

Cannabis and Psychosis in Adolescence

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Amy M. Mayhew, MD, MPH

Adult, Child & Adolescent Psychiatrist

Clinical Director

Maine Medical Center Child & Adolescent Psychiatry Outpatient Clinic

PIER Program

A close-up, top-down view of a black frying pan on a stovetop. A hand is cracking a white egg into the pan. Inside the pan, there is already a sunny-side-up egg with a bright yellow yolk. The oil in the pan is bubbling and sizzling. The background shows the white surface of the stove with black control knobs.

This is your brain on drugs. Any questions?

- Passage of laws in many states making both medicinal and recreational use legal
- Increase of tetrahydrocannabinol (THC) content by six or sevenfold in today's products
- Explosion of options for ingesting marijuana
- Lack of FDA oversight
- General view of the public that marijuana is safe and 'natural'
- General lack of public health information that examines marijuana usage and risks and benefits



CDC Youth Risk Behavior Survey 2017

- Ever used marijuana: 35.6% (compared to peak rate of 47.1 % in 1997)
- Currently use marijuana: 19.9%
- Tried marijuana before 13 yo: 6.5%
- Currently use alcohol: 29.8%
- Tried alcohol before 13 yo: 15.5%
- Ever tried cigarettes: 28.9%
- Ever vaped electronic products: 42.2%
- Currently vape electronic products: 13.3%
- Ever used illicit drugs (heroin, cocaine, meth, etc): 14.0%
- Ever took pain pills not prescribed: 14.0%



Varying Use

- African-American students: 42.8%
- Latino students: 42.2%
- White students: 32%
- LGBTQ students: 30.6%
- Heterosexual students: 19.1%
- 'not sure' students: 18.9%
- 9th graders: 13.1%
- 10th graders: 18.7%
- 11th graders: 22.6%
- 12th graders: 25.7%
- Youth who engage in substance use in later years (>17 yo) less likely to develop substance use disorders
- Positive attitudes towards school, parental monitoring and strong disapproval of peer substance use also protective



Cannabis 101

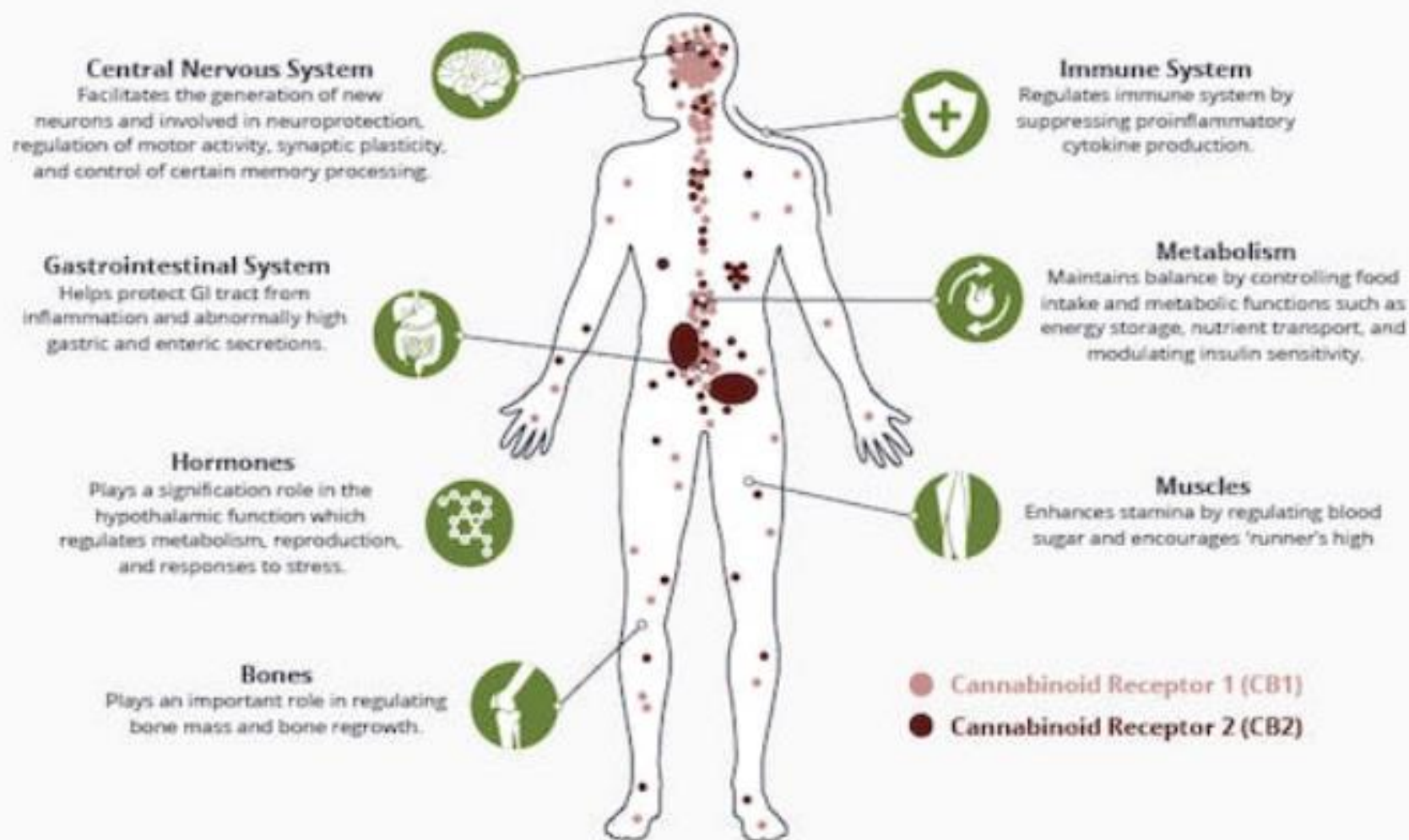
- Cannabis products contain terpenes, flavonoids, alkaloids, and >100 cannabinoids
- Phytocannabinoids, plant-derived cannabinoids, have several classes
 - tetrahydrocannabinol (THC) and cannabidiol(CBD) are the most abundant and studied forms
 - THC is considered the main psychoactive component of the plant
- there is no 'standard' form of cannabis; each extract or product has varying forms of ingredients
- There is no general regulating body of these products, much like supplements
- THC content can range from 17%-95%, compared to 4% from 20 years ago
- Average THC content of MJ sold legally in Colorado is 18%



