EXPLORING THE MENTAL HEALTH IMPACT OF MODERN MARIJUANA

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OBJECTIVES

1. Examine existing epidemiological data regarding the relationships between cannabis use and mental health outcomes.
2. Identify the neurobiological underpinnings and cannabinoid-related factors associated with cannabis use.
3. Assess the current understanding of how THC and CBD influence psychosis, anxiety, and mood based on analyses of clinical trials.
4. Acquire essential knowledge to engage in informed conversations regarding cannabis use and its effects on mental health.

CONFLICT OF INTEREST

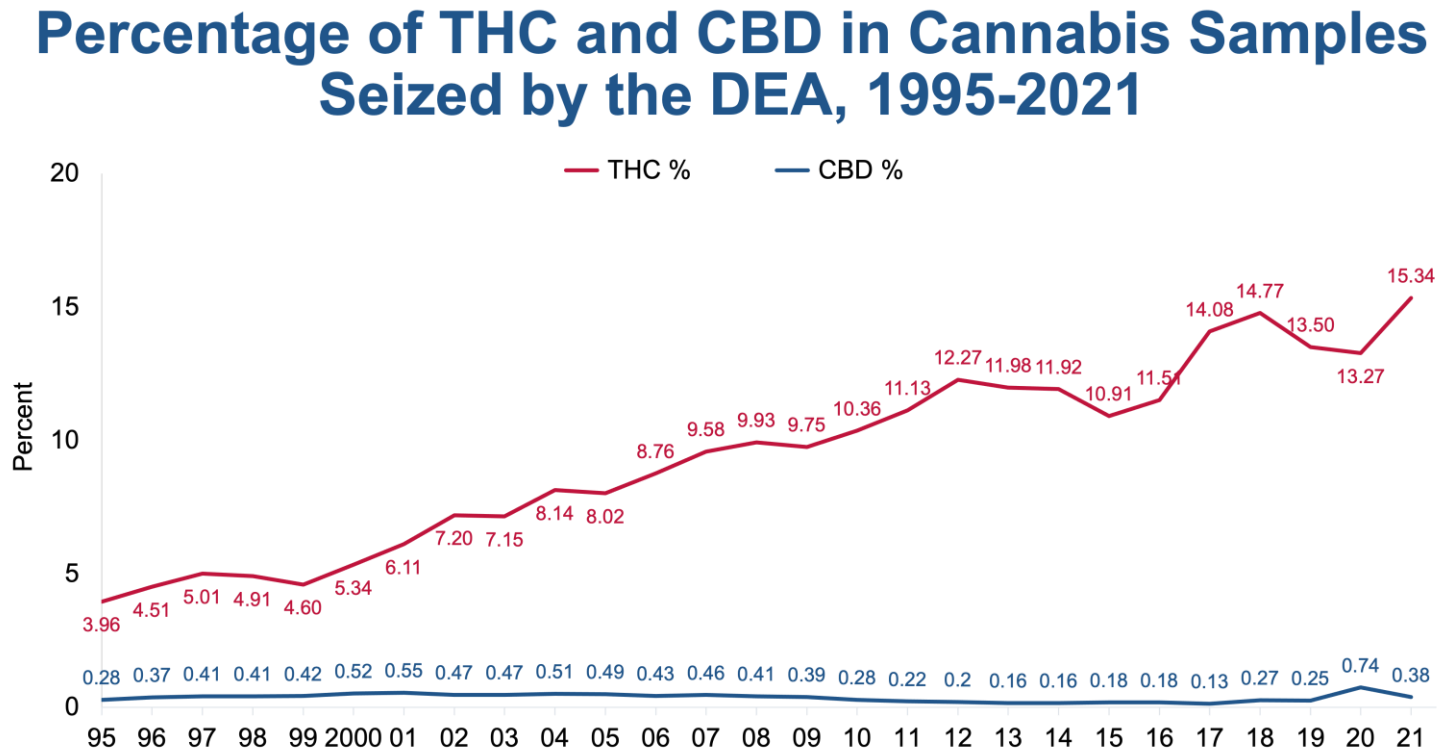
Dr. Stanciu served on the N.H. Therapeutic Cannabis Medical Oversight Board and has published on topics related to the impact of cannabinoids on mental health however, he has no financial conflicts of interests or other disclosures relevant to the content of this presentation

Genus: *Cannabis*

- indigenous to Central Asia, specifically in regions of present-day Mongolia and southern Siberia.

	CANNABIS SATIVA	CANNABIS INDICA	CANNABIS RUDERALIS
Physical appearance	Tall, lanky plant up to 12 feet high with thin, pointed leaves  THC high CBD high uplifting 	Short (2-4 feet high) bushy plant with broad chunky leaves  THC high CBD low relaxing 	Small (1-2 feet high) shaggy bush with light green leaves  THC low 

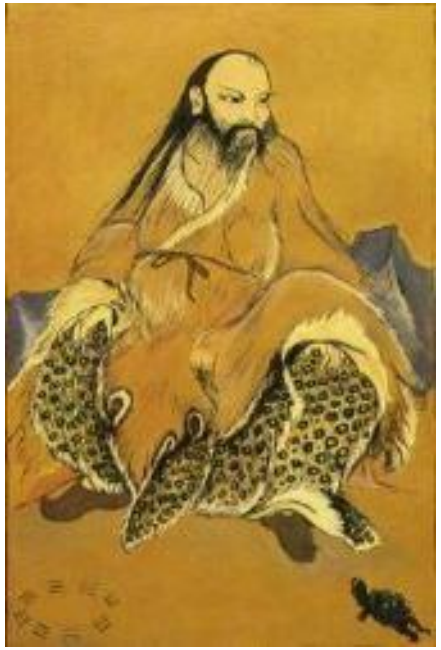
Chemical constituent classes
Cannabinoids (66)
Nitrogenous compounds (27)
Amino acids(18)
Proteins/ enzymes (11)
Sugars (34)
Hydrocarbons (50)
Simple alcohols (7)
Simple aldehydes (12)
Simple ketones (13)
Simple acids (21)
Fatty acids (22)
Simple esters/lactones (13)
Steroids (11)
Terpenes (20)
Non-cannabinoid phenols (25)
Flavoroids (21)
Vitamins (1)
Pigments (2)
Elements (9)
Total known compounds (483)

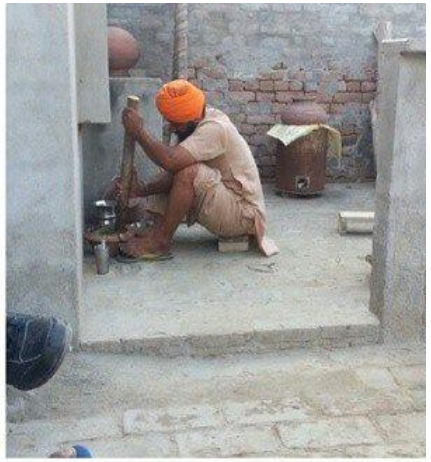


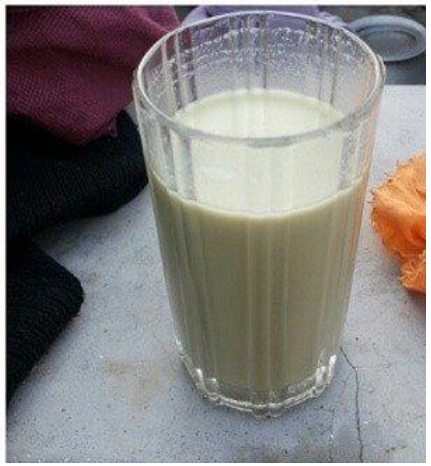
SOURCE: U Miss, Potency Monitoring Project

Historical Background

2900 BC: Chinese Emperor Fu Hsi – referenced "Ma", a very popular medicine that possessed both yin and yang.







1213 BC: In Egypt cannabis was used for glaucoma, inflammation of uterus, and enemas.

1000 BC: Bhang used in India as an anesthetic and anti-phlegmatic in addition to a wide variety of maladies.

1578: Chinese medical textbook outlined benefits of cannabis to treat vomiting, parasitic infections, and hemorrhage. The general population also used it as a remedy for diarrhea and to stimulate appetite.

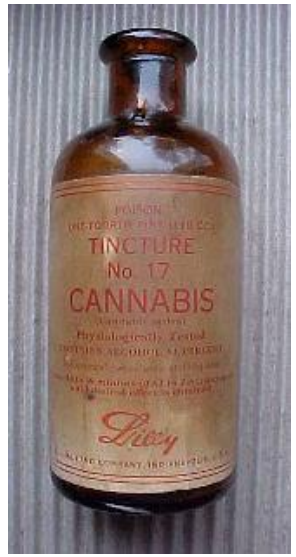
1611: Jamestown settlers brought the marijuana plant (hemp) to North America.

1842: William O'Shaughnessy introduced medical cannabis to the U.K. for use for a variety of ailments (insomnia, muscle spasms, menstrual cramps, rheumatism, and convulsions of tetanus, rabies and epilepsy).

French psychiatrist Jean-Jacques Moreau de Tours experimented with cannabis in mental disorders - described the plant as hypnotic, analgesic, and anticonvulsant

1850: Cannabis (patented medical tinctures) added to United States Pharmacopeia as treatment for: neuralgia, tetanus, typhus, cholera, rabies, dysentery, alcoholism, opioid addiction, anthrax, leprosy, incontinence, gout, convulsive disorders, tonsillitis, insanity, excessive menstrual bleeding, and uterine bleeding, among others.

