Understanding the Effects of Marijuana in Psychosis and Schizophrenia

Filoli, May 24, 2018

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Outline

I. Cannabis use and risk for cannabis use disorders
II. Cannabis use and risk for onset of psychiatric disorders
III. Is there a role for cannabidiol in the management of psychotic disorders?
IV. Effects of cannabis on the dopamine system
V. Cannabis use and risk for psychosis
VI. The effect of cannabis on brain circuitry in schizophrenia
   I. Brain reward circuit
   II. Cognitive and default mode networks
VII. Summary
VIII. Discussion
I. Cannabis use and the risk for cannabis use disorders

With legalization of cannabis spreading across the USA
• Rates of cannabis use are rising
• Rates of cannabis use disorders are rising

In 2015, 4 million Americans met criteria for a Cannabis Use Disorder
• Primary side effect of medical cannabis

People with schizophrenia are particularly vulnerable
• INSPIRE clinic experience
• Cannabis use is very common in lead-up to psychosis
• Many people struggle to stop using cannabis despite onset of psychosis, often strong affinity
• Continued cannabis use increases risk for relapse
• Attempts at substitution
Prevalence of Substance Use Disorders in Mental Illness

% of respondents with substance use disorder

Gen pop | Schiz | Bipolar | MDD | OCD | Panic

Regier D, JAMA, 1990
II. Cannabis use and the risk for onset of psychiatric disorders

Numerous studies show association between cannabis use and risk for schizophrenia

Chicken vs. egg?
• Cannabis may trigger onset of psychosis in vulnerable people
• Evolving psychosis may increase vulnerability to substance use disorders
  • social marginalization
  • dysphoria
  • reward deficiency
The Dunedin Birth Cohort Study

The development of 1037 children was assessed 10 times from age 3. This included psychiatric interview at age 11 and measurement of drug consumption at ages 15 and 18. At age 26, 96% were interviewed using the Diagnostic Interview Schedule (DIS) for DSM-IV.

Percentage of Cannabis Users Who Become Psychotic

Users by age 18: 4.7%

Users by age 15: 10.3%

Schizophreniform disorder

Susceptibility to Psychosis Related to Genotype

Complications of Substance Use in Schizophrenia

- Earlier onset
- Higher relapse, hospitalization rates
- Treatment non-adherence
- Poorer medication response
- Increased risk for violence
- Increased risk for HIV, hepatitis
- Increased cost of care

Green AI, AJP, 164:402-408, 2007
Response to Antipsychotic Treatment at First Episode

12 weeks
37% SUD, 28% CUD, 21% AUD
CUD earlier onset
SUD >Positive sxs,
< Negative sxs
SUD longer DUP & lower response rate

Green, Schizophr Res, 66:125-135, 2004
SURVIVAL CURVES OF TIME UNTIL PSYCHOTIC RELAPSE BY NO ABUSE AND ABUSE OF CANNABIS

III. Is there a role for cannabidiol (CBD) in management of psychiatric disorders?

Cannabidiol is one of 113 cannabinoids in cannabis
- Accounts for up to 40% of cannabinoids
- CB1 & CB2 antagonist
- Serotonin 1A partial agonist
Why do we have cannabinoid system?

Regulates a variety of physiologic and cognitive processes
• Fertility, appetite, pain, mood, memory

Endocannabinoids – derived from Omega-3 fatty acids

- AEA (anandamide)
  › mimicked by THC
  › act at CB1 receptors
  › released after intense exercise
  › euphoria, derealization, perhaps relaxation and calm

- 2-AG (2-arachidonoylglycerol)
  › mimicked by CBD
  › act at CB1 & CB2 receptors
  › appetite, immunity, pain

- Use of exogenous cannabinoids may alter endogenous system
Can CBD help manage psychiatric disorders?