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

THE BODY'S ENDOCANNABINOID SYSTEM



Marriage of Endocannabinoids and Phytocannabinoids

- THC an 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
- 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)
- Antiemetics (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)



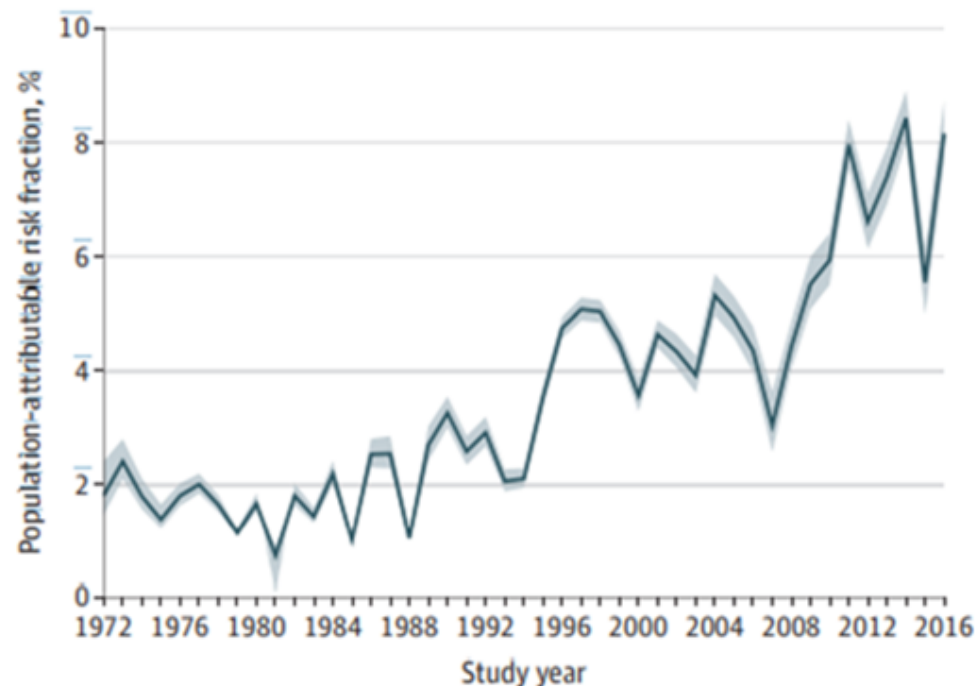
Research supporting the use of smoked cannabis for medical conditions is limited to less than 10% THC