1930s: Parke-Davis and Eli Lily produced drugs from hemp selling standardized extracts for use as an analgesic, an antispasmodic and sedative and for asthma.

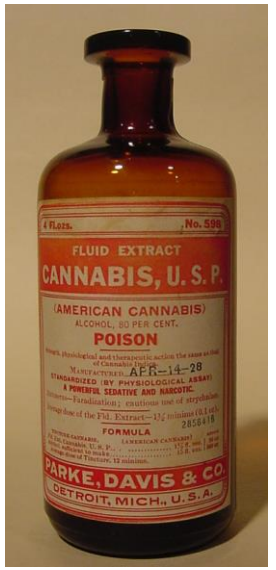


1937: Marihuana Tax Act passed imposing registration and reporting requirements and a tax on the growers, sellers, and buyers of marijuana. The population maintained the right to use marijuana for medicinal purposes but required physicians and pharmacists who prescribed or dispensed marijuana to register with federal authorities and pay an annual tax or license fee. After the passage of the Act, prescriptions of marijuana declined.

1942: Marijuana removed from US Pharmacopeia

1970: Controlled Substances Act (CSA) places cannabis in Schedule I.

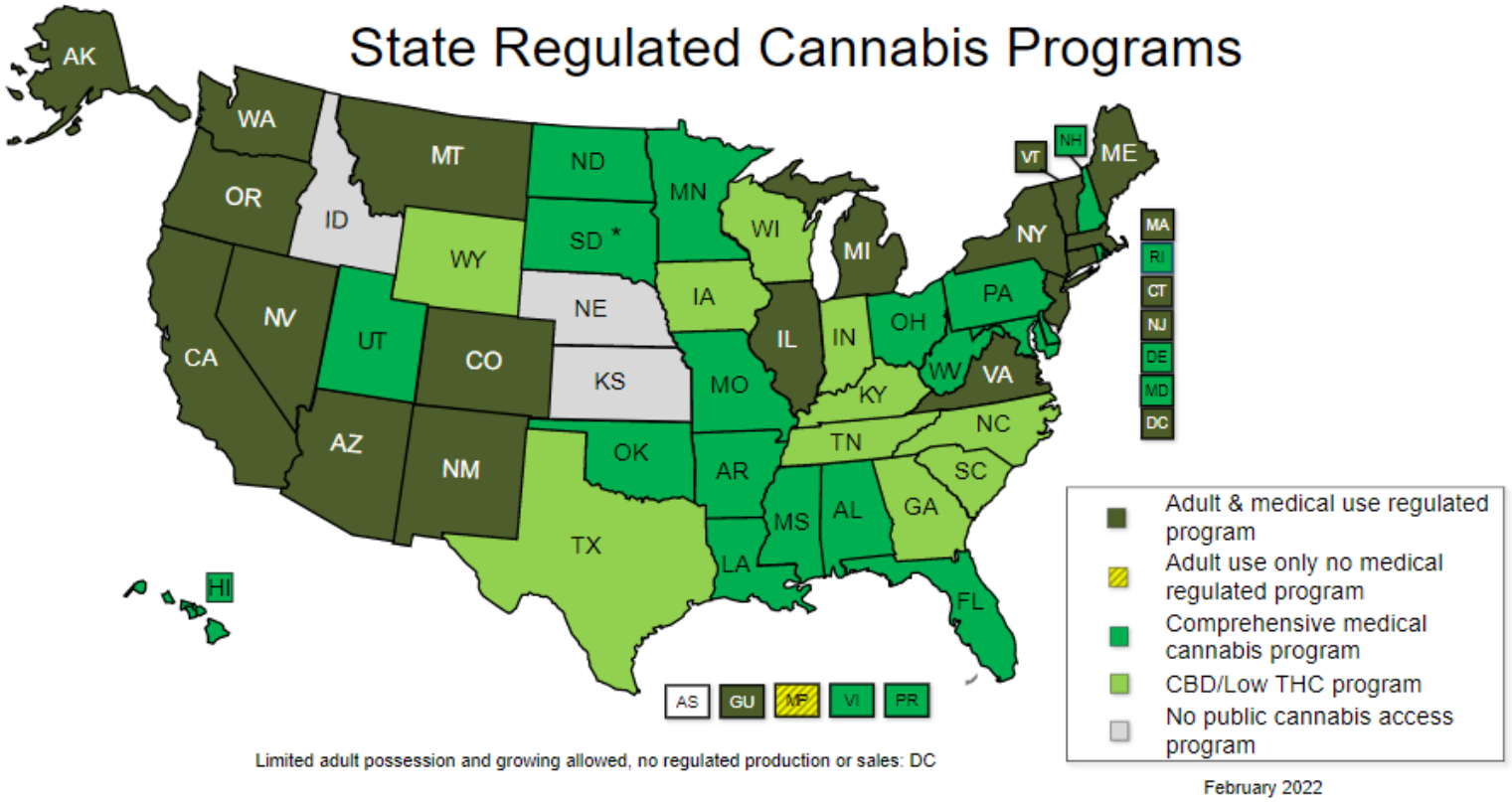
1980: Dronabinol (Marinol) tested against smoked cannabis in cancer patients. Approval granted for treatment resistant nausea and vomiting associated with chemotherapy (and later for anorexia associated with weight loss in patients with AIDS).



1996: California legalized medical cannabis

2006: Joint report FDA, NIDA, & SAMHSA - "No sound scientific studies support the medical use of marijuana " because it is not better than any available medical treatments

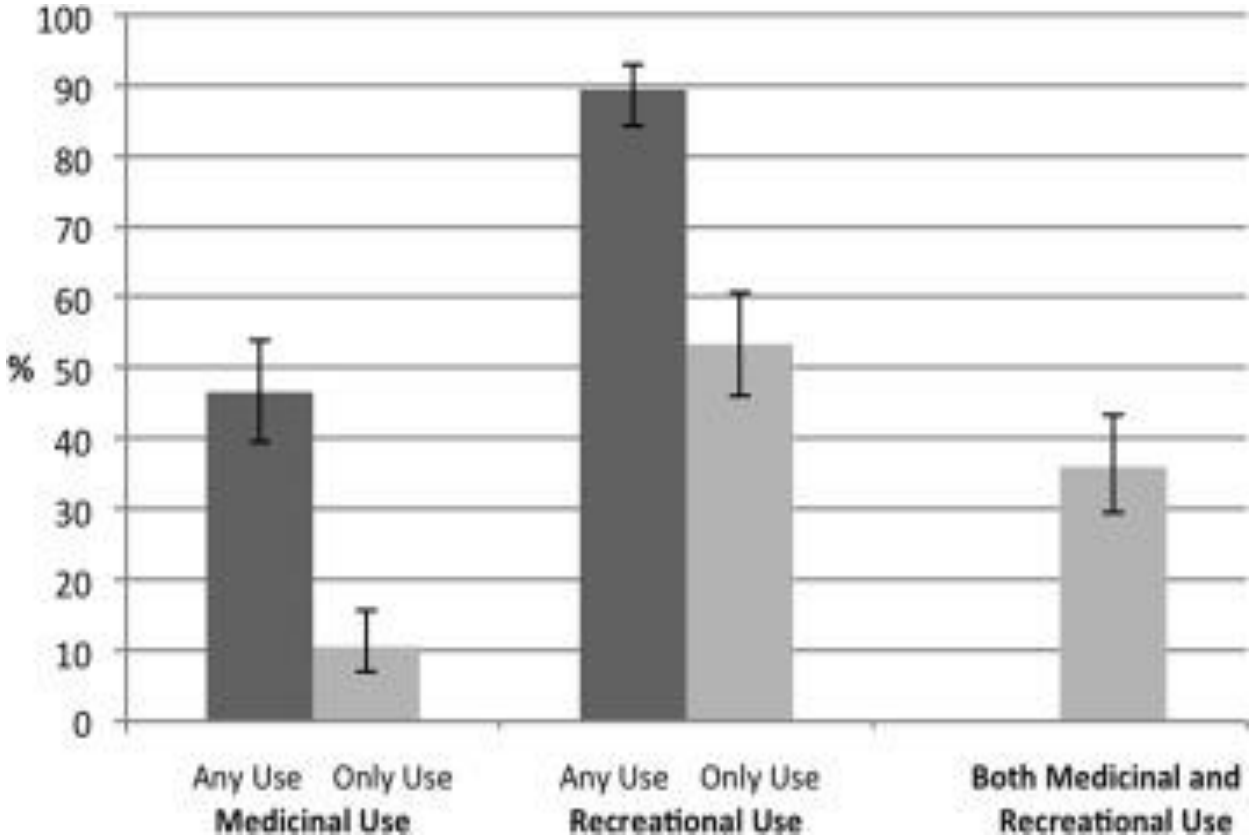
2019: National Survey on Drug Use and Health (NSDUH) – 15-20% of Americans 12+ used cannabis in the past year



Epidemiology

Summer styles survey:

