Cannabis and Psychosis in Adolescence

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Pediatric Psychiatry in Primary Care-ECHO Series

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This is your brain on drugs. Any questions?

CDC Youth Risk Behavior Survey 2021

- Ever used marijuana: 27.8% (29.2% Maine)
  - compared to peak rate of 47.1 % in 1997
- Currently use marijuana: 15.8% (17.5% Maine)
- Tried marijuana before 13 yo: 4.9% (5.7% Maine)

- Currently use alcohol: 22.7% (17.7% Maine)
  - 29.8% in 2017
- Tried alcohol before 13 yo: 15% (11% Maine)

- Ever tried cigarettes: 17.8% (17.7% Maine)
- Ever vaped electronic products: 36.2% (31.7% Maine)
- Currently vape electronic products: 18% (17.5% Maine)

- Ever used illicit drugs (heroin, cocaine, meth, etc): 13.3% (no Maine data)
- Ever took pain pills not prescribed: 12.2% (19.7% Maine)

Endocannabinoid System

- Endocannabinoids and endocannabinoid receptors are widely distributed in the brain and spinal cord (lipophilic)
- Regulatory role in many processes:
  - inflammation
  - appetite regulation
  - immune function
  - cardiovascular function
  - connective tissues
  - neural development
  - pain
  - sleep and wake cycle
  - psychiatric functions
  - GI functions

- Endocannabinoids interact with endocannabinoid receptors CB1 and CB2
- Phytocannabinoids interact with the body through these receptors
- CB1:
  - CNS: prefrontal cortex, basal ganglia, hippocampus, amygdala, hypothalamus, and cerebellum
  - also smooth muscle, myocardium, adipocytes, and preganglionic sympathetic neurons
- CB2: peripheral blood mononuclear cells, adipocytes, smooth muscle, myocardium, and vascular endothelium

THC versus CBD

- THC a partial agonist at CB1 and CB2 sites and reduces neurotransmission, effecting:
  - learning and memory
  - gut motility
  - thyroid levels
  - attention
  - heart rate and blood pressure
  - analgesia
  - anti-inflammatory effects
- Metabolism of THC through the liver by the cytochrome P450 system
- Can decrease efficacy of certain drugs (i.e. risperidone)
- Synthetic cannabinoids (i.e. Dronabinol, Nabilone) work like THC; approved for nausea, vomiting, anorexia assoc. with chemotherapy

- CBD has weak affinity to CB1 receptors and does not bind directly to CB2 receptors
- CBD acts as an inverse agonist/antagoinst
- Activates TRP1 receptors that control pain perception, body temperature, inflammation
- CBD also inhibits fatty acid amide hydrolase (FAAH), which increases feelings of well-being
- CBD inhibits cytochrome oxidases and interferes with metabolism of many common medications (i.e. increasing levels of anti-epileptic medications)
- CBD has a regulatory effect on THC and may inhibit some adverse effects (tachycardia, anxiety, sedation)
- Most studies for CBD have been on adults
- Is approved for some juvenile epilepsy conditions

Medical Uses of Cannabis- some data

- Lennox-Gastaut syndrome (children- 2nd line)
- Dravet syndrome (children- 2nd line)
- Chronic pain (adults)
- Anti-emetics (adults)
- Spasticity in multiple sclerosis (adults)
- Irritable bowel syndrome (adults-weak evidence)
- Social anxiety (CBD)
- Sleep and PTSD (weak evidence)
- No benefit found for depression (Sams, 2020)