- 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

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

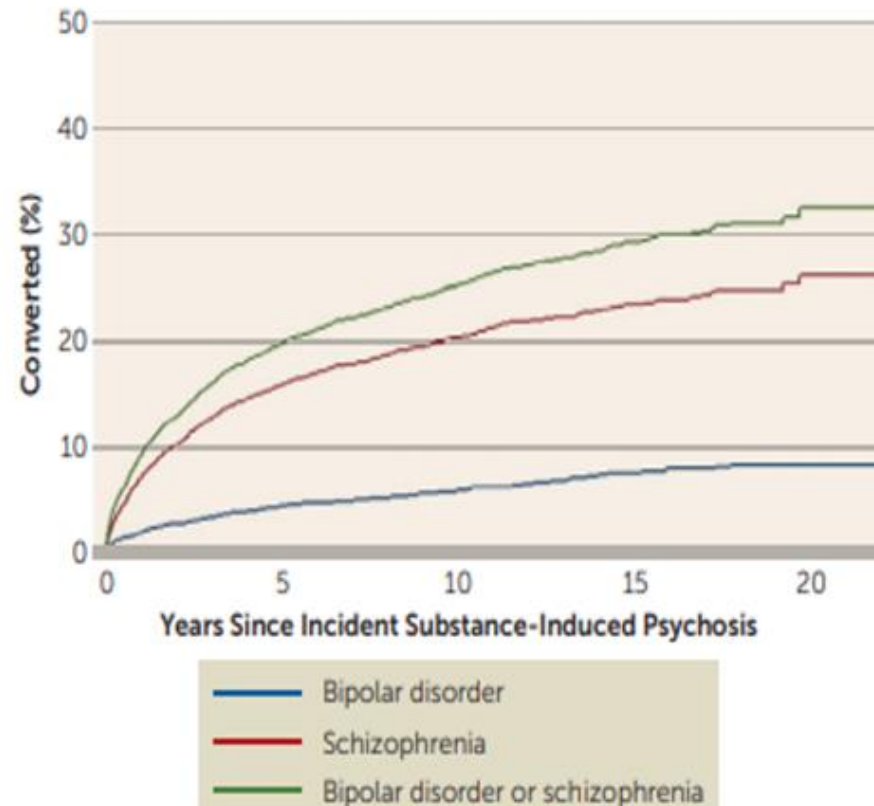
Figure 2. Development of the Population-Attributable Risk Fraction (PARF) of Cannabis Use Disorder in Schizophrenia in Denmark



Shaded areas indicate 95% CIs.

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

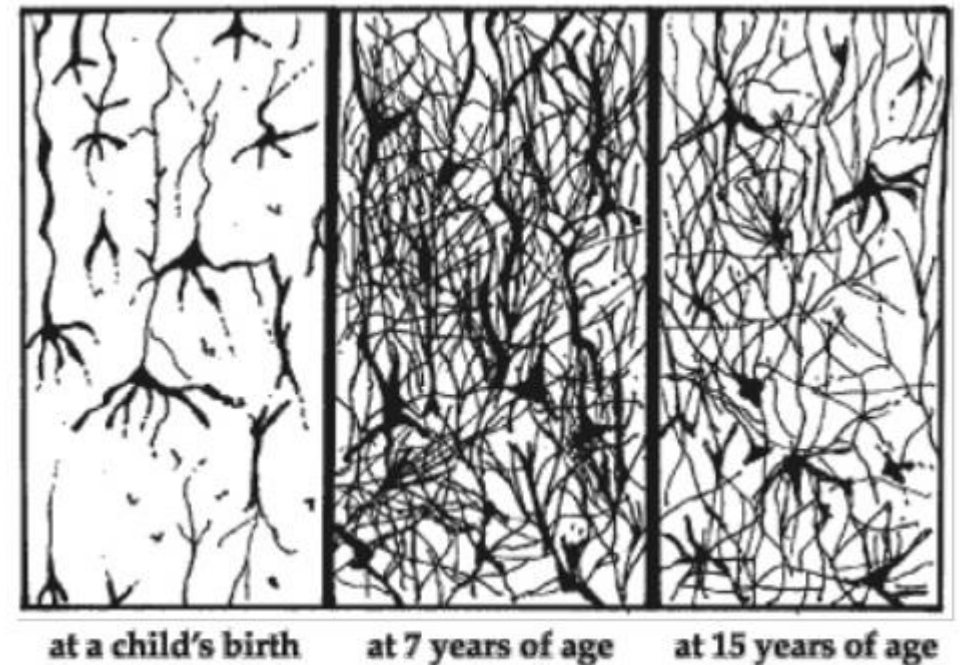
FIGURE 1. Rates of Conversion to Schizophrenia and Bipolar Disorder Following Incident Substance-Induced Psychosis in a Registry Study (N=6,788)



