Cannabinoids and Mental Health

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https://upload.wikimedia.org/wikipedia/commons
Objectives

• Describe the underlying cause of clinical depression and the primary mechanism for current treatments
• Explain the possible uses of cannabinoids or CB1 antagonists as antidepressants, and cautions
• Discuss the inconsistencies related to the effects of cannabinoids on psychoses as they relate to known antipsychotic effects
• Explain how cannabinoid receptors are involved in anxiety responses
• Outline the animal studies that support the use of cannabinoids to treat anxiety disorders
• Discuss the problems with current treatment of PTSD
• Give evidence to support the use of cannabis in treatment of PTSD
Psychiatric illness

- Psychosis
  - Schizophrenia
    - Mania
    - Depression
  - Bipolar

- Neurosis
  - OCD
  - Phobia
  - Anxiety
  - PTSD

Psychosis: Pt is not aware of illness and refers to treatment
Neurosis: Less serious and insight present
(Obsessive compulsive disorder, Post traumatic stress disorder)
Cannabinoids and Depression
Normal Mood Requires a Balance between Several Neuronal Signaling Pathways
Cannabis Effects Overlap with Treatments for Mental Disorders and Drugs of Abuse
Mental Disorders are Associated with Dysfunctional Neurotransmitters

- Parkinson-like Symptoms
  - slow reaction time
  - anergia
- Anhedonia
  - “pleasure center” dysfunction
- Depression & Craving
- OCD-like Symptoms
  - obsessive thoughts
  - compulsive behaviors
- Impulsivity
  - suicide/aggression
  - susceptibility to “cue triggers”
Antidepressant Mechanism

• Problem: too little NE and 5-HT (primarily 5-HT1 receptor activity)
• Most effective agents block reuptake of serotonin and/or norepinephrine
• **Fluoxetine (Prozac™)**
  - SSRI (selective serotonin reuptake inhibitor)
• **Duloxetine (Cymbalta™)**
  - SNRI (serotonin norepinephrine reuptake inhibitor)
Many Classes of Antidepressants

- Most Antidepressants act by raising levels of Serotonin, Norepinephrine, or Dopamine
- They are NOT receptor agonists that could result in tolerance
- Side effects mostly mild: nausea/headache and reduced libido
Do Cannabinoids have Antidepressant Effects?

- CB1 receptor antagonist activity
- Direct agonist effects on 5-HT1 receptors
- Effects on other receptor signaling
CB1 receptor antagonists may stimulate neurotransmitter release.
CB1 antagonist stimulates neurotransmitter release in Rat brains

- CB1 antagonist induced DA release in the prefrontal cortex (mPFC)
- Cortex levels of DA, NA and 5-HT were also increased

SR, CB1 antagonist; DA, dopamine; NA, norepinephrine; 5-HT, serotonin

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CB1 receptor antagonists

• CB1 receptor antagonists show changes in neurochemicals similar to other antidepressants
• CB1 receptor antagonists show effects in animal models of depression
• What about CBD? It’s not a great antagonist (low binding affinity).
A Cautionary Tale

Clinical CB1 antagonist: Rimonabant

• Rimonabant is a selective CB1 blocker
  – Developed by Sanofi-Aventis

• Clinically approved for treatment of obesity in Europe in 2006…..withdrawn in 2008
  – Never approved by US FDA

• Caused depressive symptoms in 10% of patients, 1% with suicide ideation
CBD has slight antagonist activity at CB1 receptors and potential agonist activity at other receptors.

Could these interactions explain the effects of CBD and cannabis on mental health?
CBD is a weak agonist at 5-HT1 receptors

- CBD displaced the 5-HT1 agonist 8-OH-DPAT from 5-HT$_{1A}$ receptors in cultured cells transfected with the receptor.
- CBD caused an increase in Gi activity and a decrease in cAMP formation.