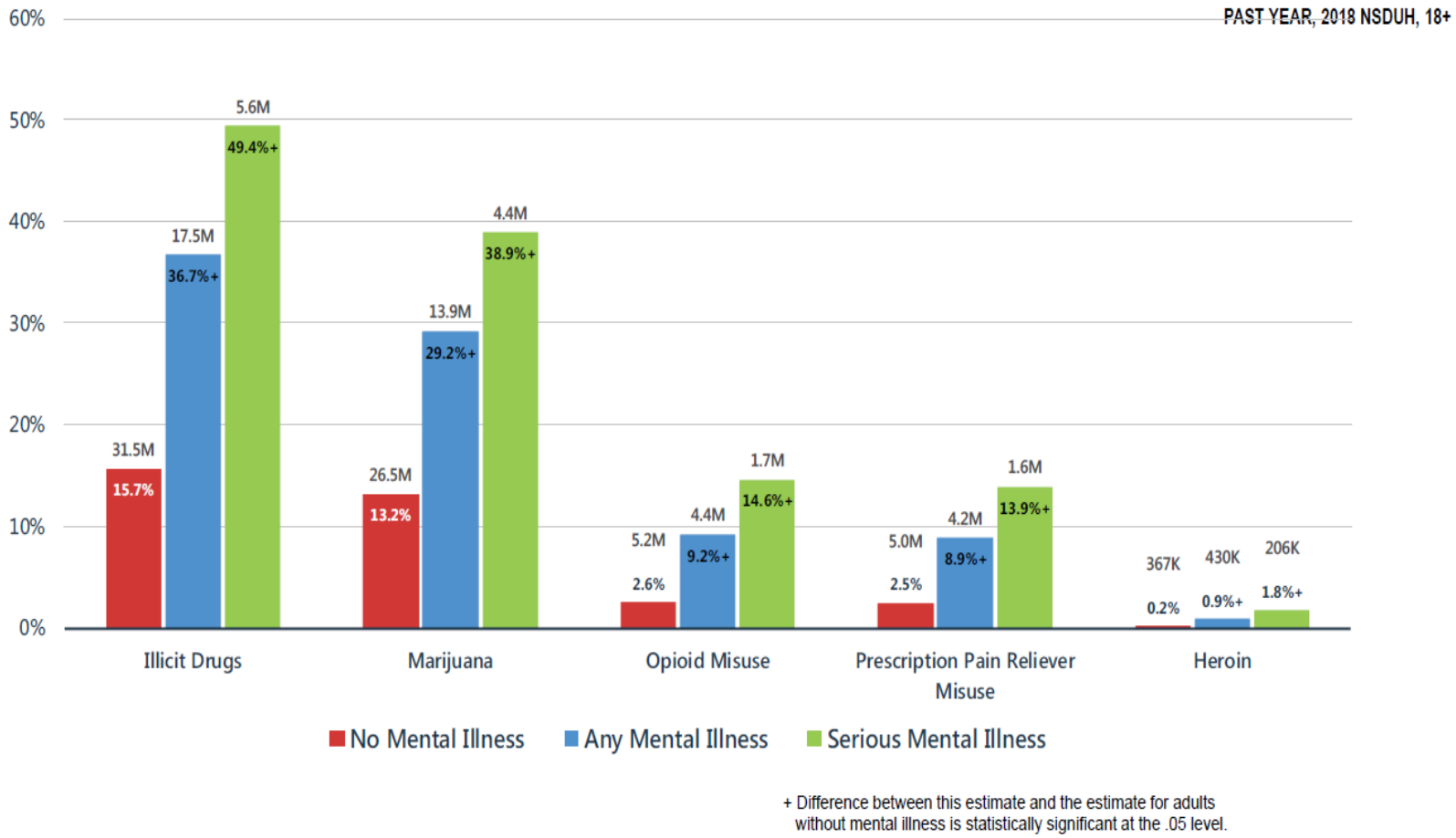
- 89.5% of adult marijuana users endorse recreational use.
- 46.6% use marijuana, in part or entirely, for medicinal purposes.
  - 10.5% use solely for medicinal purposes.



Risk / Benefit survey:

- 81% of U.S. adults believe marijuana has 1+ benefit; 17% believe it has no benefit.
  - Most common: pain management (66%), epilepsy and multiple sclerosis (48%), and relief from anxiety, stress, and depression (47%).
- Perceived risks: legal problems (51.8%), addiction (50%) and impaired memory (42%).
  - 7.6% believe it is safe for children; 7.3% think it is safe during pregnancy.

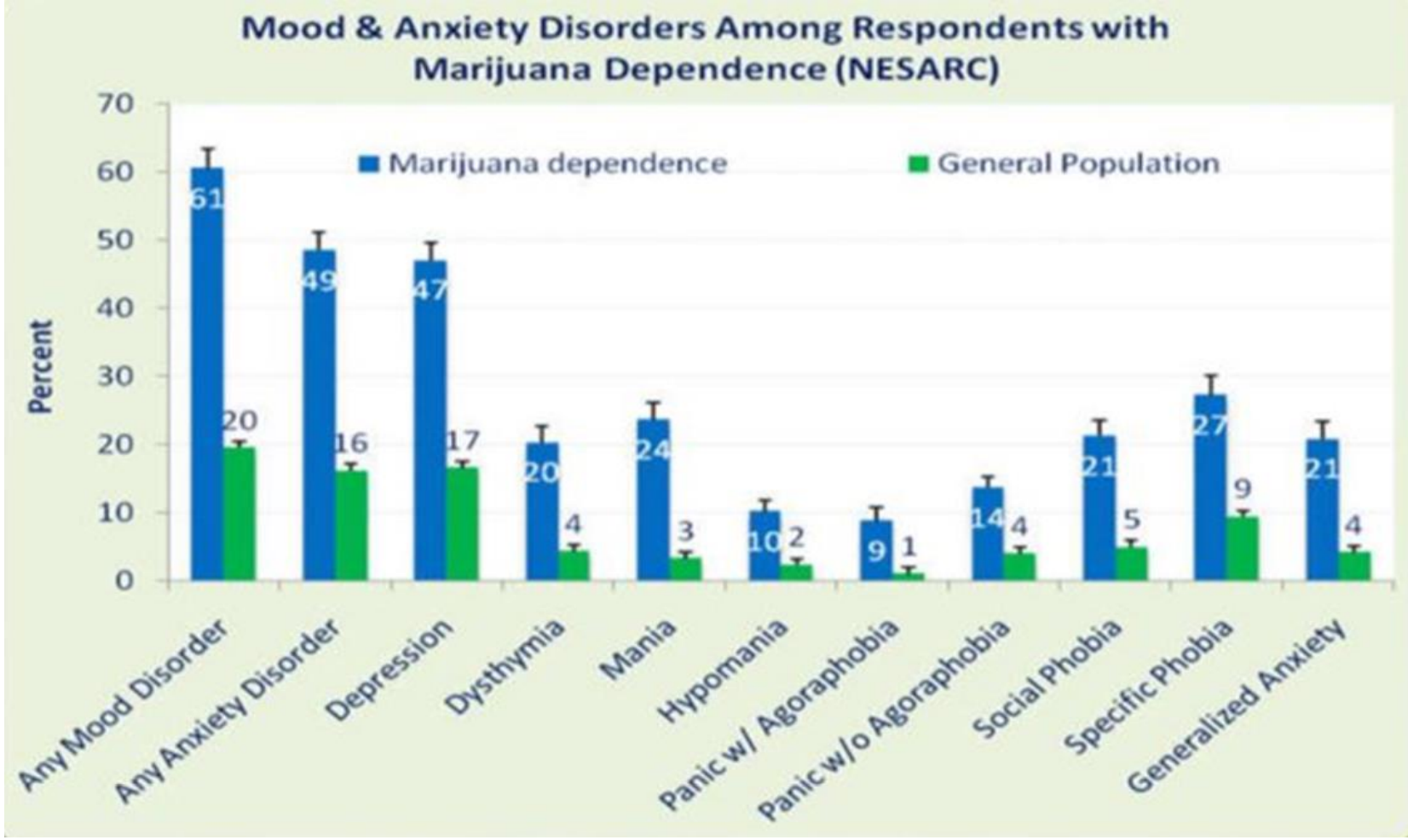
Epidemiology



National Survey on Drug Use and Health (NSDUH) data:

- Cannabis is the most commonly used illicit.
  - Use doubled since 2008.
  - Increases in adults >26.
  - Use among young females is trending upwards.
- Increase in Cannabis Use Disorder diagnoses among those 18-25.
- Cannabis use parallels severity of mental health conditions.

Epidemiology



Cannabis and Mental Health

- Two systematic reviews of longitudinal, population-based studies indicate that 27 studies have shown that chronic cannabis use is related to suicide ideations, attempts and death by suicide in a dose dependent manner.

  (Borges et al. 2016, Moore et al. 2007)

- In adolescents cannabis use is associated with increased depression, suicidal ideation, use of other substances and risky behavior among adolescents.