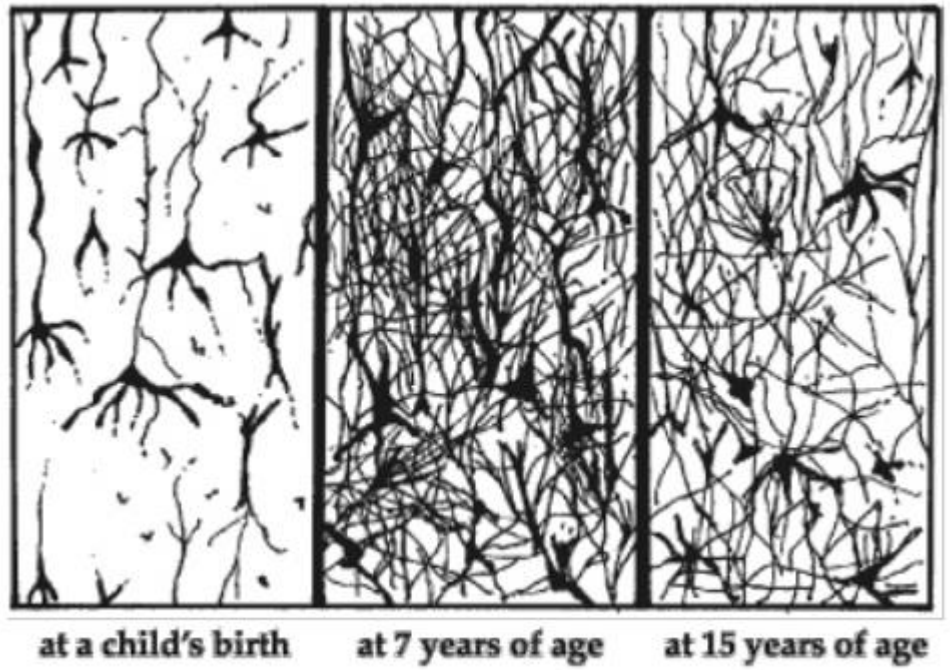
Research supporting the use of smoked cannabis for medical conditions is limited to less than10% THC

- All studies of smoked medicinal cannabis showing benefit – done with less than 10% THC
  Whiting PF, Wolff RF, Deshpande S et al. Cannabinoids for medical use a systematic review and meta-analysis. JAMA 2015;313:2456-2473
- No legitimate science exists to validate medicinal cannabis greater than 10% THC
- A study in healthy volunteers on cannabis effects in capsaicin-induced pain found a window of modest analgesia for smoked cannabis. Wallace M et al. Anesthesiology 2007;107:785-796
  - 2% THC provided no benefit
  - 4% THC provided significant pain decrease
  - 8% THC caused increased pain or hyperalgesia

Credit to Dr. Elizabeth Stuyt, MD

Neurocognitive Adverse Effects

- Because of role in the prefrontal cortex and hippocampus, maturation of circuits regulating attention, executive functioning, and memory can be affected by cannabis use during adolescence (Rubino, 2009)
- Persistent neurocognitive changes and lower functioning even after abstaining from cannabis use, even after a year (Meier, 2012)
- Cannabis use was adverse effects on IQ and executive functioning and declines in neural connectivity (Camchong, 2017)
- Those who start using before 17 yo have reduced odds of high school graduation, more likely to have cannabis use disorder, more likely to use other illicit substances and tobacco, and more suicide attempts (Silins, 2014)



Potential Adverse Effects with CBD and THC

CBD

- Psychiatric: depression, agitation, aggression, panic attacks, suicidal behavior
- Hepatic: liver injury (often mild)
- GI: decreased appetite, diarrhea, nausea, vomiting, abdominal pain

THC

- Psychiatric: anxiety, depression, psychosis
- Pulmonary: chronic bronchitis, infections
- Cardiovascular: increased risk for MI, CVA, TIA
- Cognitive impairment: academic and driving

Huestis, 2019

Potential Drug Interactions

CBD

- Hepatic metabolism by CYP2c19, CYP3A4, CYP1A2, CYP2C9, CYP2D6
- Potential interactions include:
  - Rifampin
  - Ketoconazole
  - Clobazam
  - Valproate
  - Stiripento
  - Midazolam
  - Warfarin