- 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](http://ajpp.psychiatryonline.org)

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)



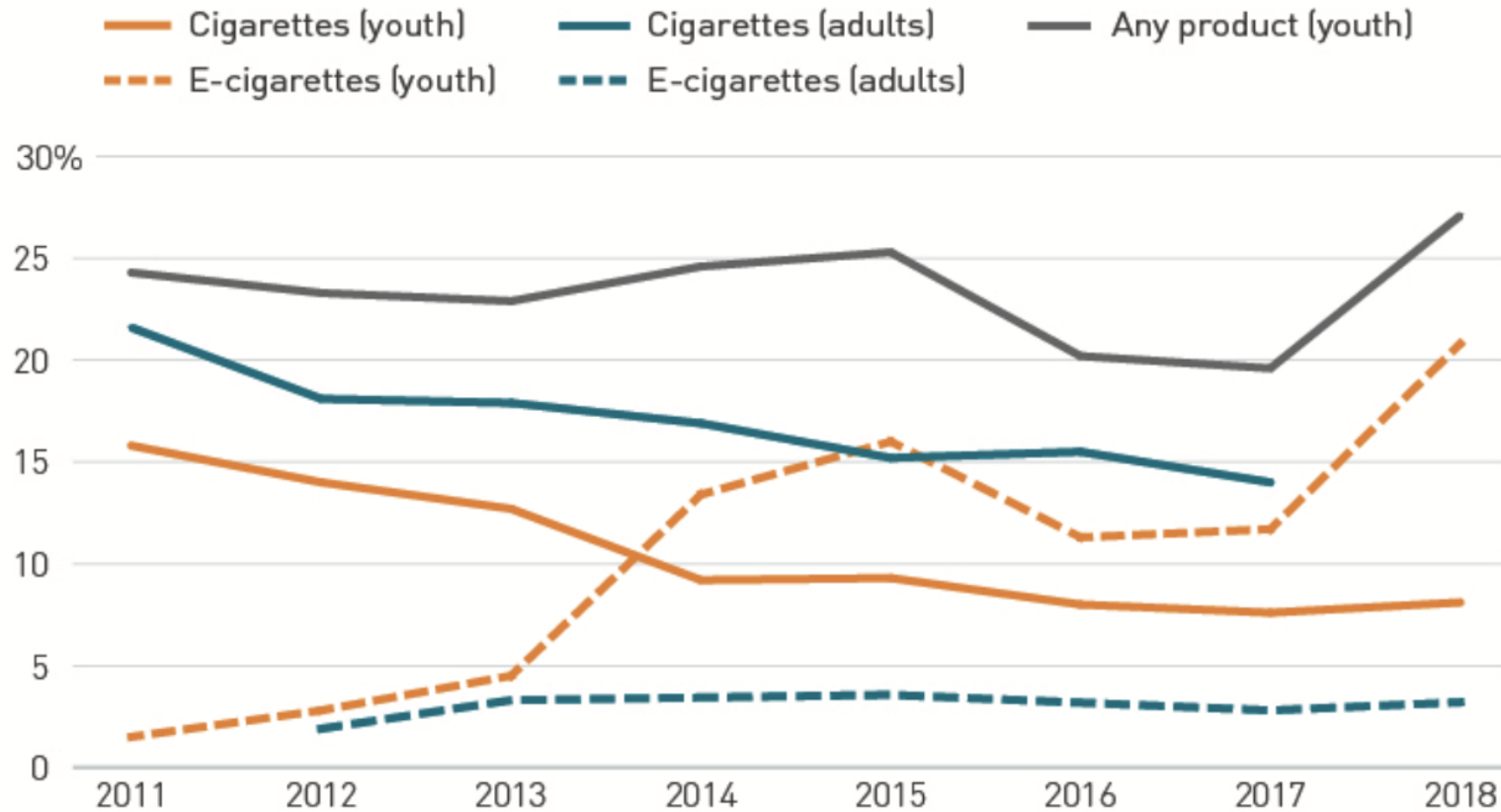
Big Tobacco and the Search for Big Money