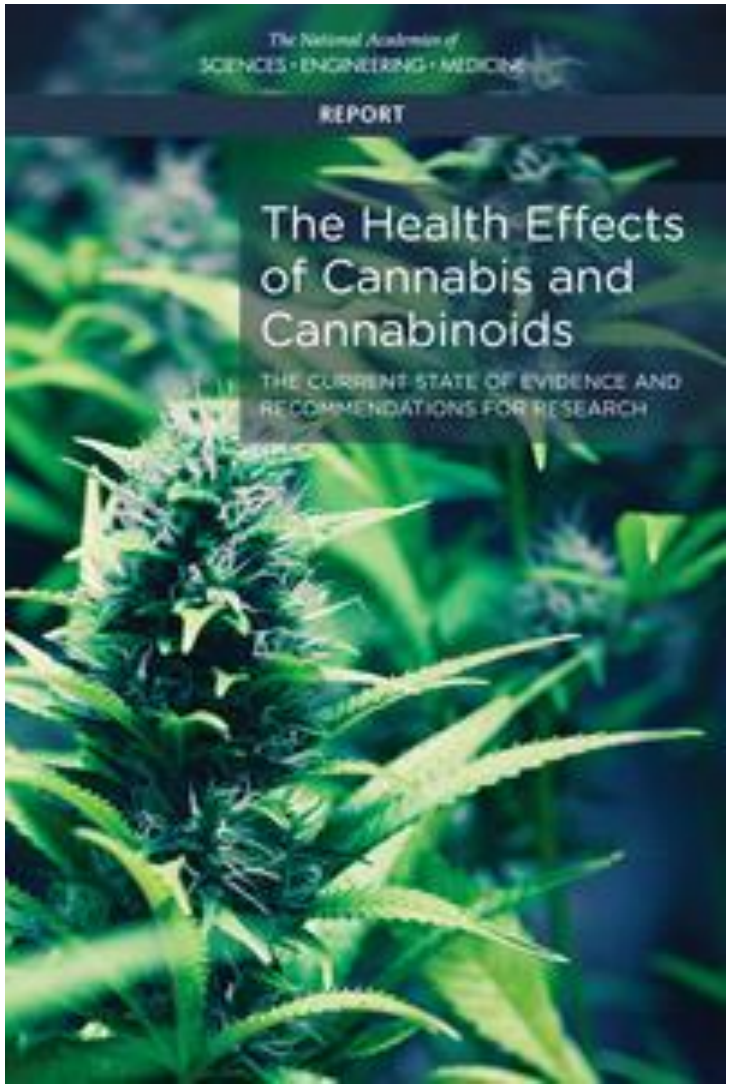
  Degenhardt L et al 2013

- A 2017 cross-sectional multi-site VA study of 3,233 Veterans found that veterans with cannabis use disorder compared to those with no lifetime history of cannabis use disorder was significantly associated:

  - Current suicidal ideation ($p<.0001$)
  - Lifetime history of suicide attempts ($p<.0001$)

  (Kimbrel NA et al. 2017)

National Academies of Sciences, Engineering, Medicine



Substantial evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

Moderate evidence of a statistical association between cannabis use and:

- Cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

Hypothetical Interactions

- Shared risk for cannabis use and psychiatric conditions
- Cannabis use predisposes to psychiatric conditions
- Psychiatric conditions predispose to cannabis use
- Cannabis use affects course of psychiatric conditions
- Psychiatric conditions affect course of cannabis use
- Overlapping symptoms of cannabis use and psychiatric conditions

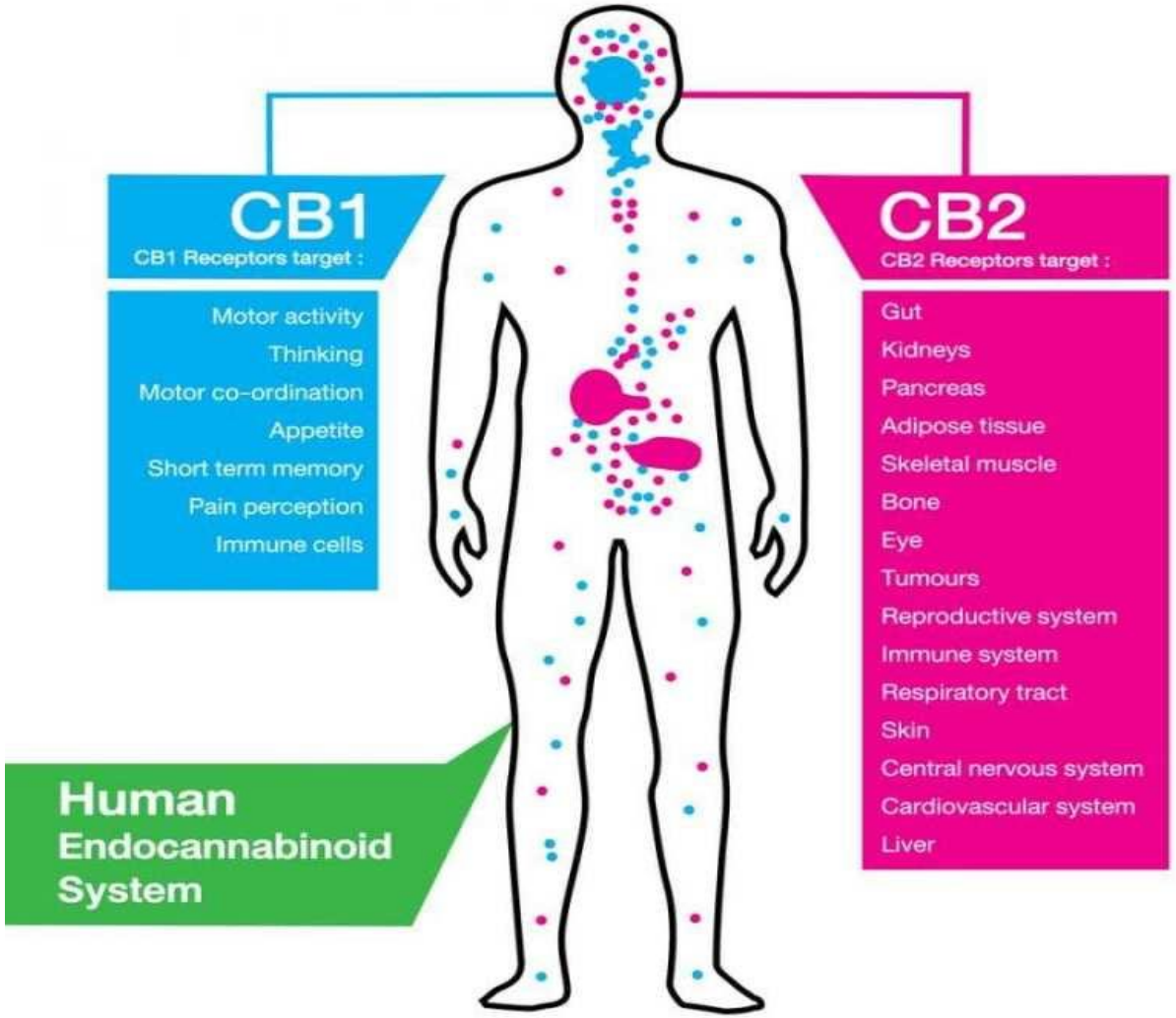
Cannabinoids

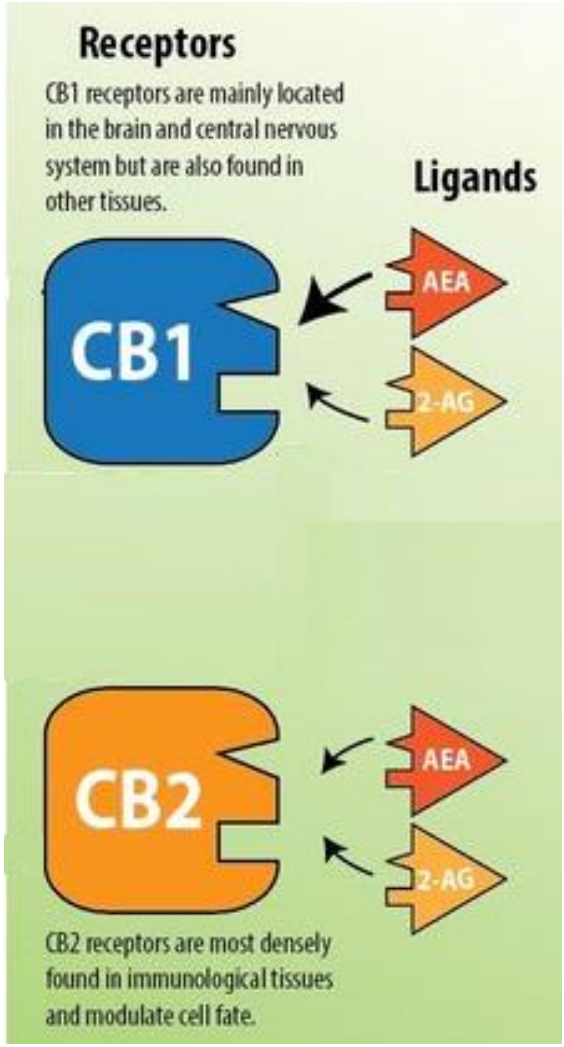
- Endocannabinoids (human tissues, serve as neurotransmitters)
  - Anandamide (AEA) -- brain
  - 2-Arachidonoylglycerol (2-AG) -- peripheral

- Phytocannabinoids (plants)
  - Delta9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)

- Synthetic cannabinoids (laboratories)
  - Pharmaceutical grade: dronabinol; nabilone; CBD; nabiximols
  - Illicit: “spice”