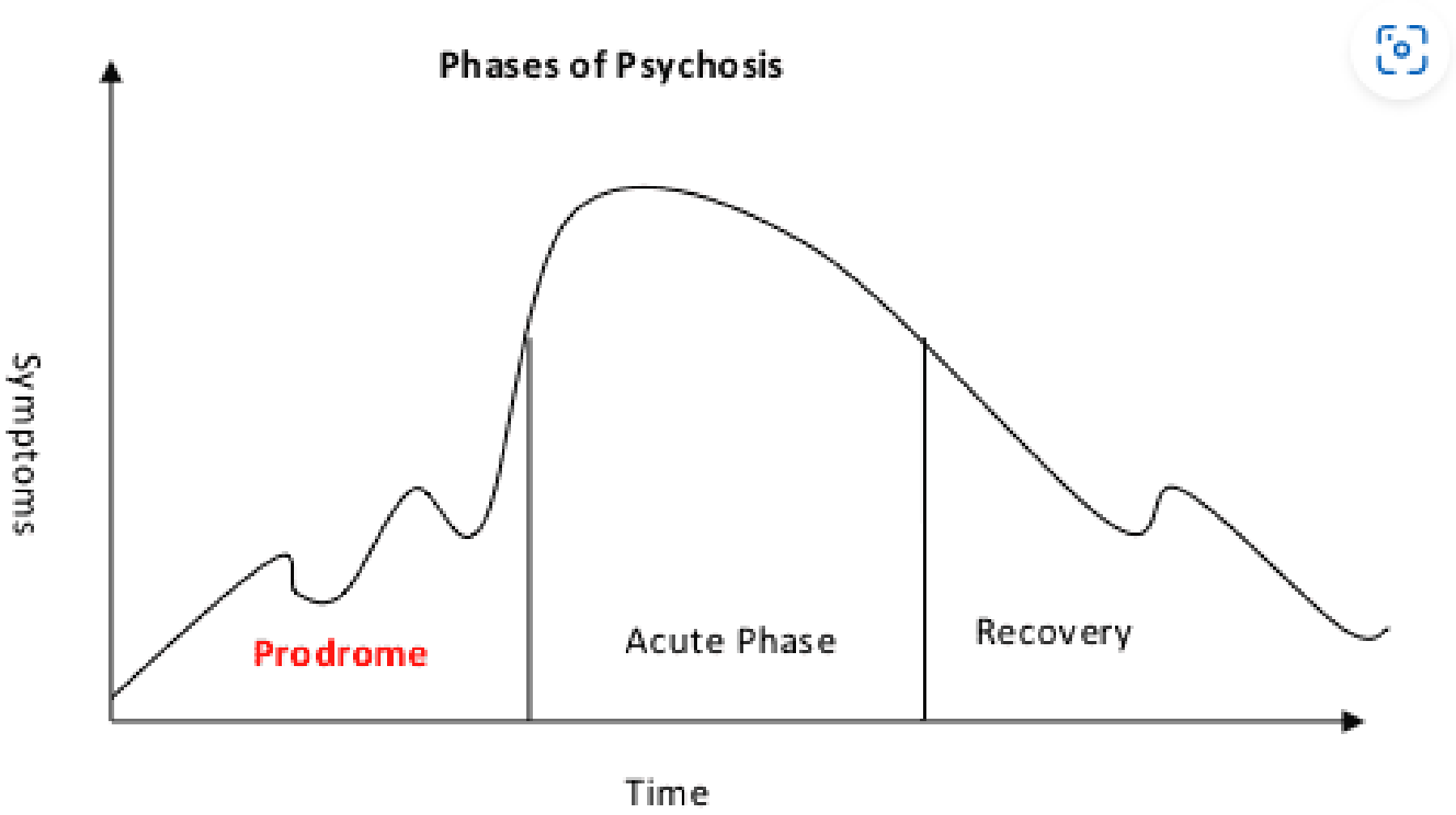
THC

- Hepatic metabolism through CYP2C9, CYP2C19, CYP3A4
- Potential interaction include:
  - fluoxetine
  - disulfiram
  - risperidone