*Agonistic properties of cannabidiol at 5-HT1a receptors.*
*Russo EB$^1$, Burnett A, Hall B, Parker KK.*
Increasing CBD reduces restraint stress response in animals

- Animal restraint leads to increased blood pressure and heart rate
- CBD reduced these responses
- CBD effect was reversed by a 5-HT1 receptor antagonist

CBD antidepressant effects through 5-HT1 receptors

Clicker Question: What would be a primary concern in using CBD as a 5-HT1 agonist to treat depression?

A. It might cause psychoses like LSD
B. It might cause downregulation of receptors resulting in tolerance
C. It might cause migraine headache
D. It might cause nausea
Serotonin Actions on CNS Neurons

- Anti-migraine
- Anxiolytic
- Anti-psychotic
- Anti-nausea

Block reuptake: antidepressant
Clinical Trials for CBD in Depression: Systematic reviews

• CBD trials (Nabiximols)
  – Three separate trials, none favored treatment over placebo
Not much known about whole plant cannabis and depression except Negative Associations

- Heavy cannabis consumers more likely to report thoughts of suicide
- Cannabis consumers are more likely to complete suicide
- Regular cannabis use is associated with an increased risk of developing social anxiety
Cannabinoids and Psychosis
Psychosis: Schizophrenia

• Positive Effects
  – Delusions
  – Excess D2 receptor signaling

• Negative Effects
  – Depression and withdrawal
  – Excess 5-HT2 receptor signaling or too little 5-HT1 signaling

• Treatment
  – D2 receptor blockers
  – Selective 5-HT2 receptor blockers
Current Antipsychotic

• Aripiprazole (Abilify™)
  – Newest antipsychotic (FDA 2002)
  – D2 and 5HT-1 receptor partial agonist/antagonist
  – Also approved for mania and major depression
  – #1 drug in sales in 2014: heavily marketed for depression.
Endocannabinoid System in Psychoses

- Endocannabinoids affect neural development
- CB1 receptors are altered in psychotic patients
- Anandamide levels are higher in psychotic patients
CBD treatment for Psychosis: Systematic Review

- CBD: 2 trials vs. amisulpride, huge variability in responses, so no significance

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<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Measure</th>
<th>Mean difference (95% CI)</th>
<th>P value</th>
<th>CBM</th>
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<td>Amisulpride</td>
<td>Mental health Brief Psychiatric Rating Scale Follow-up 4 weeks</td>
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<td>Tic severity Shapiro Tourette Syndrome Severity Scale (0-6) Follow-up 6 weeks</td>
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Note: Amisulpride is an antipsychotic. It is not a US drug; acts by blocking D2/D3 and possibly 5-HT7 receptors
Cannabis Negative Effects on Psychoses

- Cannabis produces symptoms of psychoses
- Heavy use in young adolescents is associated with increased risk of developing schizophrenia

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)
Evidence against Negative Effects of Cannabis on Psychoses

There is moderate evidence of no statistical association between cannabis use and:

• Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

• An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
• The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
• The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
• Increased symptoms of anxiety (near daily cannabis use) (12-9)
• Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)
Cannabinoids and Anxiety
Anxiety symptoms can overlap with depression symptoms

- More sympathetic responses
- More role for the amygdala—worrying
- More overall increase in neuronal activity
- Treatment is with SSRI or with benzodiazepines
Most prescribed anxiolytics are Benzodiazepines

- **Diazepam** (Valium)
- Lorazepam (Ativan)
- Clonazepam (Klonopin)
- Triazolam (Halcion)
- Chlordiazepoxide
  - Alprazolam
- Clorazepate=>nordiazepam
  - Halazepam
  - Oxazepam
  - Prazepam
Clicker Question: Benzodiazepines affect the GABA<sub>A</sub> Chloride channel receptor. To treat anxiety, which mechanism would be most beneficial?

