Cannabis, Psychosis, and Schizophrenia
A brief review for clinicians

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Objectives

1. Describe the association between cannabis and psychosis
2. Estimate the likelihood of cannabis causing psychosis
3. Describe the association between cannabis use and schizophrenia risk
4. Estimate the magnitude of risk for schizophrenia associated with regular cannabis use
5. Review neurochemical explanations for these effects or associations
6. Summarize cannabidiol (CBD) studies in schizophrenia
Definitions

**Cannabis**  A genus of flowering plants in the family Cannabaceae. Includes *C. sativa*, *C. indica*, *C. ruderalis*

**Marijuana**  Colloquial name for cannabis.

**Hemp**  Cannabis with very low THC content

**THC**  Tetrahydrocannabinol. A CB1 receptor partial agonist. The intoxicating constituent of cannabis. Historically ≈ 4% of plant weight, now > 20% strains are available

**CBD**  Cannabidiol. A neuro-active yet non-intoxicating constituent of cannabis.

**State Definitions** of cannabis or marijuana may allow *any form of THC at any concentration* to be called cannabis, marijuana, or *medical marijuana*.
Objective 1. Describe the association between cannabis and psychosis
Cannabis, THC Can Cause Psychosis. We know this based on…

**Animal Laboratory studies**
- THC given to rats causes a sensory information processing abnormality (prepulse inhibition deficit) typically seen in people with psychosis or schizophrenia (reviewed by Renard et al., 2016).

**Human Laboratory Studies**
- The prepulse inhibition abnormality and other clinical features of psychosis or schizophrenia can be created in healthy human volunteers by giving them THC or cannabis extracts under controlled laboratory conditions (reviewed by Sherif et al., 1996).

**Human Clinical Studies**
- Paranoia, abnormal thinking, depersonalization, and hallucination are described in the FDA’s THC prescribing information.
Objective 2.
What’s the Probability that THC or Cannabis Will Provoke Psychosis?

• Between **3% to 10%** from therapeutic dosing of THC, per FDA prescribing information.

• Survey of 1000 New Zealand adults (18 – 35 yo) found **15%** of cannabis consumers reported psychotic symptoms following use (Thomas, 1996)
Objective 3. Describe the association between cannabis use and schizophrenia risk
Significant Association Between Regular Cannabis Use and Risk for Schizophrenia

Earlier age of onset of schizophrenia among cannabis consumers.
- 1.8 to 3.2 years earlier onset of illness (Dekker et al., 2012; Di Forti, 2014; Helle et al., 2016)

This "acceleration effect" is more pronounced among consumers of higher-THC products.
- 6.2 years earlier onset of illness (Di Forti et al., 2014)

There is also an exposure-risk relationship seen in population studies. Higher cumulative cannabis exposure → higher odds of schizophrenia diagnosis.
- Reviewed by Marconi et al., 2016
Cannabis Can Significantly Impede Recovery from Schizophrenia

Cannabis use is associated with increased risk of:
- Medication non-response
- Medication non-adherence
- Higher rates of psychosis symptoms recurrence
  reviewed by Reid & Bhattacharyya, 2019

Human laboratory studies of THC/Cannabis effects in people with schizophrenia show:
- Transient worsening of positive and negative symptoms, and cognitive impairments
- Generally enhanced sensitivity to the effects of cannabis
  reviewed by Sherif et al., 2016
Objective 4. Estimate the magnitude of risk for schizophrenia associated with regular cannabis use

Mean Odds Ratio 3.9
Marconi et al., 2016
Objective 5.
Neurochemical hypotheses for cannabis’ effects on psychosis or schizophrenia risk
<table>
<thead>
<tr>
<th>Signaling Molecule</th>
<th>How It’s Changed in Psychosis</th>
<th>Action of Cannabis and/or THC</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Increased release of dopamine</td>
<td>Increases release of dopamine</td>
<td>Bloomfield et al., 2017</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Decreased signal strength</td>
<td>Decreases release of glutamate</td>
<td>Sánchez-Blázquez et al., 2014</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Possible contribution via serotonin 2a receptor</td>
<td>Hypersensitive serotonin 2a receptor with chronic THC exposure</td>
<td>Ibarra-Lecue et al., 2018</td>
</tr>
<tr>
<td>Anandamide (brain’s endogenous cannabinoid)</td>
<td>Anandamide is neuroprotective, anti-inflammatory</td>
<td>Cannabis use decreases levels of anandamide → possible loss of protection</td>
<td>Morgan et al., 2013</td>
</tr>
</tbody>
</table>

• *CBD (cannabidiol) ≠ Cannabis

• Much of the preclinical work showing antipsychotic potential for CBD involves studies where psychosis was provoked by THC