Luca, et al, 2018; Patsalos, 2020

Psychosis

- A range of conditions that affect the mind in which there has been some loss of contact with reality
- Hallucinations and delusions can be very real and distressing
- Also changes to thought processes, mood, sleep, and behavior
- Majority of cases first occur between 13-30
- Use of THC in particular may trigger psychosis in certain individuals, especially with earlier use and more potent strains
- Accelerated loss of grey matter volume in those with schizophrenia


Phases of Psychosis
Symptoms
Prodrome
Acute Phase
Recovery
Time

Epidemiology of psychotic illnesses

- Schizophrenia and schizophrenia spectrum disorders are a worldwide causes of disability in young people
- Described by Kraepelin 100 years ago
- Prevalence 1% worldwide
- Median age of onset 19 years old, 85% by age 25
- Monozygotic twin concordance 50%
- 40% have good symptoms outcome, but often there are impairments in daily functioning
- Only 1 in 7 patients have ‘true recovery,’ that is symptom remission and adequate social functioning
- Duration of untreated psychosis often directly linked to prognostic factors

Clinical High Risk and Ultra High Risk for Psychosis

- High risk: individuals with a first degree relative, usually a parent or a sibling
  - Risk of psychosis is relatively low at 10-20% in this group
- Australian group (McGorry and the PACE clinic) have studied and treated those with subclinical or attenuated symptoms that may reflect those at ultra high risk for developing a psychotic illness
- Identified as attenuated psychotic syndrome, brief intermittent psychotic symptoms, and those who meet criteria for schizotypal personality disorder that deteriorate rapidly
- 15-30% of those who meet UHR criteria are likely to develop a psychotic disorder within 12 months
- Risk increases to 36% after 3 years
- *Use of cannabis increases these risk factors*

Case vignette of someone that is ultra high risk for psychosis:

Claire is a 17-year-old high school student

- In the past few weeks, she has been experiencing increasingly distressing symptoms that occur at least once a week. While reading books, for example, she noticed that she does not understand the meaning of words and passages as effortlessly as before and needs to reread them. She also has difficulty finding the right words and putting them in order to make meaningful sentences.
- At times, she loses her train of thought or her mind is flooded by insignificant thoughts, which makes it impossible to concentrate.
- More than a year ago she started to experience visual disturbances. Colors of objects seem brighter, and she feels that she cannot always rely on her perception of distance or movement; for example, sometimes she thinks objects are moving, although in reality they are not.
- She also sometimes has the impression that people are talking about her or looking at her, although at the same time she knows that this is actually not possible.
- She has asked her family and friends if she seems odd or changed in any way, but they have not observed any changes.

Discussion

Claire experiences several cognitive basic symptoms:

- disturbance of receptive and expressive speech
- thought interference
- thought blockage
- unstable ideas of reference.
- Moreover, she experiences visual perception disturbances
- The fact that the symptoms are not observed by others is not relevant, as earlier symptoms are often exclusively subjective