- 1965: 43% of American smoked cigarettes
- 2019: 14% of American smoked cigarettes
- Most Americans recognizing smoking is addictive and one of the leading preventable causes of poor health
- Tobacco industry introduced vapes to expand its base
- 2018: 20% of high schoolers had used an e-cigarette in past 30 days
- 2019: 27.5% of high schoolers
- Use by adults relatively steady at 3% since 2013

www.Truthinitiaive.org



Trends in youth and adult tobacco use over time

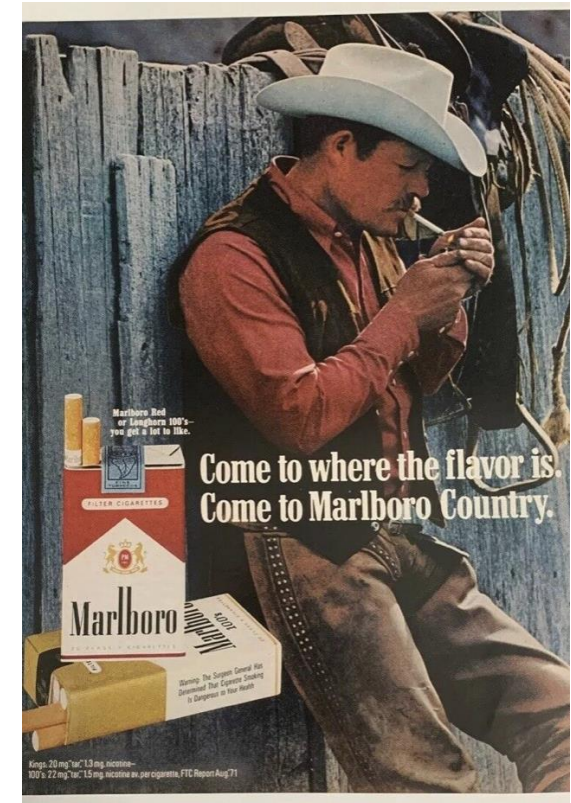


Source: NHIS (2011-2017), NATS (2012, 2013, 2015, 2017); YRBS (2011-2018); Adult e-cigarette use estimate for 2018 derived from Truth Initiative. Preliminary analysis of 2018 NHIS data.

New Product, Old Tricks

- Since the 1960s, the tobacco industry has tried to market to youth
- 1998 Master Settlement restricted this marketing, leading to steep declines in tobacco sales
- Despite declines in cigarette consumption, tobacco industry profits are growing, based on e-cigarettes
- 2005: \$10 billion industry
- 2016: \$18.4 billion industry
- BY marketing to young people, create a new pipeline of users, many of whom were not smokers previously
- 2000: 28% of high school student smoke cigarettes
- 2019: 5.8% of high school students smoke cigarettes, but **27.5% vape**

www.Truthinitiaive.org



Vaping and Psychosis

- Those who use e-cigarettes are more likely to use cannabis and cigarettes and vice versa
- Both vaping nicotine and THC linked with increased psychosis
- THC delivery in vape system much higher concentration than previously found in plants
- 15-30% THC is considered high potency
- Possible to find up to 95% THC concentration
- Healthy Minds Survey: 29,232 college students
 - Past month vaping nicotine: almost twice as likely to have psychotic experiences
 - Daily use of high potency THC: five times increase in psychosis
- Genetics and amount of exposure can influence how likely someone is to have these experiences