Many claims about cannabis are based on minimal science
• Pain regulation has strongest evidence

Recent study CBD as adjunctive therapy in people with schizophrenia
• 6 week randomized: CBD (N=42) v. placebo (N=44)
• People with schizophrenia
• Continued prior antipsychotic medication
• CBD associated with:
  • Greater reduction in PANSS positive subscale (-1.4)
  • More likely improved on CGI-I (-0.5)
  • Less likely severely ill on CGI-S (-0.3)
  • More GI upset, less sedation and insomnia

McGuire AJP 175:225-231, 2018
FIGURE 1. Positive and Negative Syndrome Scale, Positive Symptom Subscale in a Study of Adjunctive Cannabidiol in Schizophrenia (Intention-to-Treat Analysis Set)
FIGURE 2. Clinical Global Impressions Severity Scores at End of Treatment in a Study of Adjunctive Cannabidiol in Schizophrenia (Intention-to-Treat Analysis Set)
Problems with using CBD as a treatment

No reliable source

Labeling of CBD vs THC content may not be accurate

People lapse into THC use

Cannabis impairs motivation and cognition, and produces sedation
  • Unclear relationship to CBD v. THC

CBD substitution for cannabis use is most supportable at this time
Introduction to Brain Reward

Rewarding activity
- Eating good food
- Falling in love
- Intimacy
- Run/hike in the redwoods
- Winning the State Championship

Neurobiologic response
- Norepinephrine, dopamine
- Endorphins
- Endocannabinoids
Introduction to Brain Reward

Reward circuit
- Dopamine rich neurons
- Nucleus accumbens to ventral tegmental area

Reward signal
- That felt good, do it again
- Associated with people, activities, settings, items
- Triggers for craving and reward

Natural reward response – inherently rewarding
- Reinforce healthy lifestyle
- Achievement
- Advances the species
What if I could bottle that feeling?

- That would be great!
- Or would it?
- All the reward without the achievement
Substances of abuse are a shortcut to brain reward

Mimic neurotransmitter actions
- Stimulate norepinephrine, opioid or cannabinoid receptors
- Trigger brain reward circuit

Fake reward signal
- That felt good, do it again
- And again, and again, and again
- Triggers for craving and reward

Empty association triggers
- Money or sex to obtain drugs
- Dealer
- Drug use rituals
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FILOLI, MAY 27, 2018

Adina S. Fischer, MD, PhD
Resident Physician
Postdoctoral Research Fellow
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IV. Effects of THC on the Brain

THC Effects on Dopamine System

Dopaminergic neurons are modulated by the endocannabinoid system
Anandamide and 2-AG
Retrograde feedback
- GABA
- Glutamate
THC = CB1R and CB2R partial agonist

Bloomfield et al, Nature Reviews 2016
The Brain Reward Circuit (BRC)

- **Nucleus Accumbens (NAc)**
- **Ventral Tegmental Area (VTA)**
- **Anterior Cingulate Cortex**
- **Orbitofrontal Cortex**
- **Dorsal Striatum**
  - Caudate
  - Putamen
- **Limbic Components**
  - Hippocampus
  - Amygdala

- **Dopamine (DA)** key neurotransmitter
- **CB1 receptors** mediate DA response
Modulation of Brain Reward Circuitry

- Activation of VTA DA neurons results in increased DA release in the PFC.
- Activation of VTA DA neurons via "disinhibition" and direct activation results in increased DA release in the NAc shell.
- CB1 receptor activation also results in increased dendritic arborization and length in the NAc shell.
- THC mediated CB1 receptor activation on GABA neurons results in reduced GABA release causing DA neuron "disinhibition".
- THC also activates CB1 receptors on DA neurons in VTA.
V. Cannabis Use and Risk for Psychosis

Any Cannabis Use

<table>
<thead>
<tr>
<th>Study (symptom of psychosis)</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHDS (any)*</td>
<td>1.28</td>
<td>1.04–1.57</td>
</tr>
<tr>
<td>Dunedin (schizophreniform)*</td>
<td>2.91</td>
<td>2.07–4.04</td>
</tr>
<tr>
<td>ECA (any)</td>
<td>1.30</td>
<td>0.98–1.73</td>
</tr>
<tr>
<td>EDSP (any)</td>
<td>1.67</td>
<td>1.21–2.26</td>
</tr>
<tr>
<td>NEMESIS (any)</td>
<td>2.11</td>
<td>1.78–5.41</td>
</tr>
<tr>
<td>NPMS (any)</td>
<td>0.72</td>
<td>0.30–1.74</td>
</tr>
<tr>
<td>Swedish (schizophrenia)†</td>
<td>1.50</td>
<td>1.11–2.02</td>
</tr>
<tr>
<td>Overall</td>
<td>1.41</td>
<td>1.20–1.65</td>
</tr>
</tbody>
</table>