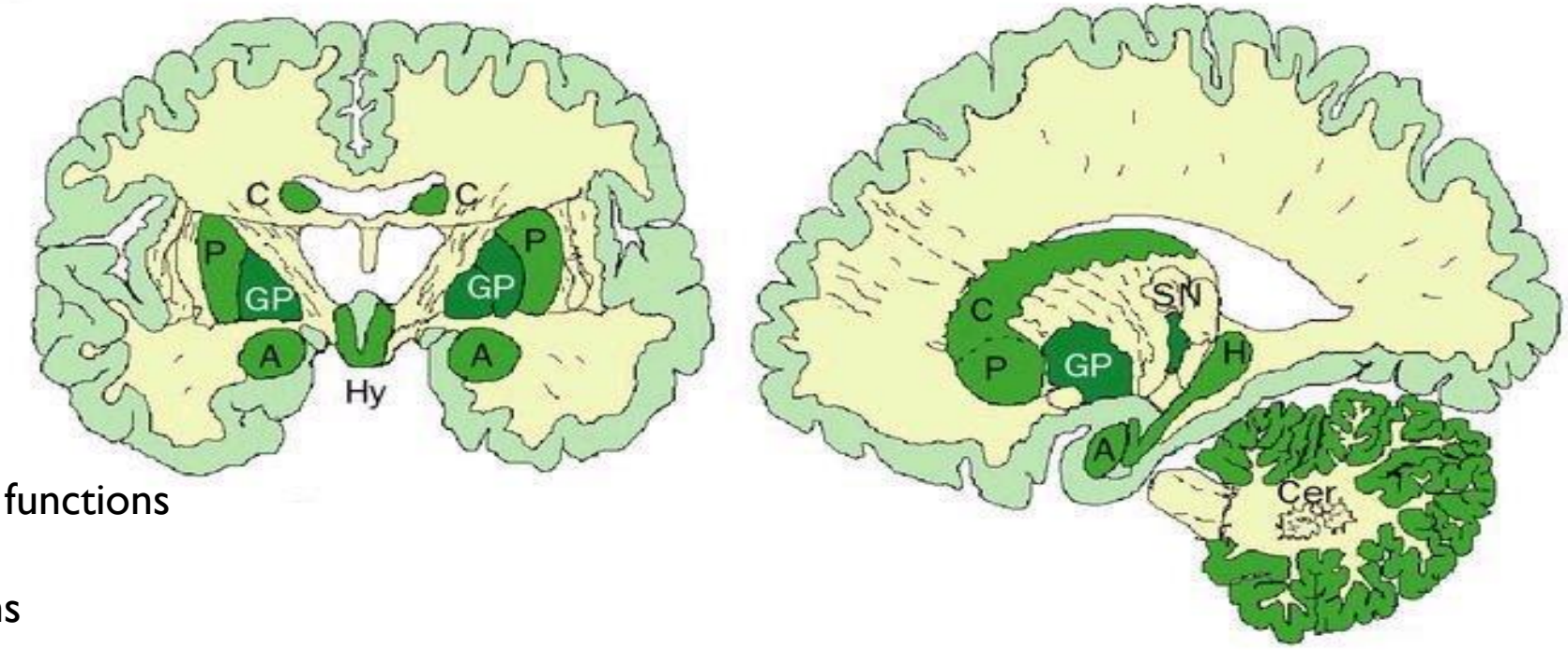
Endocannabinoid System (ECS)



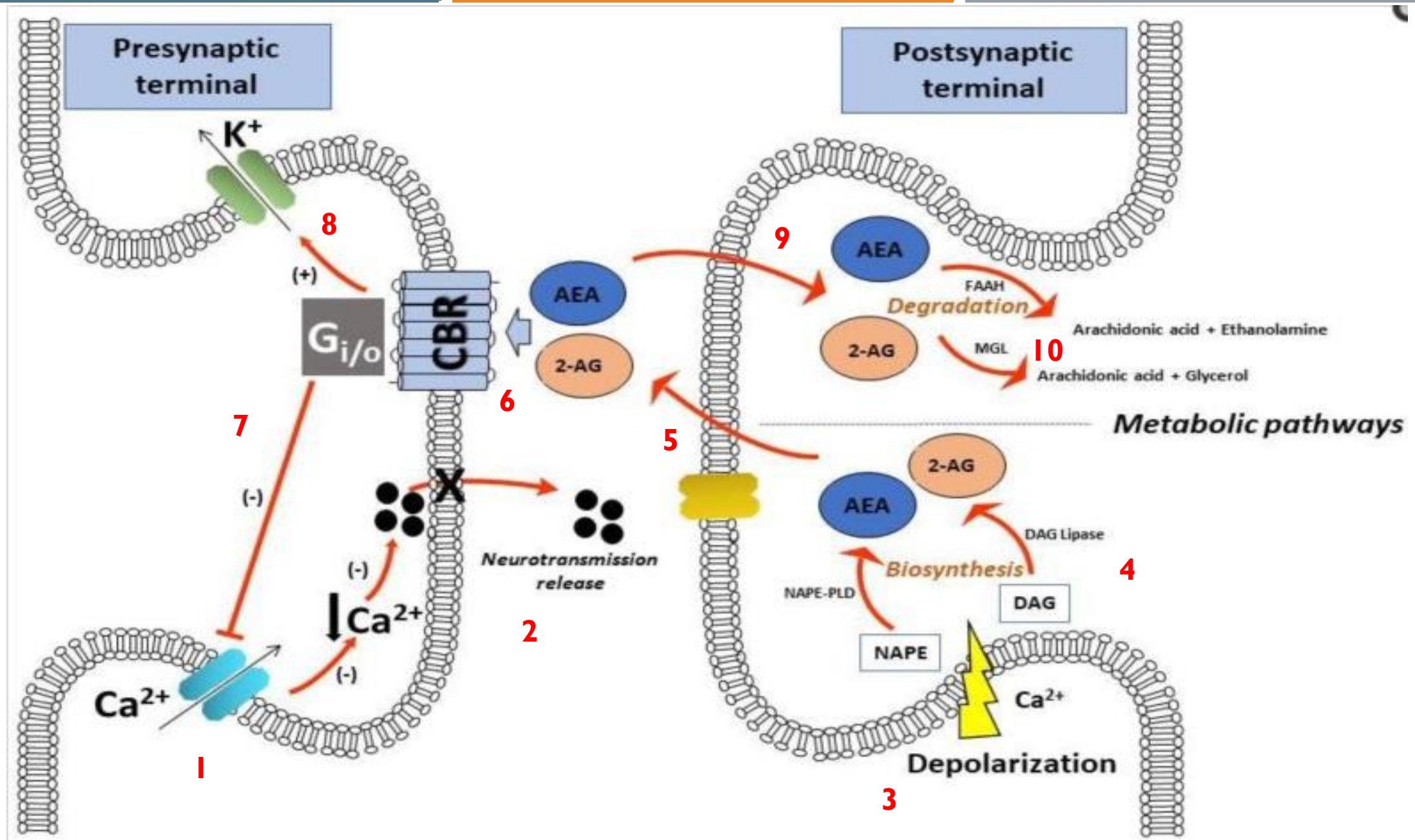


Boggs et al 2018; Fogaca et al 2014

- CB1 receptors are widely expressed and present in glutamatergic and GABAergic neurons
- CB2 also in the brain – ?neuroprotective



CB 1 modulate many CNS physiologic functions
- Metabolism, appetite – hypothalamus
- Reward Systems – nucleus accumbens
- Pain – cortex
- Mood – limbic system
- Movement – cerebellum, basal ganglia
- Posture – basal ganglia


Presynaptic terminal
Postsynaptic terminal
K+
8
(+)
Gi/o
CBR
AEA
2-AG
6
9
AEA
FAAH
Degradation
Arachidonic acid + Ethanolamine
2-AG
MGL
10
Arachidonic acid + Glycerol
Metabolic pathways
7
5
(-)
X
Neurotransmission release
2
2-AG
AEA
DAG Lipase
Biosynthesis
4
NAPE-PLD
DAG
NAPE
(-)
Ca2+
(-)
Ca2+
Ca2+
Depolarization
1
3

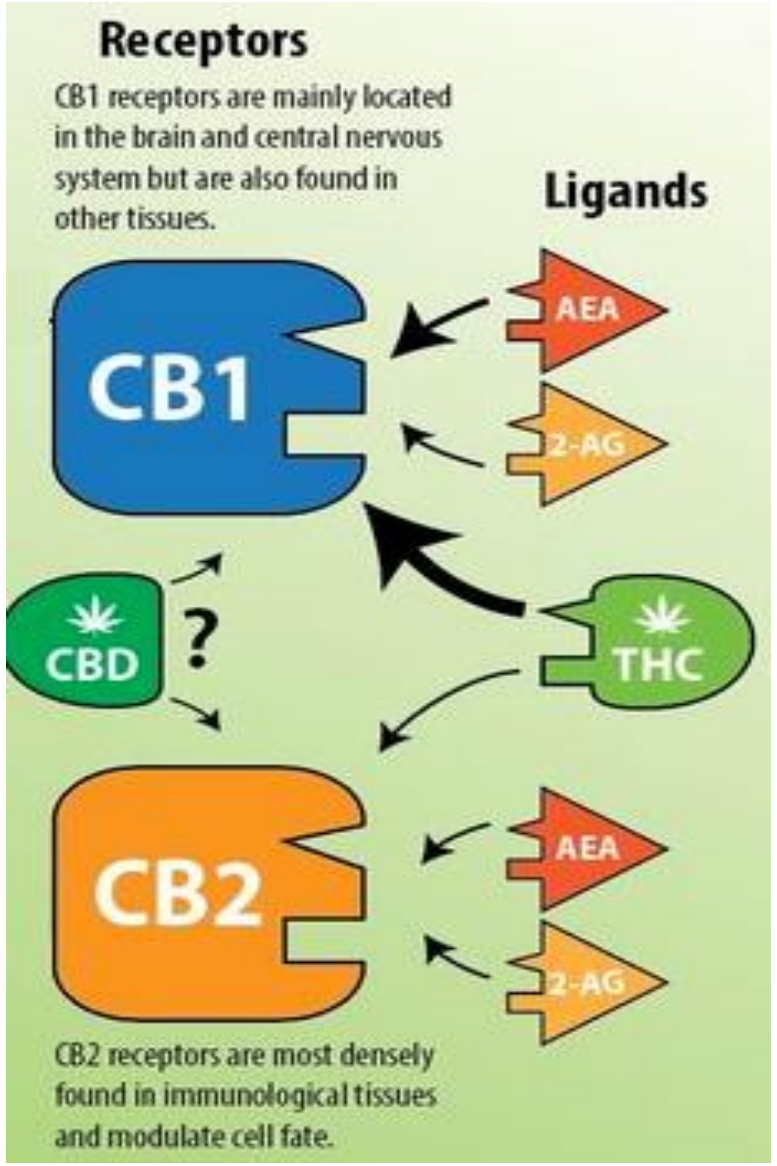
Phytocannabinoids

THC is a partial agonist at:

- CB1 (regions responsible for psychoactive effects)
- CB2 (regions responsible for anti-inflammatory effects)
- Other receptor interactions

The role of CBD at these two receptors is not as well defined.

