A Proposed Mechanism to Adolescent Cannabis Induced Psychosis

David Perekopskiy, Dr. Tyler Lesh, and Dr. Cameron Carter

UC Davis School of Medicine

Abstract

As the rate of cannabis induced psychosis increases in many parts of the world, it is important to understand the pathophysiology of this disorder. In this review we will attempt to connect cannabis induced physiological changes with new PET data on CB1 receptors in patients with schizophrenia to provide a theoretical mechanisms of cannabis-induced psychosis in adolescence. We propose that adolescent cannabis induced psychosis is possibly induced by chronic usage of cannabis during an important neurodevelopmental timeframe. This induces CB1 receptor down regulation due to tolerance, a similar pathophysiological state seen in patients with schizophrenia. The risk of developing cannabis induced psychosis is proposed to be a combination of when cannabis use is first initiated, potency of cannabis, frequency of usage and genetic predisposition. After reviewing these steadily increasing data, we propose future studies and policy changes to further understand this mechanism and decrease the incidence of adolescent cannabis induced psychosis.

Cannabis Physiology, Usage and Epidemiology

Cannabis is one of my most commonly consumed recreational drugs in the world. It's major psychoactive effects are through Δ9-tetrahydrocannabinol (THC).

Usage:

- In the US, 42 million people have tried cannabis at least once.[1]
- High school usage: 37% of students have used at least once.[2]
- Daily usage per grade[3]:
  - 8th : 1.1 %
  - 10th : 4.4 %
  - 12th : 6.9 %
- Adolescents are **4 to 7 times** more likely to develop a cannabis use disorder if marijuana use is started before the age of 18 when compared to adults.[4]

Potency:

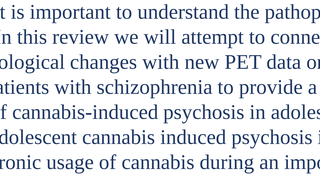
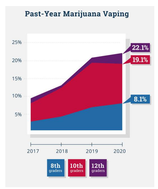


Figure 1: Graph shows data of seized cannabis samples by the DEA from 1995 to 2019.[5]

- 70+ % of cannabis advertised online is 15+ % THC[6]
- Average THC content of cannabis found online[6]:
  - Recreational: **21.5% ± 6.0**
  - Medical: **19.2% ±6.2**

Forms of Consumption:



The quantity of adolescences trying cannabis through vaping is increasing.

Figure 2: Demonstrates the percentage of students that have consumed cannabis through vaping by grade from 2017 to 2020.[7]

Endocannabinoid System

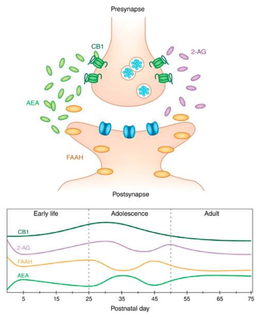


Figure 3: Illustrates the CB_1 receptor on the presynaptic terminal. Around it are AEA (arachidonoylethanolamide) and 2-AG (2-arachidonylglycerol) the normal physiological ligand of the CB_1 receptor. The bottom chart presents the quantity of enzymes and ligands through development.[8]

Endocannabinoid system is a group of ligands and receptors involved with many different processes such as neuronal development, regulation of neuronal transmission, mood, memory formation, etc[9] . The major receptors in the endocannabinoid system are the CB_1 and CB_2 receptor.

The **CB_1 receptor** is a presynaptic, **inhibitory G-protein receptor**. It is most concentrated in the PFC where it refines **excitatory glutamatergic**[10] and **inhibitory GABAergic**[11] signaling during adolescences.

CB_1 Receptors in Schizophrenia

Author	Year	Radioligand	Patients with Schizophrenia	Controls	Outcomes
Wong et al.[13]	2010	[^{11}C]OMAR	9	10	↑ CB_1R : pons
Ceccarini et al.[14]	2013	[^{18}F]MK-9470	67	12	↑ CB_1R : nucleus accumbens, insula, cingulate cortex, inferior frontal cortex, parietal and mediotemporal lobe
Ranganathan et al.[15]	2016	[^{11}C]OMAR	25	18	↓ CB_1R : amygdala, caudate, posterior cingulate cortex, hippocampus, hypothalamus, and insula
Borgan et al.[16]	2019	[^{11}C]MePPEP	40	20	↓ CB_1R : anterior cingulate cortex, hippocampus, striatum, and thalamus

Table 1: *An overview of PET studies in humans looking into CB1R in patients with Schizophrenia.*

In this study we looked into CB_1 receptor levels in humans using PET. The results are shown above (Table 1).

Though the results are mixed, a few articles have been written to explain the mixed results.