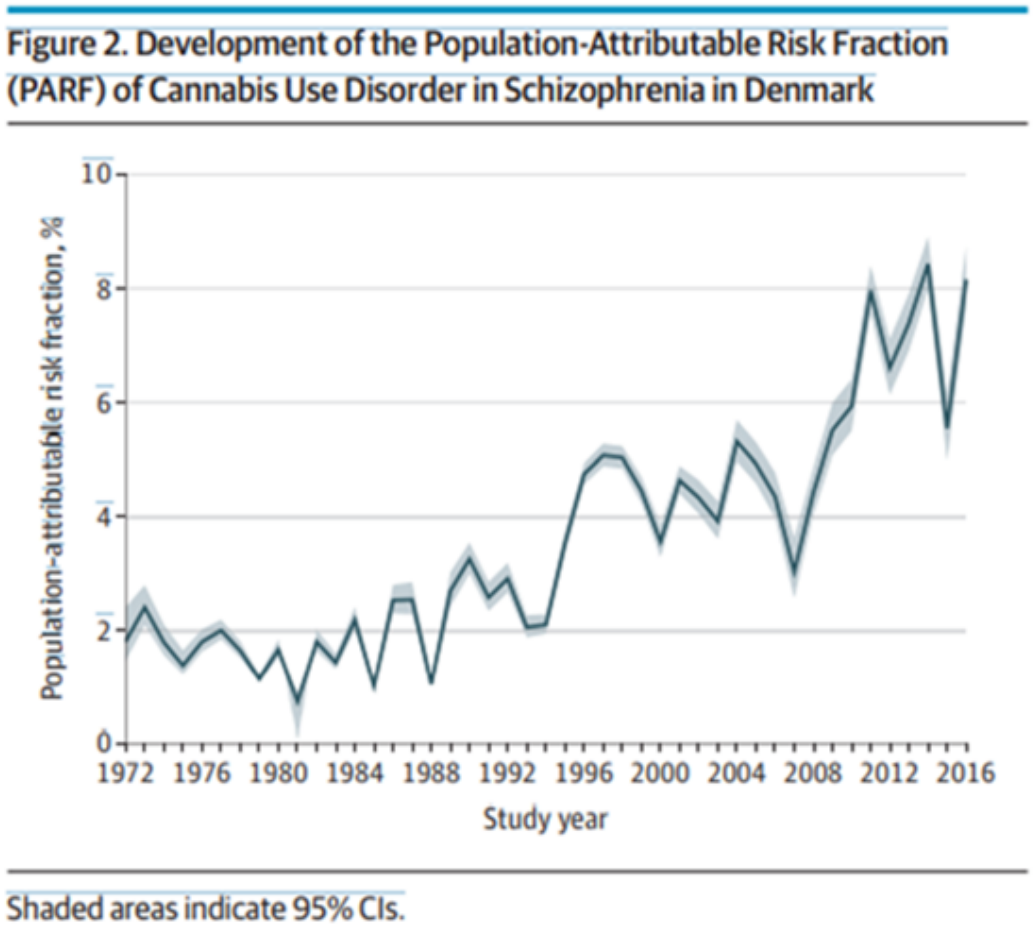
Prevalence of cannabis use in early psychosis

- 33-54% of individuals with clinical high risk symptoms use cannabis
- 22-50% of individuals with first episode of psychosis use cannabis
- Cannabis use increases risk for having psychosis symptoms, both attenuated and acute
- Youth may use cannabis to alleviate depression, anxiety, or negative symptoms of psychosis
- After the onset of positive symptoms, may be used as a way of coping with those symptoms
- Earlier age of use and higher usage of high THC is associated with poorer outcomes

West, 2023

Increased potency in past 2 decades has resulted in a 4-fold increase in cannabis use and Schizophrenia

- Very large longitudinal population-based study of **7,186, 834 individuals** in Denmark
- The population-attributable risk fraction for cannabis use disorder in schizophrenia increased from approximately 2% in the period to 1995 to approximately 6% to 8% since 2010.
- This study challenges the often-cited argument against causality that an expected increase in cases of schizophrenia attributable to cannabis use has not been observed.
- Hjorthøj C et al. JAMA Psychiatry July 21, **2021**