- may inhibit FAAAH, activate 5HT1, TRPV1, etc



Boggs et al 2018; Fogaca et al 2014

Neuroimaging Studies in Healthy Volunteers

- BOLD hemodynamic responses during fearful face task:
  - CBD:
    - Decreased activation of amygdala, anterior parahypocampal and cingulate gyrus (structures involved in emotions).
  - THC:
    - Increased BOLD response in the left precuneus and bilaterally in the primary sensory cortex (regions involved in memory recollection).

(Fusar-Poli et al 2009).

- Connectivity analysis:
  - CBD decreased forward connectivity with the amygdala and anterior cingulate cortex (neural system involved in anxiety, PTSD).
  - THC enhanced amygdala – prefrontal connectivity (enhancing amygdala's reactivity to unpleasant images).

(Fusar-Poli et al, 2010; Gorka 2015).

Neurobiological Studies in Depression/Anxiety

Studies about alterations of the different components of the ECS in the brain of patients with depression or anxiety-related disorders.

ECS element	Finding (% change)	Brain region	Cohort (n: disease-Ct)	Method/sample	References
CB1 (mRNA)	↑ (60%)	DLPC (BA46)	MDD:Ct 26:46	Gene expression microarray/PMBT	[71]
CB1 (protein)	=	DLPC (BA46)	MDD:Ct 14:14	IHC/PMBT	[72]
	↑ (38%)	DLPC (BA9)	MDD with suicide:Ct 10:10	WB/PMBT	[70]
	↓ (22.1%)	Glial$^+$ cells in ACC GM	MDD:Ct 15:15	IHC/PMBT	[73]
	=	Neurons$^+$ cells in ACC	MDD:Ct 15:15	IHC/PMBT	[73]
	↓ (~8.5–9.5%)	Neurons$^+$ cells in ACC	MDD + SSRI:MDD no-SSRI	IHC/PMBT	[73]
CB1 (density)	↑ (31%)	DLPC (BA9)	MDD with suicide:Ct 10:10	[^{3}H]CP-55,940 binding/PMBT	[70]
CB1 (functionality)	↑ (45%)	DLPC (BA9)	MDD with suicide:Ct 10:10	[^{3}H]CP-55,940 and [^{35}S]GTPγS binding/PMBT	[70]
CB1 (availability)	↑ (19.5%)	Brain-wide	PTSD:Ct 25:23	*In vivo* brain PET scan [^{11}C]OMAR	[100]
	↑ (14.5%)	Brain-wide	PTSD:TC 25:12	*In vivo* brain PET scan [^{11}C]OMAR	[100]
	↑	Amygdala	PTSD:TC:Ct 12:4:4	In vivo brain PET scan [^{11}C]OMAR	[101]
CNR1 gene rs1049353 (A)	↑ activity associated to emotional processing	Bilateral amygdala, putamen and pallidum	MDD(AG) MDD(GG) 13:20	Genetic association study with fMRI/peripheral cells	[80]
CB1-HINT1 (protein)	=	PFC (BA9)	MDD:Ct 24:24	Co-IP/PMBT	[86]
CB1-NR1 C1 (protein)	=	PFC (BA9)	MDD:Ct 24:24	Co-IP/PMBT	[86]
CB2 (mRNA)	=	DLPC (BA46)	MDD:Ct 26:46	Gene expression microarray/PMBT	[71]

↑ Increase; ↓ decrease; = no significant change. ACC: anterior cingulate cortex; BA: Brodmann's area; CB1, CNR1: cannabinoid receptor 1; CB2: cannabinoid receptor 2; Co-IP: co-immunoprecipitation; Ct: control; DLPC: dorsolateral prefrontal cortex; FAAH: fatty acid amide hydrolase; fMRI: functional magnetic resonance image; GM: grey matter; HINT-1: histidine triad nucleotide binding protein 1; IHC: immunohistochemistry; MDD: major depression disorder; PET: positron emission tomography; PFC: prefrontal cortex; PMBT: post-mortem brain tissue; PTSD: posttraumatic stress disorder; SSRI: serotonin selective reuptake inhibitor; TC: trauma controls; WB: western blot.

<u>Variations in</u>:

1. **Receptors**
2. **Metabolizing enzymes**
3. **[Endocannabinoids]**

Inés Ibarra-Lecuea et al, 2018.

Randomized Controlled Trials in Clinical Populations

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Evidence for Use of Cannabinoids in Mood Disorders, Anxiety Disorders, and PTSD: A Systematic Review

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Abstract

Objective: Two primary compounds of the cannabis plant (*Cannabis sativa*), delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), differentially and dose-dependently affect mood and anxiety. In this systematic review, the authors summarize the design and results of controlled trials assessing the effects of THC and CBD on affective disorders, anxiety disorders, and posttraumatic stress disorder (PTSD).

Methods: A keyword search of eight online literature data-bases identified eight randomized controlled trials of defined CBD or THC doses for the target populations.

Results: A 1-month trial of daily THC (up to 3 mg per day) for *DSM-II* anxiety disorder reduced anxiety symptoms, but symptoms were very low throughout the study. Another trial of sequential, single-day, low-dose THC in social anxiety disorder found no symptom changes. Two studies reported that single-dose CBD pretreatment reduced anxiety in laboratory paradigms among individuals with social anxiety disorder. A study of daily CBD for 4 weeks among adolescents with social anxiety disorder indicated modest symptom improvements. One crossover trial involving 10 patients with PTSD showed that THC added to standard pharmacotherapy reduced self-reported nightmares. Two small studies of THC for hospitalized patients with unipolar or bipolar depression found no improvement of depression; instead, anxiety and psychotic symptoms emerged in >50% of patients.

Conclusions: With only eight very small studies, insufficient evidence was found for efficacy of CBD and THC to manage affective disorders, anxiety disorders, or PTSD. Therefore, medical cannabis should not be recommended for treating patients with these disorders. Further research should investigate the safety and efficacy of managing psychiatric disorders with cannabinoids.

The Impact of THC and CBD in Schizophrenia: A Systematic Review

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Background: People with schizophrenia are more likely to develop cannabis use disorder (CUD) and experience worse outcomes with use. Yet as cannabis is legalized for medical and recreational use, there is interest in its therapeutic potential.

Objectives: To conduct a systematic review summarizing the design and results of controlled trials using defined doses of THC and CBD in schizophrenia.

Method: A keyword search of eight online literature databases identified 11 eligible reports.

Results: One placebo controlled trial (13 stable patients without CUD) found that intravenous THC increased psychosis and worsened learning/recall. Two reports of a functional magnetic resonance (fMRI) study of smoked or oral THC in 12 abstinent patients with schizophrenia and CUD found no change in symptoms and cognition, and an amelioration of impaired resting state brain function in areas implicated in reward function and the default mode network. One 4 week trial in acutely psychotic inpatients without CUD (mean age 30 y) found 800 mg CBD to be similarly efficacious to amisupride in improving psychosis and cognition. Two 6 week studies of CBD augmentation of antipsychotics in stable outpatients reported mixed results: CBD 600 mg was not more effective than placebo; CBD 1,000 mg reduced symptoms in a sample that did not exclude cannabis use and CUD. A brain fMRI and proton magnetic resonance spectroscopy study of single dose CBD in a sample that did not exclude CUD and cannabis use found that CBD improved symptoms and brain function during a learning/recall task and was associated with increased hippocampal glutamate.

Discussion: There is substantial heterogeneity across studies in dose, method of drug delivery, length of treatment, patient age, whether patients with cannabis use/CUD were included or excluded, and whether patients were using antipsychotic medication.

Conclusion: There is insufficient evidence for an effect of THC or CBD on symptoms, cognition, and neuroimaging measures of brain function in schizophrenia. At this time, research does not support recommending medical cannabis (THC or CBD) for treating patients with schizophrenia. Further research should examine THC and CBD in schizophrenia with and without comorbid CUD and consider the role of CBD in mitigating symptom exacerbation from THC.