Most Frequent Cannabis Use

<table>
<thead>
<tr>
<th>Study (use)</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHDS (daily)</td>
<td>1.56</td>
<td>1.20–2.03</td>
</tr>
<tr>
<td>ECA (daily)</td>
<td>2.00</td>
<td>1.27–3.16</td>
</tr>
<tr>
<td>EDSP (daily)*</td>
<td>2.23</td>
<td>1.30–3.83</td>
</tr>
<tr>
<td>NEMESIS (weekly)*</td>
<td>6.81</td>
<td>1.79–25.91</td>
</tr>
<tr>
<td>NPMS (dependence)*</td>
<td>1.47</td>
<td>0.55–3.93</td>
</tr>
<tr>
<td>Swedish (&gt;50 times)</td>
<td>3.10</td>
<td>1.72–5.58</td>
</tr>
<tr>
<td>Overall</td>
<td>2.09</td>
<td>1.54–2.84</td>
</tr>
</tbody>
</table>

Moore et al, Lancet, 2007
Effects in Healthy Individuals

D’Souza et al, Neuropsychopharmacology, 2004
Cannabis use and risk for psychosis

• Cannabis use is considered a preventable risk factor for psychosis
• Longitudinal studies – consistent association between adolescent cannabis use and psychosis

Adolescents are particularly vulnerable to negative effects of cannabis

• Critical neurodevelopmental period – synaptic pruning and myelination.
• Endocannabinoid system regulation of neurodevelopmental processes

_Approximately 50% Lifetime prevalence U.S. high school students_
Adolescent health brief

Impact of Marijuana Legalization in Colorado on Adolescent Emergency and Urgent Care Visits

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Article history: Received September 14, 2017; Accepted December 19, 2017

Figure 1. Annual marijuana-related emergency department (ED) and urgent care (UC) visits from a tertiary care children’s hospital in Colorado.
Dopamine Synthesis in Cannabis Users vs. Non Users

Bloomfield et al, Biological Psychiatry 2014
VI. Cannabis Use Disorder In Schizophrenia

• Up to 50% lifetime prevalence

• Chronic cannabis use dramatically worsens the course of schizophrenia
  › Increased chance of relapse, hospitalization
  › Symptom exacerbation
  › Poorer response and compliance to medication
  › Decreased global functioning

• Limited treatments available
Theories of Cannabis Use in Schizophrenia

Self Medication Hypothesis
- Amelioration of negative symptoms
  - Anhedonia
  - Flattened affect
  - Apathy
  - Lack of motivation
- Lessen side effects of antipsychotic medication

Reward Dysregulation Model
- Brain reward circuitry impairment underlies elevated use of cannabis in schizophrenia (Green et. al., 1999)
- Cannabis transiently normalizes underlying brain reward circuitry impairment
Reward Circuit Dysfunction in Schizophrenia

- Behavioral tasks

- PET and fMRI task-based paradigms
  - Beautiful faces
  - Food reward
  - Pleasant smells
  - Monetary reward

- Dysregulation of the endocannabinoid system
  - Decreased CB1R density especially in PFC (post-mortem)
  - Maternal deprivation/social isolation animal models → reduced expression and function of CB1Rs (striatum, amygdala, hippocampus)

(Juckel et. al., 2006)
Pilot Study: Marijuana’s Effects on Brain Circuitry in Schizophrenia

- Abstinence for 7 days
- T1 and T2 sessions

- Randomized design double-blinded

Patients divided into:

**Cannabis group**
3.6% THC cannabis cigarette

**THC group:**
15 mg oral THC

Fischer et al., Schizophrenia Research 2014
Change in Symptoms, Craving, Heart Rate

Fischer et al., Schizophrenia Research, 2014
BRC Patients with Schizophrenia and CUD

Fischer et al., Schizophrenia Research, 2014
NAc-to-mPFC Connectivity with Cannabis

Fischer et al, Schizophrenia Research, 2014
Default Mode Network (DMN)

Anatomically and functionally defined system preferentially active when individuals are not focused on the external environment.

Mediates task independent brain function.

Spontaneously active at rest when individuals engaged in internally focused thought:

- Self referential processing
  - Introspection
  - autobiographical memory retrieval
  - envisioning/simulating future events

- Theory of mind
  - Considering thoughts and perspectives of others
DMN Hyperconnectivity in Schizophrenia

- Misattributions of thought
- Positive Symptoms
  - Altered perceptions of reality
  - Auditory Hallucinations
  - Delusions
- Cognitive Impairment

Whitfield-Gabrieli at al., PNAS 2009
DMN-to-TPN Anticorrelation

- **DMN** is negatively correlated (anticorrelated) with the “task positive network” (TPN)
- **TPN** is active during external focused attention and goal oriented task performance.