A. Inhibit GABA activity
B. Stimulate GABA activity
Benzodiazepines increase activity of the GABA$_A$ Chloride Channel

Benzodiazepines like [diazepam] cause an increase in the frequency of the GABA channel openings, resulting in inhibition of action potentials and sedation.
Side Effects of Benzodiazepines

• Related primarily to the CNS depression and include: drowsiness, excess sedation, impaired coordination, nausea, vomiting, confusion and memory loss. Tolerance develops to most of these effects.

• Dependence with these drugs may develop.
• Serious withdrawal syndrome can include convulsions and death.
• Patients are often prescribed an SSRI first
Clicker Question: What effect does CB1 receptor activation have on GABA secreting neurons?

A. Inhibits GABA release
B. Stimulates GABA release
C. No effect on GABA release, not found on GABA receptors
Cannabinoids and Anxiety: Animal models

• Preventing anandamide breakdown by FAAH reduces anxiety in animal models
• CB1 receptor knockout has higher anxiety
  – Knockout in selective neurons changes behavior
• TRPV1 activation causes anxiety--opposite of CB1 receptor activation
  – TRPV1 knockout shows less anxiety
Effects of THC change when CB1 receptors are deleted from specific neuron types

Distinct subpopulations of neurons are responsible for different behavioral effects

Effects of Cannabinoids on Anxiety in Humans

- Clearly a complex patient-specific response
- Low doses are anxiolytic
  - Sedation?
- High doses cause anxiety
  - Paranoid feelings
  - More intense with edibles
Anxiety: Systematic Reviews

• THCs, Dronabinol, Nabilone: greater short-term benefit for anxiety and sleep disorders (high risk of bias)
• CBD: greater improvement in anxiety score than placebo (randomized, p=0.01)
• Cannabis: no good trials

• Overall conclusion is that cannabinoids have good potential as anxiolytic agents
Anxiety: Negative effects

- Daily cannabis use is associated with increased anxiety
- Heavy use is associated with social phobias.
Cannabinoids and PTSD
PTSD (post-traumatic stress disorder)

• A physiological and behavioral response to exposure to emotional trauma

• To be diagnosed with PTSD, an adult must have all of the following for at least 1 month:
  – At least one re-experiencing symptom
  – At least one avoidance symptom
  – At least two arousal and reactivity symptoms
  – At least two cognition and mood symptoms
Highest Risk

- High intensity: Combat veterans, Rape victims, Refugees
- Vulnerable age: Childhood trauma
- Preexisting mental disorder or substance abuse

**STATISTICS**

- PTSD among general U.S. population at some point in life: 6.5% – 8%
- PTSD among rape victims and combat veterans: 10% – 30%
- PTSD among Cambodian refugee genocide survivors: 62% – 86%

Sources: Medicinenet.com; National Institute for Mental Health

Paul Penzella Staff Artist
Treatments for PTSD

- Refractory to treatment
- Most patients treated with antidepressants or anxiolytics, with poor success
- Behavioral therapy has some benefit
A cellular model of endocannabinoid-controlled fear relief

Excess signaling by neurons leads to activation of mGluR triggering the formation of endocannabinoids
Negative emotional load triggers the endocannabinoid response

2 stages: CB1 and TRPV1

CB1 reduces fear response
TRPV1 enhances fear

A malfunctioning endocannabinoid system leads to excess fear conditioning or PTSD
Cannabinoids in PTSD: Animal models

• CB1 agonists reduces recurrent fear in animal models of PTSD (reconsolidation)
  – Very time-dependent, needed signal at time of fear

• FAAH inhibitors to increase endocannabinoid levels reduced PTSD
Testimonial: Medical Marijuana for PTSD

• https://www.youtube.com/watch?v=M_GDFoJE0gA
Future Directions:

• CBD Clinical Trials
  – 39 clinical trials using CBD in mental health disorders
  – Mostly related to anxiety and psychosis
• Altering Endocannabinoids
• CB1 receptors agonists and antagonists
• Medical Marijuana Testimonials
  – Clinical trials for cannabis in PTSD