Keywords: cannabis, marijuana, Schizophrenia, psychosis, CBD, THC, legalization, fMRI

Anxiety, Depression, PTSD

Clinical Condition	Author / Year	Title	Type of Study	Intervention	N	Results
Social Anxiety Disorder	Masataka. 2019	Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers With Social Anxiety Disorders	DB RCT	Four weeks of 300 mg **CBD** daily dosing	37	Decrease in anxiety
Social Anxiety Disorder	Bergamaschi et al 2011	CBD reduces the anxiety induced by simulated public speaking in treatment-naive patients SAD.	DB RCT	Single Dose of 600 mg **CBD**	24	Decrease in anxiety
Social Anxiety Disorder	Crippa et al 2011	Neural basis of anxiolytic effects of CBD in generalized social anxiety disorder: a preliminary report.	DB RCT Crossover	Single Dose of 400 mg **CBD**	10	Decrease in anxiety
Anxiety	Fabre et al. 1981	The efficacy and safety of nabilone (a synthetic THC cannabinoid) in the treatment of anxiety.	DB RCT	28 days of 1 mg TID **Nabilone**	20	Decrease in anxiety
Anxiety	Glass et al. 1981	Single-dose study of nabilone in anxious volunteers.	SB controlled Latin-Square	One time 2 mg **Nabilone**, then weekly 0.5-5 mg dosing for 5 weeks	8	No improvement
PTSD	Jetly et al. 2015	The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study.	DB RCT Crossover	7 weeks of 0.5-3 mg **Nabilone**	10	Improvement in nightmares and CGI-C
Unipolar and Bipolar Depression	Ablon et al. 1974	High frequency of dysphoric reactions to tetrahydrocannabinol among depressed patients.	DB RCT	Daily BID **THC** dosing at 0.3 mg/kg	13	No antidepressant effect
Unipolar and Bipolar Depression	Kotin et al. 1973	9 -Tetrahydrocannabinol in depressed patients.	DB RCT Crossover	7 days of 5 mg daily – 20 mg BID **THC** dosing	8	No antidepressant effect

Schizophrenia spectrum

References	Participants	Design	Substance use criteria	Primary outcome measures	Findings	Symptom scores
Studies of THC						
D'Souza et al. (55)	13 medicated outpatients with SCZ or SCZAF (DSM-IV), mean age 44.46 ± 10.4, 76.9% male. 22 HC, mean age = 29 ± 11.6, 63.6% male	RCT double blind, repeated-measures (at least 1 week apart), within-subject cross-over design of single dose intravenous Δ-9-THC 2.5 mg, 5 mg, or PLB	Excluded Lifetime CUD or recent substance abuse (3 m) or dependence (1 yr), other than nicotine. Abstain from all substances, verified via self-report and urine drug screen	Symptoms: PANSS, CADSS, VAS (high, calm and relaxed, tired, panic) Cognitive: HVLT, Gordon CPT, verbal (letter) fluency test Side effects: BAS, SAS, AIMS	THC worsened: verbal learning and recall; positive symptoms; more prominently for patient group; negative symptoms; clinician- and self-related perceptual alterations THC resulted in a trend toward increased VAS ratings of "panic" and "tired" and rigidity, worse AIMS score and akathisia, and increased plasma prolactin and cortisol	PANSS Total, screening: 34.1 ± 9.4 Post THC scores not provided
Fischer et al. (56)	12 medicated outpatients with SCZ and CUD (DSM-IV-TR), mean age [smoked cannabis 36.2 ± 9.6; THC capsule 32.17 ± 8.32, male), 583% male 12 HC, mean age 33.5 ± 7.8, 75% male	RCT double blind, parallel group study of smoked 3.6% THC cannabis cigarette immediately prior to scan (n = 6), or 15 mg THC capsule 3 h prior to scan (n = 6) Two scan sessions (T1, no drug; T2, drug) at least 1 week apart	Required to have a CUD and recent cannabis use. Excluded other substance use disorders. Abstain from all substances, except nicotine and caffeine >7 days prior to scan verified via TLFB, urine screens, plasma THC	Symptoms: PANSS, VAS (high, liking and craving), CWS, MCQ Imaging: fMRI resting state functional connectivity of BRC	Reduced connectivity at BL in patients between nucleus accumbens and prefrontal cortical BRC regions (i.e., anterior prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex). Both oral and smoked THC incr connectivity between these regions, which correlated with incr in plasma THC levels	No change after THC (PANSS scores not reported)
Whitfield-Gabrieli et al. (57)	Same as Fischer et al. (56)	Same as Fischer et al. (56)	Same as Fischer et al. (56)	Symptoms: PANSS, VAS (high, liking and craving), CWS, MCQ Cognition: LNS Imaging: fMRI resting state functional connectivity of DMN	At BL, patients had DMN hyperconnectivity that correlated with positive symptoms, and reduced anticorrelation between DMN and ECN. THC reduced DMN hyperconnectivity and increased DMN-ECN anticorrelation. The magnitude of anticorrelation in controls, and in patients after THC, correlated with working memory)	PANSS Positive Score BL—T1 (13.82 ± 3.19) or Pre-drug—T2 (12.91 ± 3.21) No change after THC (PANSS scores not provided separately from smoked cannabis and oral THC and not reported for T2 after THC)

Schizophrenia spectrum

References	Participants	Design	Substance use criteria	Primary outcome measures	Findings	Symptom scores
Studies of CBD						
Zuardi et al. (57)	3 unmedicated inpatients with treatment-resistant SCZ (DSM-IV), age 21–22 years, all male	Case Series of 6 week CBD titration up to 1,280 mg/day, PLB lead in and washout, then switch to olanzapine	None reported	Symptoms: BPRS, PANSS-N Functional: CGI Side effects: BAS, SAS, UKU Side effect Rating Scale	CBD 1,280 mg/day associated with: Pt 1—trend toward improved BPRS (general, positive, and negative symptoms); Pt 2—no benefit; Pt 3—"very minimal improvement" of positive and negative symptoms In two patients, symptoms worsened after CBD discontinued. No side effects reported	*BPRS Total*: Patient 1: PLB 19, CBD 10 Patient 2: PLB 30, CBD 28 Patients 3: PLB 29, CBD 26 PANSS-N scores not reported
Hallak et al. (58)	28 outpatients with SCZ (DSM-IV), all BPRS scale scores <2, at least 18 years of age, 64.3% male	Single dose non-randomized, double blind, parallel group study of CBD augmentation 300 mg (*n* = 9) or 600 mg (*n* = 9) or PLB (*n* = 9)	History of substance abuse or adverse reaction to marijuana were excluded	Symptoms: BPRS, PANSS Cognition: SCWT Other: electrodermal responsiveness	PLB and 300 mg CBD: less SCWT interference errors during 2nd session, but only a trend for 600 mg CBD group, indicating worse selective attention No group differences in electrodermal responsiveness or symptoms, but no analysis of within-group symptom change reported	*BPRS Total*: PLB: BL 8.6 ± 4.1, drug 7.9 ± 5.76 CBD 300 mg: BL 11.3 ± 7, drug 10.9 ± 6; CBD 600 mg: BL 8.9 ± 5.1, drug 8.2 ± 5.9 *PANSS Total*: PLB: BL 21.9 ± 6.9, drug 21.9 ± 7.2; CBD 300 mg: BL 23.6 ± 9.4, drug 23.4 ± 9.6 CBD 600 mg: BL 20.2 ± 7.7, drug 19.1 ± 7.0
Leweke et al. (59)	42 acutely ill unmedicated inpatients with SCZ (DSM-IV), BPRS Total ≥ 36 and BPRS THOT ≥ 12, 18–60 years of age (CBD mean 29.7 ± 8.3 yr, amisulpride mean 30.6 ± 9.4 yr, 82.1% male	4 week RCT, double blind, parallel group study of CBD augmentation 800 mg (*n* = 20) or amisulpride 800 mg (*n* = 19), 1 week titration and 3 weeks treatment (modified intent-to-treat)	History of SUD or positive urine drug screen (including cannabinoids) were excluded	Symptoms: BPRS, PANSS Functional: CGI Side effects: SAS, EPS	BPRS and PANSS (total, positive, negative, general scores) improved over time in both groups. CBD group had less: extrapyramidal symptoms, weight gain, and prolactin elevation. Serum anandamide levels were higher in CBD than amisulpride group, with extent of increase associated with PANSS Total score improvement	PANSS Total Scores CBD score at BL 91.2 (14.0) Changed—18.8 (10.7) on day 14, −30.5 (16.4) on day 28 Amisulpride score at BL 95.9 (17.1) Changed—18.8 (19.9) on day 14 −30.1 (24.7) day 28
Leweke et al. (60)	Same participants as above 42 acutely ill unmedicated inpatients with SCZ (DSM-IV), BPRS Total ≥ 36 and BPRS THOT ≥ 12, 18–60 years of age (CBD mean 29.7 ± 8.3 yr, amisulpride mean 30.6 ± 9.4 yr, 82.1% Male	Same as above 4 week RCT, double blind, parallel group study of CBD augmentation 800 mg (*n* = 20) or amisulpride 800 mg (*n* = 19), 1 week titration and 3 weeks treatment (modified intent-to-treat)	Same as above History of SUD or positive urine drug screen (including cannabinoids)	Symptoms: BPRS, PANSS Functional: CGI Cognition: Visual Backward Masking Task, CPT, LNS, SOPT, DRT, AVLT, RCFT, Digit Symbol, TMT, Verbal Fluency Task	From pre- to post-treatment, both groups improved in visual memory processing speed CBD improved sustained attention and visuomotor coordination Amisulpride improved working memory performance Changes in neurocognitive performance were not systematically associated with symptom improvements nor change in serum anandamide	Differences in cognitive improvement not statistically significant after correction for multiple tests Visual memory (CBD: 0.49, $p = 0.015$ vs. AMI: 0.63, $p = 0.018$); processing speed (CBD: 0.41, $p = 0.004$ vs. AMI: 0.57, $p = 0.023$). Sustained attention (CBD: 0.47, $p = 0.013$ vs. AMI: 0.52, $p = 0.085$); visuomotor coordination (CBD: 0.32, $p = 0.010$ vs. AMI: 0.63, $p = 0.088$). SOPT–AMI: 0.53, $p = 0.043$ vs. CBD: 0.03, $p = 0.902$ and LNS–AMI: 0.67, $p = 0.017$ vs. CBD: 0.08 $p = 0.755$)