Cannabis Use and Sequellae

- Most adolescents do not perceive MJ use as harmful or addictive
- As opposed to ETOH, drivers feel MJ is safer to use while driving, yet do not understand the effects (Keyes, 2016)
- Animal studies show MJ does prime the brain to the effects of other substances
- Those who use MJ have a 2.78 increased risk of opiate use disorder, as well as increased risk of stimulants, cocaine, and injection drugs (Olfson, 2018)
- 8-12% of MJ users will develop moderate to severe cannabis disorders
- Withdrawal is not fatal, but within a week of stopping can be linked to irritability or aggression, anxiety, decreased appetite, depressed mood, abdominal pain, tremor, fever chills and headaches



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





The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study

Marta Di Forti, PhD • • Diego Quattrone, MD • Tom P Freeman, PhD • Giada Tripoli, MSc •
Charlotte Gayer-Anderson, PhD • Harriet Quigley, MD • et al. [Show all authors](#) • [Show footnotes](#)

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Marijuana and psychosis

- Daily cannabis use associated with increased odds of developing a psychotic disorder compared to never users (OR 3.2 95% CI 2.2-4.1)
- Daily use of high potency cannabis increased the odds to almost 5 times that of never users (OR 4.8, CI 2.5-6.3)
- Eliminating high potency MJ would decrease incidence of first episode psychosis by 12.2% in all 11 sites, 30.3% in London and 50.3% in Amsterdam

Anandamide-Depletion Hypothesis

- Inflammation is a major contributor to psychosis
- Brain's cannabinoid substance, anandamide, rises during inflammation, and is part of the natural anti-inflammatory process
- Regular exposure to plant-based cannabinoids reduces body's ability to produce its own
- Frequent marijuana use may make the brain more vulnerable to inflammation
- Anandamide rise in response to inflammation
- In one study, there were CSF and autoantibodies abnormalities in 54.4% of 180 psychotic patients
- In combination with cMRIs and EEGs, evidence of abnormalities in 75.6% of psychotic patients

(Endres, 2015, Koethe, 2009)

Anandamide-Depletion Hypothesis

- Bioactive lipid that binds to cannabinoid receptors
- A homeostatic role has been suggested in schizophrenia
- Dopamine/endocannabinoid interaction: (over-)activation of dopamine D_2 receptors is associated with an increased release of anandamide, counterbalancing dopamine-mediated psychotic symptoms by strengthening an endogenous feedback loop
- Another study measured levels of anandamide and its structural analogue (oleoylethanolamide) in CSF and serum of prodromal patients (n=27) and healthy volunteers (n=81)
- Levels of anandamide significantly elevated in CSF of patients compared to volunteers
- Prodromal patients with LOWER levels at significant risk of developing psychosis earlier
- Anandamide a protective mechanism against development of a frank psychotic illness

Anandamide levels in cerebrospinal fluid of first-episode schizophrenic patients: impact of cannabis use

F Markus Leweke ¹, Andrea Giuffrida, Dagmar Koethe, Daniela Schreiber, Brit M Nolden, Laura Kranaster, Miriam A Neatby, Miriam Schneider, Christoph W Gerth, Martin Hellmich, Joachim Klosterkötter, Daniele Piomelli

- CSF from patients with schizophrenia have higher levels of anandamide than healthy volunteers
- Anandamide levels inversely correlated to psychotic symptoms; release counters neurotransmitter abnormalities in psychosis
- Comparing people with schizophrenia to healthy controls (high and low users of MJ in both groups), those with high MJ use and psychosis had lower levels of anandamide; those with low MJ use and psychosis had ten-fold increase in CSF anandamide
- Frequent cannabis exposure may down-regulate anandamide signaling in the CNS of schizophrenic patients, but not of healthy individuals

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

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



- “Regular” suburban kid, who turned 14 yo the year Colorado legalized MJ
- Started dabbing at 14 yo
- Maintained a 4.0 GPA
- Scholarship to college
- Became paranoid, thought the mob was after him, university was a base for the FBI
- Jumped off a 6 story building



Cannabis and Bipolar Disorder



- Relatively well-known association between marijuana and psychotic spectrum illnesses
- Several articles have shown that marijuana may worsen manic symptoms in those with bipolar disorder
- Cannabis may also be a causal risk factor, with an increased incidence of up to three-fold
- *Cannabis use and mania symptoms: a systematic review and meta-analysis, Gibbs, M, et al; J Affective Disord Jan 2015*

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)



Marijuana and Anxiety



- Anxiety is often cited by adolescence as a reason they use marijuana
- 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)

(Cancelliere, 2018)

Thank you!

Questions
and
Comments?



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