

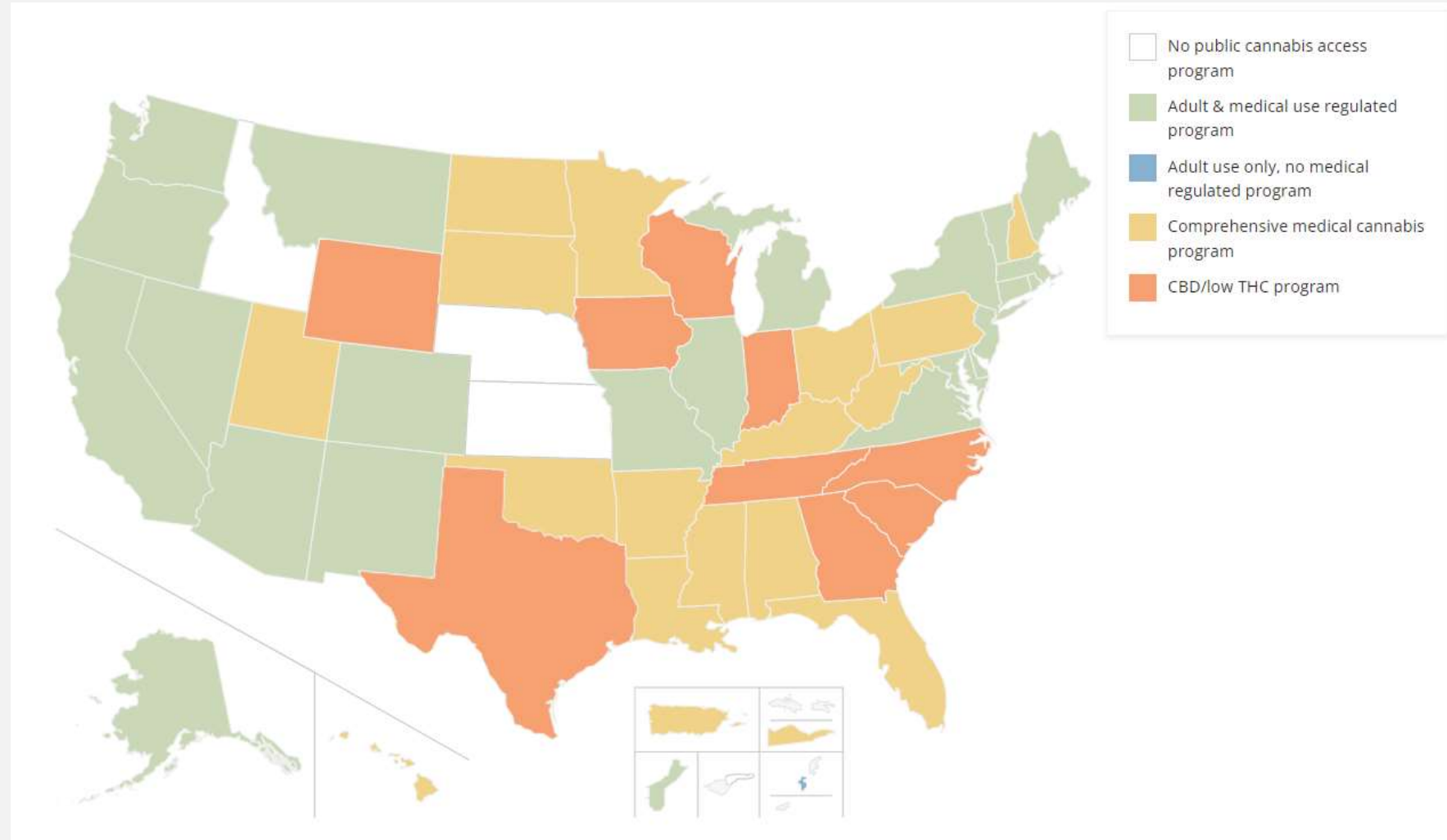
CANNABIS AND ANXIETY AND MOOD DISORDERS (AMD)

Melissa Quill, PA-S

May 9, 2023

EPIDEMIOLOGY

- Cannabis use is widespread and becoming more common
 - NSDUH Survey 2019: 18% had used in past year, 6% in past month (doubled over past 20 years)
- Public perceptions and attitudes shifting



MECHANISM OF EFFECT

- Human endocannabinoid system regulates mood, cognition, appetite, sleep
 - Interactions between endogenous cannabinoids and G-protein receptors (CB1 and CB2)
 - THC and CBD interact with CB1
 - Deficiency of cannabinoid production in anxiety + mood disorders?
- Biphasic Effect
 - Low doses versus higher doses act on CB1 receptors in different areas of brain
 - Animal studies with mixed results, but generally:
 - Low dose: anxiolytic
 - High dose: anxiogenic
 - Lack of human studies on dosing

Mammen G, Rueda S, Roerecke M, Bonato S, Lev-Ran S, Rehm J. Association of Cannabis With Long-Term Clinical Symptoms in Anxiety and Mood Disorders: A Systematic Review of Prospective Studies. *J Clin Psychiatry*. 2018;79(4):17r11839. Published 2018 Jun 5. doi:10.4088/JCP.17r11839

Sharpe L, Sinclair J, Kramer A, de Manincor M, Sarris J. Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. *J Transl Med*. 2020;18(1):374. Published 2020 Oct 2. doi:10.1186/s12967-020-02518-2