  “**Functional coupling**” of DMN and TPN
  attention shift from internally directed thoughts to external stimuli
  • anticorrelation is directly associated with superior attention and working memory

- **Impaired network coupling**
- Reduced anti-correlation →
  • Cognitive impairment

Fox, 2005
DMN Connectivity in Schizophrenia and CUD

Fischer et al., Schizophrenia Research 2017

p < 0.05, FDR corrected
Change in Network Coupling

Whitfield-Gabrieli & Fischer et al., Schizophrenia Research 2018

p < 0.05, FDR corrected
VII. Summary

Cannabis (THC) has effects on multiple neurotransmitter systems and brain circuits
- Acute → increased dopamine release
- Chronic → blunting of the dopamine system

Increased risk of psychosis (psychotic symptoms) with cannabis
- Adolescents particularly vulnerable
- Cannabis use is a preventable risk factor for psychosis
  - Increased risk of any psychotic outcome in individuals who had ever used cannabis
  - Dose response effect

Cannabis use disorder in Schizophrenia
- Approximate 50% prevalence, worsens the course of schizophrenia – increased relapse, more severe symptoms, more refractory, increased risk psychiatric hospitalization
- Reward dysregulation model - Hypoconnectivity of the BRC
- Hyperconnectivity of the DMN → Positive symptoms and effect on cognition (DMN/TPN)
- Limited treatments available
  - Potential for cannabidiol or low dose cannabis as adjunctive treatment?
Future Avenues of Research

Is there a role for cannabis or THC in treatment of schizophrenia?

- Effects of THC vs Cannabidiol

Is blunted dopamine release and synthesis seen in chronic users a pre-existing vulnerability factor or a direct result of repeated THC exposure?

How do gene variants modulate the endocannabinoid and dopamine systems --> influence the sensitivity to the rewarding effects of THC and vulnerability to addiction, amotivation and psychosis following chronic exposure?

Mechanisms underlying the complex dose–response effects of THC on dopaminergic function

Mechanisms of regional differences in dopaminergic effects and the functional significance of these on behavior

Are long-term effects of THC reversible with abstinence?
References


VIII. Discussion

Implications of Brain Reward Circuit Deficiency

- Emotional distance, flat, blunting
- Hard to feel alive, engaged in outside world
- Vulnerability to SUD
- Will benefit from alternate pathways to stimulate BRC activity
  - Social
  - Mindfulness
  - Physical exercise
How Does Exercise Exert Beneficial Effects?

• Neurotransmitter effects
  – Endorphins, endocannabinoids (AEA)¹
  – Norepinephrine, serotonin, dopamine²

• Neurotrophic effects
  – Brain Derived Neurotrophic Factor (BDNF)¹

• Glycogen storage in astrocytes
  – Frontal cortex + hippocampus³

• Tighter glucose regulation⁴

AEA, N-arachidonoylethanolamide; BDNF, brain-derived neurotrophic factor
Aerobic Exercise Improves Cognitive Functioning in People with Schizophrenia

Cognitive deficits pervasive, treatment options limited
10 controlled trials, 385 patients
20-60” 2-4x/week, 4-24 weeks aerobic or mixed
Exercise significantly improved global cognition
Effect size = 0.43
Greater exercise → greater cognitive gain
Exercise trainer → greater efficacy
Working memory: g = 0.39
Social cognition: g = 0.71
Attention/vigilance: g = 0.66
Processing speed, verbal memory, visual memory, problem solving = NS

Figure 1. Average Change in Visual Analog Scales

Symptoms/Domains

Average Change +/- 1 STD in VAS after Workout Session (cm)
Spontaneously Exercising People with Schizophrenia

Figure 2. Average Change in Subjective Exercise Experiences Scale

SEES Response Domains
Summary

- Brain Reward Circuit encourages repeating adaptive behaviors
- Substances of abuse turn on BRC
  - May lead to compulsive use
- People with schizophrenia have impaired BRC, leading to negative and cognitive symptoms and vulnerability to addiction
- Cannabis normalizes BRC activity, but carries risk of worsening schizophrenia
- People with schizophrenia can find healthy means to activate BRC
- Physical exercise releases natural cannabinoids and stimulates BRC
  - Potential to help people with co-occurring SUD and schizophrenia