Multiple authors have stated that there could be discrepancies in these study outcomes including symptom severity, sex, age, PET tracers, statistical analysis methods, or comorbid nicotine usage [17]

The current consensus is that the CB_1 Receptor is decreased in patients with schizophrenia.

Proposed Mechanism

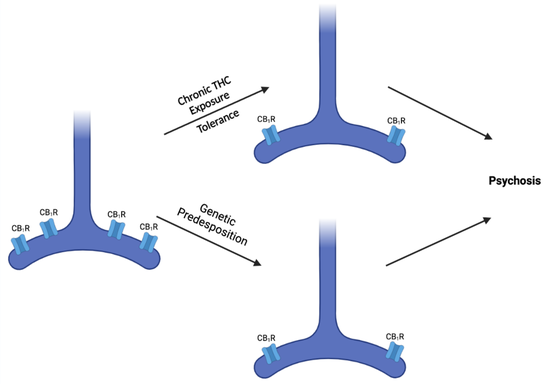


Figure 4: *Two mechanisms of Psychosis: The figure above demonstrates how both chronic THC exposure and genetic factors induce similar CB1R pathophysiological states, which both result in psychosis. Chronic THC exposure results in a downregulation of CB1R due to tolerance.*

The proposed mechanism is that both schizophrenia and chronic cannabis usage create a similar pathophysiological state:

- **Schizophrenia**: Genetic and environmental factors decrease CB1 receptor availability
- **Chronic cannabis usage**: Tolerance induced by partial cannabinoid THC in cannabis causes a down regulation of the CB1 receptor.

Both mechanisms induce a disruption in proper neurodevelopment during adolescences which results in a lack/decrease of refining by the CB1 receptor during adolescence. The lack of refinement induces psychosis.

Why doesn't everyone who smokes cannabis during adolescence develop psychosis?

We propose there are 4 factors:

1. Age of onset
2. Consistency of use
3. Potency of Cannabis
4. Genetic predisposition

Age of onset is important because it seem there is a specific window of susceptibility where THC can induce neuro disfunction in adolescence unlike in adulthood.

Consistency of usage determines how much tolerance is seen with the CB_1 receptor. The more usage the greater the effect.

Potency of Cannabis influences the effect of tolerance. Higher levels of THC leads to a great down regulation.

Genetic predisposition makes certain populations more susceptible to cannabis induced psychosis. Genetic variations in COMT [19]and AKT1[20] have both demonstrated increased risk of cannabis induced psychosis.

Summary: Future Research

Proposed Future research:

- How do **high potent cannabis** products effect neurodevelopment and risk of developing psychosis?
- What are the **pathophysiological mechanisms of CB_1 receptor dysfunction** which possibly lead to cannabis induced psychosis?
- Use **PET to analyze CB_1 receptor availability** within adolescence during **cannabis usage** and **after cessation**.
- Determine the **neurodevelopmental timeline** where adolescences are most susceptible.
- Continue to look into **genetic variations** which can increase cannabis induced psychosis.

Policy Proposal:

- **Increase education** of students as early as **middle school** on the affects of cannabis on the brain.
- Promote **Cannabis screening** among pediatrician and family medicine physicians.
- **Identify** cannabis use disorder and refer patients to appropriate treatment: Cognitive behavioral therapy

References

1. Substance Abuse and Mental Health Services Administration, "Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health," Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD, 2020.

2. Jones CM, Clayton HB, Deputy NP, Roehler DR, Ko JY, Esser MB, Brookmeyer KA, Hertz MF. Prescription Opioid Misuse and Use of Alcohol and Other Substances Among High School Students – Youth Risk Behavior Survey, United States, 2019. MMWR Suppl. 2020 Aug 21;69(1):38-46.

3. *NIDA. 2020, December 15. Study: Surge of teen vaping levels off, but remains high as of early 2020. Retrieved from https://nida.nih.gov/news-events/news-releases/2020/12/study-surge-of-teen-vaping-levels-off-but-remains-high-as-of-early-2020 on 2022, May 18.*

4. Winters KC, Lee CY. Likelihood of developing an alcohol and cannabis use disorder during youth: association with recent use and age. Drug Alcohol Depend. 2008;92(1-3):239-247. doi:10.1016/j.drugalcdep.2007.08.005

5. Delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) Potency of Cannabis Samples Seized by the Drug Enforcement Administration (DEA), Percent Averages from 1995-2019. Source: Potency Monitoring Program, Quarterly Report # 146, NIDA Contract Number: N01DA-15-7793

6. Cash MC, Cunnane K, Fan C, Romero-Sandoval EA. Mapping cannabis potency in medical and recreational programs in the United States. PLoS One. 2020;15(3):e0230167. Published 2020 Mar 26. doi:10.1371/journal.pone.0230167

7. Monitoring the Future 2020 Survey Results. Source: *National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services.*

8. Meyer, H., Lee, F. & Gee, D. The Role of the Endocannabinoid System and Genetic Variation in Adolescent Brain Development. *Neuropsychopharmacol.* **43,** 21–33 (2018). https://doi.org/10.1038/npp.2017.143

9. Lu HC, Mackie K. Review of the Endocannabinoid System. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021 Jun;6(6):607-615. doi: 10.1016/j.bpsc.2020.07.016. Epub 2020 Aug 1. PMID: 32980261; PMCID: PMC7855189.