CBD VS THC

- THC
 - Main psychoactive component
 - May overstimulate CB1 receptors = anxiety, paranoid, memory impairment, sedation, subsequent addiction
 - Dose-dependent, low doses may have more anxiolytic effect
 - Non-users: 5 mg THC associated with more increase in anxiety scores than 2.5 mg THC
 - Frequent users: higher dose = more anxiety, but smaller increases than non-user controls
- CBD
 - Non-psychoactive
 - “Bred out” of street cannabis
 - May mitigate THC – low affinity for CB1 receptors may prevent THC acting at full strength
 - May have its own antianxiety property (interactions with other mood regulatory receptors)

Mammen G, Rueda S, Roerecke M, Bonato S, Lev-Ran S, Rehm J. Association of Cannabis With Long-Term Clinical Symptoms in Anxiety and Mood Disorders: A Systematic Review of Prospective Studies. *J Clin Psychiatry*. 2018;79(4):17r11839. Published 2018 Jun 5. doi:10.4088/JCP.17r11839

Sharpe L, Sinclair J, Kramer A, de Manincor M, Sarris J. Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. *J Transl Med*. 2020;18(1):374. Published 2020 Oct 2. doi:10.1186/s12967-020-02518-2

ASSOCIATION OF CANNABIS USE WITH LONG-TERM CLINICAL SYMPTOMS OF AMD

- Systematic review of cohort-based longitudinal studies of adults who met criteria for anxiety or mood disorder at baseline
- 12 studies (total sample = 11,959 individuals)

Disorder	# of Studies	Key Findings
PTSD	4	3 of 4: higher symptom severity 1 of 1: no association
Panic Disorder	1	More severe depressive symptoms No correlation with anxiety symptoms
Bipolar	5	5 of 5: More severe symptoms, less remission, more recurrence, more cycling
Depressive	2	2 of 2: Higher symptom severity

Limitations:

- Varying degree of cannabis use (any use in past week/month/six months, CUD, etc)
- Cannabis not necessarily the primary variable being assessed (ie other anxiety treatments focus of study)
- Did not measure dose of cannabis consumer (subjective frequency)
- Inpatient vs outpatient setting
- Varying control for confounders

IMPACT OF CANNABIS ON ILLNESS ONSET AND COURSE, AND ASSESSMENT OF THERAPEUTIC POTENTIAL

- Systematic review of longitudinal studies from 1990 to 2018
- 47 studies (32 reported on illness onset, 9 reported on illness course, 6 reported on cannabinoid therapeutics)

Disorder	Cannabis Impact on Onset	Cannabis Impact on Course	Cannabis as Therapeutic Agent
Bipolar	7 studies (N= 57.248) Varied results	5 studies (N = 3443) More severe symptoms of mania and psychosis, lower remission, increased cycling	1 study (N =2) Ineffective for treating hospitalized patient with mania and psychotic features
Depression	20 studies Varied results	1 study More depressive symptoms (anhedonia, sleep disturbance, psychomotor), no difference in remission, functional impairment, suicidality	0 studies
Anxiety Disorders	12 studies Varied results	2 studies Trend toward decreased remission, but not statistically significant	1 study (N = 24) One time dose beneficial for public speaking in those with social anxiety
PTSD	1 study (N = 674) Increased odds of developing PTSD	1 study (N = 2276, inpatient US veterans) More severe symptoms	3 studies Nabilone may improve nightmares (but adverse events may preclude use)

A NOTE ON DELTA-8 THC...

- Marketed as less potent than delta-9 THC
 - Lower affinity for CB1 receptors than delta-9
 - One study: of 51 delta-8 THC products, 76% had delta-9 THC levels above legal limit of 0.3%
- Available for purchase on the internet, less regulated
 - Confusing legality: legal at federal level, but on DEA controlled substance list
 - Within batches, may be significant variability in delta-8 levels (one study reported up to 40% difference than labeled value)
- Most research is anecdotal or done on animal models
- Lack of research on doses

PATIENT COUNSELING

- Many factors – relative amounts of THC vs CBD, acute vs chronic effect on symptoms
 - Whole cannabis has higher THC:CBD ratio
 - THC content in marijuana flower is getting higher (212% increase between 1995 to 2015)
 - Street cannabis versus more-regulated may have different effects
- There may be more benefit to CBD-containing substances than THC
- Past use may impact effects
 - Possibly due to increased tolerance -> higher dose -> anxiogenic effect
 - Conversely, some studies reported higher anxiogenic effects among infrequent or non-users
- Caution if bipolar disorder, depression, PTSD

REFERENCES

Gorelick DA. Cannabis use: Epidemiology, pharmacology, comorbidities, and adverse effects. UpToDate. December 1, 2022. Accessed May 8, 2023.

State Medical Cannabis Laws. National Conference of State Legislatures. April 24, 2023. Accessed May 8, 2023.

Mammen G, Rueda S, Roerecke M, Bonato S, Lev-Ran S, Rehm J. Association of Cannabis With Long-Term Clinical Symptoms in Anxiety and Mood Disorders: A Systematic Review of Prospective Studies. *J Clin Psychiatry*. 2018;79(4):17r11839. Published 2018 Jun 5. doi:10.4088/JCP.17r11839

Sharpe L, Sinclair J, Kramer A, de Manincor M, Sarris J. Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. *J Transl Med*. 2020;18(1):374. Published 2020 Oct 2. doi:10.1186/s12967-020-02518-2

Botsford SL, Yang S, George TP. Cannabis and Cannabinoids in Mood and Anxiety Disorders: Impact on Illness Onset and Course, and Assessment of Therapeutic Potential. *Am J Addict*. 2020;29(1):9-26. doi:10.1111/ajad.12963

LoParco CR, Rossheim ME, Walters ST, Zhou Z, Olsson S, Sussman SY. Delta-8 tetrahydrocannabinol: a scoping review and commentary. *Addiction*. 2023;118(6):1011-1028. doi:10.1111/add.16142