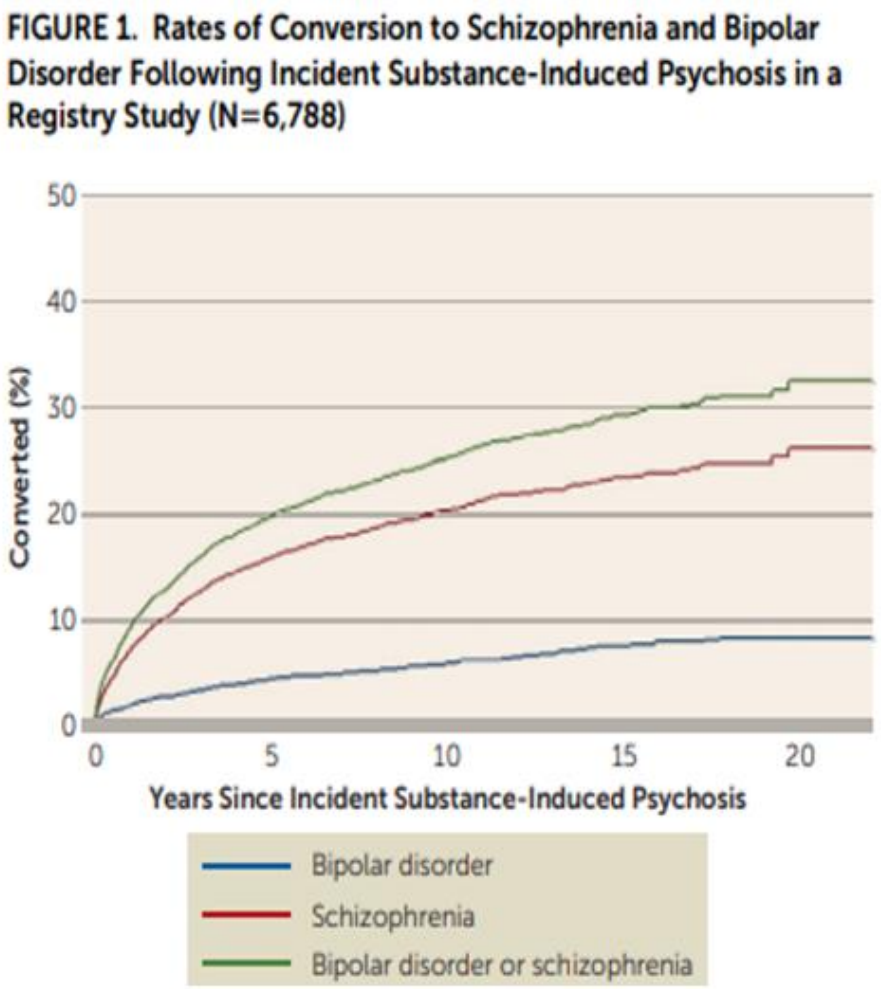
Credit to Dr. Elizabeth Stuyt, MD

Marijuana and Psychosis

- Ten European and one Brazilian site, 901 pts c 1st episode of psychosis, 1237 healthy controls (Lancet)
- Daily marijuana use and high-potency marijuana (THC>10%) are strongest predictors of a psychotic episode
- Individuals with high potency MJ 1.6 times more likely to develop psychosis than non-users
- High potency and daily use 5 times more likely to develop psychosis than non-users
- 12.2% of episodes of 1st episode psychosis could be prevented, rising to 30.3 % in London and 50.3% in Amsterdam

(DiForti, 2019)

Rates of conversion to schizophrenia or bipolar disorder after substance-induced psychosis



- 32.2% of patients c substance-induced psychosis later converted to either bipolar disorder or schizophrenia
- Highest conversion rate (47.7%) was for cannabis-induced psychosis
- Young age associated with a greater risk of conversion, risk highest in the range of 16-25 years
- Self-harm after an episode of substance-induced psychosis also linked with a greater risk of conversion to schizophrenia or bipolar disorder

Starzer, MSK, Nordentoft M,Hjorthoj 2017, AJPpsychiatryonline. org

Meta-Analysis > Subst Abus. 2021;42(4):527-542. doi: 10.1080/08897077.2021.1876200. Epub 2021 Feb 22.

