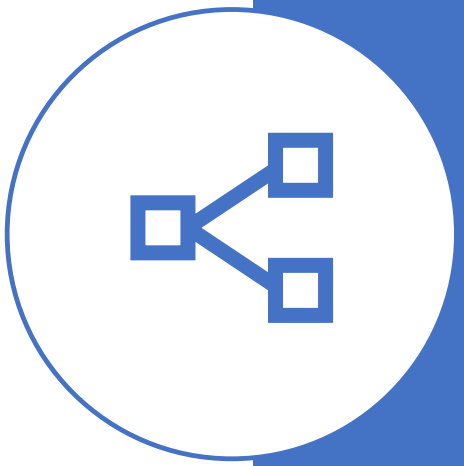
Results of Veteran's Study

After adjusted for relevant baseline covariates, marijuana use was significantly associated with worse outcomes in PTSD symptom severity ($P < .01$), violent behavior ($P < .01$), and measures of alcohol and drug use ($P < .01$) when compared with stoppers and never-users.

The authors concluded that initiating marijuana use after treatment was associated with worse PTSD symptoms, more violent behavior, and alcohol use. Further, marijuana may worsen PTSD symptoms or nullify the benefits of specialized, intensive treatment.

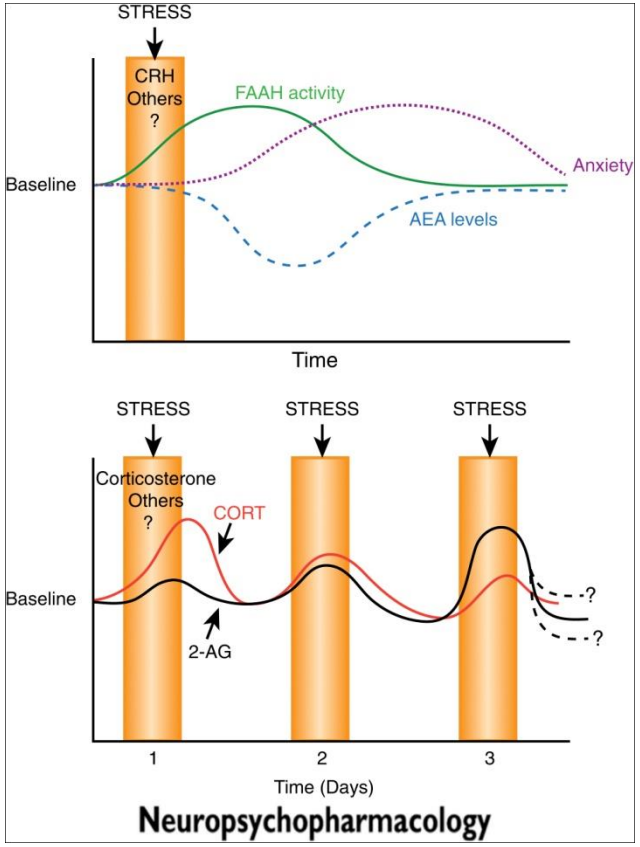
A stress endophenotype for PTSD?

- PTSD is associated with increased expression of cannabinoid receptor type 1 (CB1) and reduced peripheral levels of the eCB anandamide as well as a compensatory increase of CB1 availability, which has been linked to excessive threat processing and with features of anxious arousal.
- Therefore, a deficiency of eCB signaling possibly reflects a stress endophenotype underlying PTSD, raising the possibility that endocannabinoid manipulations could be potentially useful in a therapeutic capacity.



Stress, Endocannabinoids and PTSD

Figure 1



Neuropsychopharmacology Reviews (2018) **43**, 80-102;
doi:10.1038/npp.2017.162

Systems in PTSD implicated in the ECS

- Amygdala and ventromedial prefontal cortex (vmPFC) coupling in fear extinction
- Inflammation
- Memory Formation
- Memory Extinction
- Anxiolysis
- Sleep

Other Mental Disorders and Cannabis

ADHD and Cannabis

- ADHD users more likely to use earlier and more likely to use other substances
- Increased risk of becoming addicted to cannabis
- Very difficult to diagnosis new case of ADHD among active user of cannabis
- Several small and limited studies have shown no acute worsening of ADHD symptoms, specifically response inhibition, among adolescent ADHD/cannabis users.
- No empirical evidence that Cannabis/MJ is helpful for ADHD

Social Anxiety Disorder

- Masataka N. Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers With Social Anxiety Disorders. Front Psychol. 2019;10:2466. Published 2019 Nov 8. doi:10.3389/fpsyg.2019.02466

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- Ecker, Anthony H, and Julia D Buckner. “Cannabis-Related Problems and Social Anxiety: The Mediational Role of Post-Event Processing.” *Substance use & misuse* vol. 53,1 (2018): 36-41. doi:10.1080/10826084.2017.1322984

Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis

- Paper published in October 2019 by National Alcohol and Drug Research Center in Sydney, Australia
- 83 eligible studies
- 40 were RCT's with N=3067; 42 studies on depression, 31 for anxiety, 8 for Tourette's, 3 for ADHD, 12 for PTSD, 11 for psychosis
- No evidence of any benefit.

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