10. Gerdeman G, Lovinger DM. CB1 cannabinoid receptor inhibits synaptic release of glutamate in rat dorsolateral striatum. J Neurophysiol. 2001 Jan;85(1):468-71. doi: 10.1152/jn.2001.85.1.468. PMID: 11152748

11. Katona I, Sperlágh B, Sík A, Käfalvi A, Vizi ES, Mackie K, Freund TF. Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. J Neurosci. 1999 Jun 1;19(11):4544-58. doi: 10.1523/JNEUROSCI.19-11-04544.1999. PMID: 10341254; PMCID: PMC6782612

12. Di Marzo, V., Melck, D., Bisogno, T., & De Petrocellis, L. (1998). Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. Trends in neurosciences, 21(12), 521-528

13. Wong DF, Kuwabara H, Horti AG, Raymont V, Brasic J, Guevara M, Ye W, Dannals RF, Ravert HT, Nandi A, Rahmim A, Ming JE, Grachev I, Roy C, Cascella N. Quantification of cerebral cannabinoid receptors subtype 1 (CB1) in healthy subjects and schizophrenia by the novel PET radioligand [11C]OMAR. Neuroimage. 2010 Oct 1;52(4):1505-13. doi: 10.1016/j.neuroimage.2010.04.034. Epub 2010 Apr 18. PMID: 20406692; PMCID: PMC6580862

14. Ceccarini J, De Hert M, Van Winkel R, Peuskens J, Bormans G, Kranaster L, Enning F, Koethe D, Leweke FM, Van Laere K. Increased ventral striatal CB1 receptor binding is related to negative symptoms in drug-free patients with schizophrenia. Neuroimage. 2013 Oct 1;79:304-12. doi: 10.1016/j.neuroimage.2013.04.052. Epub 2013 Apr 25. PMID: 23624489.

15. Ranganathan M, Cortes-Briones J, Radhakrishnan R, Thurnauer H, Planeta B, Skosnik P, Gao H, Labaree D, Neumeister A, Pittman B, Surti T, Huang Y, Carson RE, D'Souza DC. Reduced Brain Cannabinoid Receptor Availability in Schizophrenia. Biol Psychiatry. 2016 Jun 15;79(12):997-1005. doi: 10.1016/j.biopsych.2015.08.021. Epub 2015 Aug 29. PMID: 26432420; PMCID: PMC4884543

16. Borgan F, Laurikainen H, Veronese M, et al. In Vivo Availability of Cannabinoid 1 Receptor Levels in Patients With First-Episode Psychosis. JAMA Psychiatry. 2019;76(10):1074–1084. doi:10.1001/jamapsychiatry.2019.1427

17. Mihov Y. Positron Emission Tomography Studies on Cannabinoid Receptor Type 1 in Schizophrenia. Biol Psychiatry. 2016 Jun 15;79(12):e97-9. doi: 10.1016/j.biopsych.2016.04.015. Epub 2016 Apr 26. PMID: 27241001

18. Borgan F, Kokkinou M, Howes O. The Cannabinoid CB1 Receptor in Schizophrenia. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021 Jun;6(6):646-659. doi: 10.1016/j.bpsc.2020.06.018. Epub 2020 Jul 6. PMID: 33077399.

19. A. Caspi, T.E. Moffitt, M. Cannon, J. McClay, R. Murray, H. Harrington, A. Taylor, L. Arseneault, B. Williams, A. Braithwaite, R. Poulton, I.W. Craig. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biol Psychiatry, 57 (10) (2005), pp. 1117-1127,

20. van Winkel, R., Risk, G., & Outcome of Psychosis (GROUP) Investigators. (2011). Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: sibling analysis and proband follow-up. Archives of general psychiatry, 68(2), 148-157.

Acknowledgements

I would like to thank Dr. Cameron Carter and Dr. Tyler Lesh for their input and mentorship with this project. I would like to thank Dr. Saul Schaefer and Holly Ly for their support in the MD/PhD program and research selective. I would like to thank UC Davis School of Medicine for their support through this research selective.