Cannabis use in adolescence and risk of psychosis: Are there factors that moderate this relationship? A systematic review and meta-analysis

Sarah Kanana Kiburi [1 2], Keneilwe Molebatsi [3 4], Vuyokazi Ntlantsana [4], Michael T Lynskey [5]

63 studies in narrative review, 18 studies in meta-analysis

Important factors for psychosis risk:

- age of onset of cannabis use
- frequency of cannabis use
- exposure to childhood trauma
- concurrent use of other substances
- genetic factors

Cannabis and Depression

- Meta-analysis of 11 studies and 23.317 individuals
- OR of developing depression in MJ users vs non-users is 1.37 (95% CI 1.16-1.62)
- OR of anxiety not statistically significant 1.18 (95% CI 0.84-1.67)
- OR of suicidal ideation of 1.50 (95% CI 1.11-2.03)
- OR for suicide attempt of 3.46 (95% CI 1.53-7.84)

(Gobbi, 2019)

Cannabis and Anxiety

- Anxiety is often cited by adolescence as a reason they use cannabis
- Anxiety is one of the most common disorders
- Acute use of MJ can either mitigate or cause anxiety; CBD often cited as being more helpful
- Anxiety returns when person is no longer using, having not learned any skills
- 27 adolescent studies: 67% found a positive relationship between anxiety and MJ use, but relationship was unclear (causal or incidental)

(Cancilliere, 2018)

Fact Sheet: Cannabis and Psychosis

The growing legalization of cannabis across the United States, in addition to the frequent use of cannabis by individuals with psychosis, has led to many questions and concerns about the impacts. The following is a summary of the latest research findings regarding the link between cannabis and psychosis.

https://medicine.yale.edu/psychiatry/step/early-intervention-services/cannabis

Risk of Psychosis from Cannabis Use:

- Studies have shown that THC in cannabis can cause short-term psychosis until the drug is metabolized in the body
- If exposed to cannabis in adolescence, research shows individuals are 2-4x more likely to develop a schizophrenia spectrum disorder, than if you were not exposed
    - Not everyone who uses cannabis develops psychosis and not everyone with a psychotic disorder was exposed to cannabis.
- Consider avoiding or delaying use of cannabis until after the age of typical expression/onset of the illness (at least 25) *(age of expression can range from ~16-35 years old)*
- Those initially diagnosed with a cannabis-induced psychosis, have greater rates of developing schizophrenia over the long-term
- Frequency and amount, time of exposure, duration of exposure, and potency of cannabis all impact amount of risk for psychosis associated with cannabis use (greater frequency and duration, earlier first use, and higher potency THC = greater risk of psychosis)
- Daily and higher potency cannabis leads to increased risk of psychosis
- Today's cannabis tends to be more potent (higher levels of THC) than several decades ago
- 15% of new cases of psychosis are attributable to cannabis use
- The risk for developing schizophrenia spectrum disorders is greatest with cannabis, although other substances such as amphetamines, hallucinogens, opioids, and sedatives also increase risk.

https://medicine.yale.edu/psychiatry/step/early-intervention-services/cannabis

Cannabis use after the onset of psychosis is associated with:

- More non-adherence to treatment
- More relapses
- More hospitalizations
- More legal problems
- More ER visits
- More homelessness

- In regard to the self-medication hypothesis, cannabis use may result in a very temporary reduction in distress associated with psychotic symptoms, however, cannabis use makes symptoms of psychosis worse in the moment and over the long-term

https://medicine.yale.edu/psychiatry/step/early-intervention-services/cannabis

CBD and Psychosis:

- CBD market is largely unregulated so ratios of CBD to THC, as well as general contents may vary greatly from what is advertised
- In a study examining the antipsychotic properties of CBD at Yale, CBD did not improve symptoms of psychosis

https://medicine.yale.edu/psychiatry/step/early-intervention-services/cannabis

Thank you!

Questions
and
Comments?

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