Schizophrenia spectrum

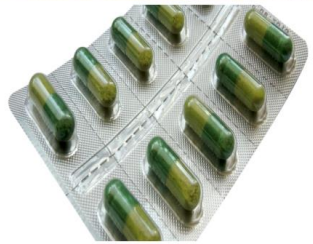
References	Participants	Design	Substance use criteria	Primary outcome measures	Findings	Symptom scores
Boggs et al. (61)	36 medicated outpatients with SCZ (DSM-IV-TR), 18–65 years of age [CBD mean 48.4 ± 9.3; PLB mean 46.4 ± 9.5], 66.7% to 72.2% male	6 week RCT, double blind, parallel group study of CBD augmentation 300 mg twice daily (n = 20) or PLB (n = 19)	Diagnosis of substance abuse within 3 months or dependence within 6 months of participation (other than nicotine) were excluded	Symptoms: PANSS Cognition: MCCB Side effects: BAS, SAS, AIMS, UKU Side Effect Rating Scale	No difference in reduction in PANSS scores (Total, General, Positive, Negative) over time. PLB but not CBD group had small improvement on MCCB (Composite score, Reasoning and Problem Solving domain scores). CBD group had greater sedation compared to PLB	*PANSS* screening *visit scores*: *Total*: CBD 76.6 ± 17, PLB 82.7 ± 8.8 *Positive*: CBD 18.8 ± 4.7, PLB 20.6 ± 3.8 *Negative*: 20.7 ± 4.6, PLB 20.9 ± 4.7 *General*: 37.1 ± 10.3, PLB 41.2 ± 5.6
McGuire et al. (62)	88 medicated outpatients with SCZ or related psychotic disorder (DSM-IV), PANSS score < 60 at screening excluded, 18–65 years of age (mean 40.6 ± 11.69), 58% male	6 week RCT, double blind, parallel group study of CBD augmentation 500 mg BID (n = 43) or PLB (n = 45)	Alcohol or substance use history allowed; use of alcohol, cannabis or other substances not prohibited during study; positive baseline urine THC test in 1 CBD and 2 PLB group patients	Symptoms: PANSS, SANS Functional: GAF, CGI-I, CGI-S Cognition: BACS Side effects: SAS	CBD group had greater reduction of positive symptoms and more likely to be rated by treating clinician as having improved and have less severe illness than PCB. CBD showed trend for greater improvement in overall level of functioning, cognition (BACS composite score and executive function domain), and motor speed. No group difference for adverse events or side effects	*PANSS Total*: CBD: BL 79.3 ± 12.5, end of Tx 68.1 ± 14.8 PLB: BL 80.6 ± 14.9, end of Tx 71.9 ± 15.5 *PANSS Positive*: CBD: BL 18.0 ± 3.9, end of Tx 14.8 ± 4.0; PLB: BL 17.5 ± 3.3, end of Tx 15.7 ± 3.7
O'Neill et al. (63)	15 outpatients (14 medicated) with SZ, SCZAF, or Brief Psychotic Disorder (DSM-IV) within 5 years of diagnosis, mean age 27.73 ± 4.61 years, 66.7% male 19 HC, mean age 23.89 ± 4.15 years, 57.9% male	RCT double blind, repeated-measures (1 week apart), within-subject cross-over design of single dose 600 mg oral CBD or PLB	Allowed: current cannabis abuse, dependence, or use Excluded: Current alcohol or substance dependence; or intoxicated or positive urine drug screen on the day of scanning. No alcohol for 24 h or caffeine for 12 h before sessions. No drugs except cannabis for 2 weeks prior to scan	Symptoms: PANNS, STAI-S Imaging: fMRI verbal paired associate learning task completed 3 h after CBD or PLB (13 patients completed both scans)	CBD associated with trend toward reduced median PANSS Total Compared to HC, patients on PLB had abnormal activation within prefrontal region during verbal encoding, and abnormal prefrontal and mediotemporal activation as well as greater hippocampal-striatal functional connectivity during recall. CBD resulted in partial normalization of activation in these regions, as well as reducing hippocampal-striatal hyperconnectivity	PANSS Total: PLB: T1 48.8 ± 18.9, T3 44.6 ± 18.07 CBD: T1 51 ± 20, T3 41.53 ± 11 *PANSS Positive*: PLB: T1 12.53 ± 5.62, T3 11.67 ± 4.99 CBD: T1 12.93 ± 5.72, T3 10.73 ± 3.41 *PANSS Negative*: PLB: T1 12.4 ± 6.4, T3 11.53 ± 6.06 CBD: T1 12.47 ± 6.56, T3 10.2 ± 3.05 Note: T1 is 60 min pre-drug and T3 270 min post-drug administration
O'Neill et al. (64)	Same participants as above 15 outpatients (14 medicated, 1 non-compliant) with SZ, SCZAF, or Brief Psychotic Disorder (DSM-IV) within 5 years of diagnosis, Mean age 27.73 (4.61, 66.7% male)	Same as above Double-blind, randomized, placebo-controlled, repeated-measures (1 week apart) within-subject cross-over design 600 mg oral CBD or PLB	Same as above Allowed: current cannabis abuse, dependence or use	Symptoms: PANSS Imaging: ^{1}H-MRS spectra were acquired 180 min after CBD or PLB administration (13 patients completed both scans)	CBD associated with greater improvement in PANSS Total and greater hippocampal glutamate levels compared to PLB ($p = 0.035$). An adjusted multivariable model showed an inverse predictive relationships between hippocampal glutamate and post intervention PANSS ($p = 0.047$), but no relationship to CBD group	PANSS symptom scores Same as above

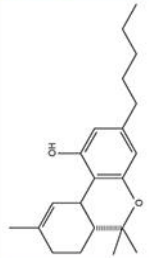
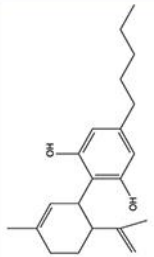
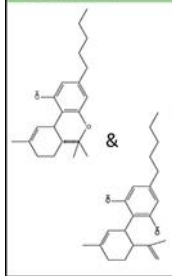
What we know

- THC:
  - Euphoria
  - Memory impairment (Englund, 2013)
  - Anxiety (Blessing, 2015)
  - Perceptual disturbances / paranoid thoughts (Englund, 2013)
  - Earlier onset, worse prognosis in Schiziophrenia

- CBD
  - Opposes THC effects (Nieserc, 2013)
    - Antipsychotic effects in Schizophrenia / partial D2 agonist ~ aripiprazole (Hahn, 2018)
    - May improve cognitive functioning in Schizophrenia
  - Anti-inflammatory
  - Anti-anxiety / 5HT1A agonist (Hill, 2012)
  - Anti-epileptic effects

What we don't know



	Cannabinoid inhibits/ induces	Medications affected	Effect	Cannabinoid metabolised by	Causal medications	Effect
THC only 	induces **CYP1A2**	Amytriptyline, Clozapine, Chlorpromazine, Cyclorpromazine, Duloxetine, Haloperidol, Naproxen, Olanzapine, Warfarin	Overall increase in medication metabolism - decreases serum concentrations.	**CYP2C9** (breaks down THC)	Amiodarone, Cimetidine, Co-trimoxazole, Fuoxetine, Fluconazole, Fluvoxamine, Metronidazole, Sodium valproate	Overall reduction in THC metabolism, leading to higher serum THC concentration
				CYP2C19 (oxidises THC)	Topiramate	Overall reduction in THC metabolism, leading to higher serum THC concentration
CBD only 	inhibits **CYP2D6†** (metabolises antidepressants, antipsychotics, pain medication)	Selective serotoin reuptake inhibitors (SSRIs), Tricyclic antidepressants, Antipsychotics, Beta blockers and Opioids	Overall reduction in medication metabolism - increases serum concentrations			
	† NB CBD can interact with epilepsy medicines such as Clobazam, causing Clobazam serum levels to increase; concomitant treatment requires careful monitoring.					
THC and CBD 	inhibits **CYP3A4** (THC and CBD inhibit at higher concentractions; metabolises 25% of all medications)	Calcium channel blockers, Macrolides, Benzodiazapines, Antihistamine, Statins, Anti-retrovirals, Sildenafil, Haloperidol, Cyclosporine, Oestradiol, Progesterone	Overall reduction in medication metabolism - increases serum concentrations	**CYP3A4*** (breaks down THC and CBD)	Ketoconazole, Itraconazole, Ritonavir, Clarithromycin, Cyclosporine, Erythromucin, Verapamil, Sodium valproate	Overall reduction in CBD metabolism, leading to higher serum CBD concentration
	inhibits **CYP2C family** (blocked by both CBD and THC at low concentrations)	Repaglinide, Clecoxib, Warfarin, Lansoprazole, Omeprazole, Diclofenac, Ibuprofen, Naproxen, Diazepam, Citalopram		* NB Rifampacin, Carabamazepine, Phenytoin, Phenobarbitol and St. John's Wort can induce or amplify te CYP3A4 pathway, thus speeding up the metabolism/breakdown of THC or CBD		

Conclusions

1. Interest in use of cannabinoid products is on the rise, paralleled by a general perception of low risk of harm.

2. The Endocannabinoid System certainly is involved in the course of psychiatric conditions.

3. A significant knowledge gap exists in our understanding of the cannabinoids' therapeutic efficacy, and there is some evidence of harm for certain psychiatric conditions.

4. Existing, pharmaceutical grade, FDA-approved products should be used in future rigorous controlled trials.