• Much of the preclinical work showing anxiolytic effects of CBD involves studies where anxiety was provoked by THC
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Numbers, assignments</th>
<th>Dose, duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGuire, 2018</td>
<td>Double-blind, Placebo-controlled, Adjunctive</td>
<td>88 (total) 43 (CBD) 45 (Placebo)</td>
<td>1000 mg/d 6 weeks</td>
<td>Small improvement in PANSS, CGI. No improvement in cognition, functioning 😐</td>
</tr>
<tr>
<td>Boggs, 2018</td>
<td>Double-blind, Placebo-controlled, Adjunctive</td>
<td>N = 36 for both groups</td>
<td>600 mg/d 6 weeks</td>
<td>No improvement in PANSS. Worse cognition v PBO group at endpoint 😞</td>
</tr>
<tr>
<td>Leweke, 2012</td>
<td>Double-blind, Randomized, Non-inferiority trial</td>
<td>42 (total) 21 to CBD 21 to Amisulpiride</td>
<td>800 mg/day (CBD) 800 mg/day (Amisulpiride)</td>
<td>CBD reduced PANSS as well as amisulpiride. Improvement correlated with increasing anandamide levels 👍</td>
</tr>
<tr>
<td>Zuardi, 2006</td>
<td>Open-label, Case series</td>
<td>3 patients with Treatment-resistant schizophrenia</td>
<td>1280 mg/day CBD For 29 days</td>
<td>1 patient showed mild improvement 2 patients did not show any improvement 😐</td>
</tr>
</tbody>
</table>
## Potential Risks from Pharmacotherapy with CBD

### Warnings
- Hepatocellular injury
- Somnolence and sedation
- Suicidal behavior and ideation

### > 10% prevalence
- Somnolence
- Decreased appetite
- Diarrhea
- Transaminase elevations
- Fatigue
- Malaise
- Asthenia
- Rash
- Insomnia
- Sleep disorder
- Poor quality sleep
- Infections

### Other CNS Effects
- Irritability, agitation
  - 5% to 9% for CBD
  - 2% for placebo
- Aggression, anger
  - 3% to 5% for CBD
  - < 1% for placebo
- Drooling
  - 1% to 4% for CBD
  - < 1% for placebo
- Gait disturbance
  - 2% to 3% for CBD
  - <1% for placebo

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This material provided by the Best Practices in Schizophrenia Treatment (BeST) Center, Department of Psychiatry, Northeast Ohio Medical University.

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Summary

Cannabis/THC can cause psychosis in an estimated 3% to 15% of consumers.

Regular cannabis use is robustly associated with higher statistical likelihood of being diagnosed with schizophrenia. Approximately 3.9-fold higher odds for schizophrenia among cannabis users.

Correlations within a population can’t establish causality, however:
- Biochemical plausibility
- Animal models
- Human laboratory studies
- Exposure-risk relationship
- Earlier age of onset among cannabis users

Are consistent with a causal role.

CBD is being investigated as a possible schizophrenia treatment. Published results to date are inconclusive. Might be most useful in low-anandamide biotypes. Doses being studied are very much higher than an average retail CBD product would deliver.
Printable Infographic

Request by email: emessamore@neomed.edu

The Cannabis - Psychosis - Schizophrenia Connection
Marijuana is popular because it alters perceptions. Psychosis revolves around misperceptions.

What is psychosis?
Psychosis is a neurological symptom involving unusual experiences or beliefs. It happens when the brain misinterprets sensory input, leading to hallucinations or delusions.

What is schizophrenia?
Schizophrenia is a mental illness characterized by symptoms such as hallucinations, delusions, disorganized thinking, and social withdrawal. It is believed to be caused by a combination of genetic and environmental factors.

The Chemical Effects of Cannabis resemble the Biochemistry of Psychosis.

- Cannabis triggers dopamine release.¹
  - Dopamine is a chemical signal for reward. Low levels of dopamine are associated with depression and other mental disorders.

- Cannabis reduces glutamate release.²
  - Glutamate is the brain's most abundant neurotransmitter. Excess glutamate can cause cell death, which is observed in schizophrenia.

- Cannabis reduces the production of anandamide.³
  - Anandamide is an endocannabinoid that regulates mood, pain, and memory. Low levels of anandamide are linked to depression and schizophrenia.

- Cannabis reduces the level of protective anandamide.³
  - Low anandamide levels correspond to more severe symptoms of psychosis in people with schizophrenia.⁴

- Cannabis reduces brain inflammation and protects the brain against schizophrenia.⁵
  - Brain inflammation is a key factor in the development of schizophrenia. Cannabis has anti-inflammatory effects.

Cannabis Causes Schizophrenia-Like Changes in Animals

- Giving THC to animals changes their behavior in ways that resemble schizophrenia in people.⁶
  - THC (delta-9-tetrahydrocannabinol) binds to CB1 receptors in the brain, affecting mood, behavior, and cognition.

- THC causes psychosis in healthy human beings and usually worsens symptoms in people with schizophrenia.⁶

Schizophrenia Risk Goes up with More Frequent Cannabis Use

- Based on 10 separate studies, frequent cannabis users have nearly 4 times greater risk for schizophrenia.⁷

Cannabis Causes Schizophrenia-Like Changes in People

- Many people with schizophrenia have abnormal 5HT2A-type serotonin receptor expression.⁸

- Many people with schizophrenia have abnormal 5HT2A-type serotonin receptors.

Canadian Warning Label

- THC causes psychosis in healthy human beings and usually worsens symptoms in people with schizophrenia.⁶

Health Canada / Santé Canada

The government of Canada requires this health warning on all cannabis packages.⁶

References: