UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

RESEARCH PROTOCOL OPEN ACCESS

Examining the Relationship between Schizophrenia and Cannabis Use: A Research Protocol

Melissa Perez, Specialized Honors Student Psychology BA [1]*

[1] Faculty of Health, York University, Toronto, Ontario, Canada M3J 1P3

*Corresponding Author: melissa.perez@mail.utoronto.ca

Abstract

Schizophrenia is a complex mental disorder depicted through positive and negative symptoms that interfere with daily functioning. Schizophrenia is characterized by an insidious loss in brain function in the dorsal lateral prefrontal cortex, a region which precipitates interference of perceptions, thought processes, and emotional affect. This proposed study aims to investigate the longitudinal effects of high potency cannabis use and the development of schizophrenia symptoms over a period of 5 years. Utilizing a cross-sequential approach, adolescent participants n = 200, ages 13-19 will be recruited from the community and self-report strains of cannabis consumed, frequency of usage, and fluctuations in mood and perceptions. Assessments will be conducted at baseline and after 5 years using standardized measures including the Positive and Negative Syndrome Scale (PANNS), Brief Negative Symptom Scale (BNSS), and Addenbrooke's Cognitive Examination-III (ACE-III). Anticipated results include a dose-dependent relationship, with higher levels of psychosis reported in the high potency cannabis group. Additionally, participants in the high potency group are expected to demonstrate higher scores on the psychometric tests used for assessing schizophrenia symptoms, as well as show signs of cognitive decline when compared to the low dose and control groups. These findings will contribute to the understanding of the long-term effects of cannabis use in adolescents and inform prevention strategies for the prodromal period of schizophrenia.

Keywords: cannabis; schizophrenia; adolescence

Introduction

Adolescent cannabis use has been identified as a potential risk factor for heightened susceptibility of psychosis in young adulthood [1, 2]. A large body of research shows individuals that initiate cannabis use earlier in adolescence are more likely to develop a psychotic disorder compared to those that commence later in life [3, 4, 5]. Genomic research suggests while genetic predisposition has long been established as a pivotal element in the etiology of schizophrenia, heightened risk is also attributed to prenatal conditions, exposure to adversity, and interactions with the environment [6]. Because of this, the cannabis flower is customarily juxtaposed as an environmental agonist in schizophrenia research [6]. Cannabis use among individuals with a genetic predisposition for schizophrenia purportedly elicits a biological response, precipitating the onset of first psychotic episodes [7]. This precise sensitivity in pathophysiology and the association between the development of schizophrenia with high-potency cannabis usage continues to elude comprehensive exploration.

Neurobiology

The cannabis sativa plant produces a psychoactive chemical substance called Δ-9-tetrahydrocannabinol (D9-THC) [6, 7, 8]. The potent sinsemilla/skunk variant of marijuana traditionally contained 4% THC in the 1990s, albeit has been rumored to circulate in the Netherlands and England with concentrations ranging up to 20% [3, 7]. According to Casadio and colleagues[3], it is suspected that there is a relationship between the overstimulation of the CB1 receptor, a prominent endocannabinoid system receptor type and psychotic episodes induced by THC.

Endocannabinoids are naturally occurring lipid neurotransmitters within the human body that bind to the cannabinoid receptors, CB1 and CB2 [3]. Casadio and partners[3] explain these compounds are complicit in the regulation of cognitive functions in regions such as the cerebral cortex, the amygdala, and within memory neurons of the hippocampus. In the peripheral and central nervous system, endocannabinoids play a mediating role in motor activity, especially in regions with high densities of CB1 receptors.

THC is a cannabinoid agonist that is known to disrupt the balance of the endocannabinoid system via overstimulation of the CB1 receptors [3]. Modern advancements in the unregulated fabrication of synthetic cannabinoids reportedly produce strains that are 10-200 times more potent than THC, instituting serious concern for unpredictable intoxication, onset of psychosis after exposure, and persistent psychosis found in schizophrenia [7].

The role of CB1 receptors is complex and not fully understood in schizophrenia. CB1 receptors are conceptualized as modulators of important neurotransmitters such as dopamine, gamma aminobutyric acid (GABA), and glutamate [6]. Dysregulation of these neurotransmitters is often associated with the cognitive deficits seen in schizophrenia, including psychosis [6, 7]. Moreover, preclinical trials in animals have shown that modulating the activity of these receptors can have therapeutic potential for regulating behaviors seen in schizophrenia [9, 10].

Preclinical Studies

During adolescence, neuroanatomical changes such as synaptic remodeling in the prefrontal cortex can facilitate cognitive efficiency [11]. Murphy and co-authors[11] examined the consequences of high potency THC administration in mice and its impact on prefrontal cortex (PFC) maturation. The administration of THC to adolescent male mice for three weeks resulted in persistent deficits in performance and repetitive behaviors, whereas these behaviors were only temporary in adult mice. Chronic administration of THC in adolescent mice led to object impairment/recognition, supporting the notion that adolescent exposure to potent THC can promote enduring cognitive deficiencies, a phenomenon absent in THC administration in adult mice.

Upon reaching adulthood, adolescent rats exposed to cannabis exhibited diminished dendritic length, arborization, and impaired synaptic plasticity in the PFC as the result of damaged synapse pathways [12]. Impairments in long term potentiation from the hippocampus to the PFC, disruption in the uptake of glutamate at the synaptic cleft and receptors has been implicated in the altered neural plasticity observed in schizophrenia [12]. Therefore, it is crucial to understand potent D9-THC contains low levels of non-psychoactive cannabidiol (CBD). CBD has purportedly demonstrated its efficacious ability to restore cognitive function in mice and alleviate feelings of anxiousness or psychotic symptoms in humans when consumed in isolation [11, 12, 13]. Thus, it is essential to review the epidemiological studies that identify risk factors and disease occurrence associated with high potency cannabis use dosage and schizophrenia.

Clinical Studies

Preclinical research can provide valuable insight into the underlying biological mechanisms involved in cannabis use and schizophrenia-like symptoms, albeit clinical research must establish a causal relationship between cannabis and schizophrenia to support such a claim.

In a cross-sectional investigation by Wainberg and colleagues [2], self-reported cannabis use exhibited a dose-dependent relationship with psychosis among adults with a known polygenic risk for schizophrenia, with a high number of individuals reporting early onset psychotic experiences before the age of 18. Individuals that experience a single psychotic episode face a 47% chance of developing schizophrenia, with adolescents showing the most vulnerability to conversion [14]. The National Prodrome Study (NAPLS) was a notable longitudinal prodromal schizophrenia project that followed clinically high-risk individuals to assess the progression of negative and positive symptoms. Both positive and negative symptoms between the 18- and 24-month marker did not show improvements [15]. Therefore, it is foreseen positive symptoms will emerge approximately around the two-year mark.

There have been several inquiries into the relationship between high potency cannabis use and the development of schizophrenia-like symptomatology. Many studies have linked the endogenous neurotransmitter of the endocannabinoid system anandamide with schizophrenia [13]. One study of first-episode schizophrenia patients revealed anandamide levels in the cerebral spinal fluid was 8 times higher than levels found in healthy controls, while another study demonstrated frequent cannabis use elevated anandamide levels in patients with schizophrenia compared to control groups [13, 16, 17].

An experimental investigation into the acute effects of D9-THC intravenous administration in humans showed a dose-dependent relationship between cannabis and injection-induced symptoms of schizophrenia by systematically administering varying doses of THC to healthy participants [8]. Higher doses of THC were associated with a greater severity in psychotic symptoms [8]. Notwithstanding, a study using positron emission tomography demonstrated striatal dopamine is increased upon inhalation of D9-THC which has been alleged to sustain symptoms of psychosis [18]. When human hair was examined for cannabis traces, individuals with elevated D9-THC traces showed high levels of delusional thought and positive schizophrenia symptoms compared to others who were placed in a CBD group [18, 19].

Potency

THC potency or strength refers to the specific quantity that is administered over time [20, 21]. THC levels can vary based on cultivation methods, strain genetics, and processing procedures [21]. In a meta-analysis by Marconi and collaborators [22], it was found that high-potency cannabis users had a greater likelihood of developing psychotic symptoms compared to those who abstained. Furthermore, a detailed assessment of a large sample of distinct first-episode profiles and patterns of cannabis usage by Schoeler and team [23] showed the likelihood of experiencing another psychotic episode was greatly reduce when regular cannabis users discontinued cannabis. Individuals with the poorest outcomes were those who continued high-potency cannabis use, with an elevated risk for additional psychotic episodes.

A multicentre case study by Di Forti and colleagues [24] examined the patterns of high potency and low potency cannabis use across 11 sites in Europe and Brazil, $n = 901$ first episode psychosis admissions, in parallel comparing these patterns to a control group. Low potency was defined as THC content below 10%. The main findings from this

investigation revealed daily use of high potency cannabis increased an individuals' likelihood of developing a psychotic illness by 4.8% CI [2.5, 6.3]. The strong point of this study is the transnational comparison of cannabis use. Moreover, one intriguing summation is that if high potency cannabis were no longer accessible, 12.2% of psychosis cases could be prevented. It was estimated 50% of psychosis cases in Amsterdam would be preventable, the world mecca for high potency cannabis with THC levels reaching a threshold of 60%.

Vulnerability of the Adolescent Brain

Di Forti and colleagues [24] concluded that adolescents who initiate cannabis use before the age of 15 have a 2.3 higher risk of developing psychosis compared to youth who commence after the age of 15, making adolescents distinctively a vulnerable population for developing psychosis. Therefore, understanding the connection between high potency cannabis use and psychotic episodes is critical for optimizing efforts aimed at preserving cognitive and behavioral functionality in young adults experiencing the onset of schizophrenia.

This study aims to examine the impact of frequent high-potency cannabis usage during adolescence in the development of inaugural psychotic episodes seen in schizophrenia later in life. This can only be addressed by following adolescent cannabis users longitudinally to determine if high-potency cannabis use is a strong predictor for schizophrenia spectrum disorders.

It is hypothesized that chronic high-potency cannabis use during adolescence is associated with an increased risk for developing schizophrenia. It is expected that the onset of psychosis and severity of schizophrenia symptoms will positively correlate with high-potency cannabis use, indicating a dose-dependent relationship between frequent high-potency cannabis consumption and the onset of schizophrenia in adolescence.

Methods

This study will use a cross-sequential research approach to examine the interaction of daily high-potency cannabis use and psychosis. This will be done through quantitative assessments and with qualitative interviews in multiple cohorts of human adolescents. A cohort with an equal gender distribution of n=200 adolescents between the ages of 13 and 19 will be recruited and followed over the course of a five-year period.

To test the association between high potency cannabis use, age, and onset of first psychotic episode, a multiple linear regression will be conducted. A sample size of 200 participants is considered sufficient for this investigation according to power calculations performed in (GPower 3.1.9.7) [41] using an alpha probability = .05, and power = .80. A sample of n = 200 is required to detect a small to moderate effect. A cross sequential design captures both cohort effects and age-related changes [25]. This method aims to demonstrate the variability of the effects for low and high potency cannabis doses between age groups. An understanding of developmental trajectories and potential implications of early exposure to cannabis use provides a nuanced perspective on age-related changes, permitting a robust analysis with results that can be generalized to the broader population. In subsequent phases of the study, an age stratified analysis will be undertaken to investigate the impacts of early initiation of cannabis use versus late initiation. This will elucidate how the timing of cannabis initiation during adolescence may distinctly influence psychotic risk and identification of developmental windows, informing preventative interventions.

This cohort group will be further subdivided into a control group CAN-NO n=100 and two experimental groups, CAN-HIGH n=50 and CAN-LOW n=50. Individuals in CAN-NO have no history of cannabis exposure or consumption and are expected to sustain this status for the entire duration of the experimental investigation.

Information on regular cannabis usage will be collected from online questionnaires: adolescents are asked if they currently consume THC products (yes/no/edible/smoke/ concentrates/other/at least 1 per day). For this study, individuals in the CAN-HIGH have a history of consuming cannabis products with concentrations exceeding 15%. The CAN-LOW group have a history of consuming THC products with concentrations lower than 10%. If these products are edibles, low THC is < 5mg and high THC is > 20mg. All concentrates will be considered highly potent, as these solvent-based products are documented as having extremely high levels of THC [26]. Frequent cannabis use is defined as daily or weekly usage with 10 or more instances of cannabis use per month.

Clinical Assessment

Adolescents will be selected from different geographical regions in Canada with varying degrees of family constellation. Exclusion criteria will consist of little to infrequent usage of other illicit substances, no previous diagnosis of schizophrenia, no neurodevelopmental disorders, and no first-time psychotic episodes reported.

Cannabis use will be electronically self-reported every 6 months. This will include disclosure of the cannabis strain name to verify potency, as well as route for consumption (e.g., inhalation, edibles, etc.). Follow-up assessments, flexible data collection at predetermined intervals, in addition to continuous monitoring of attrition rates will allow for adjustment of retention strategies. Additional questions related to seeking out medical treatment will be answered via this electronic survey over a period of 5 years, providing participants the opportunity to share sentiments about psychological functioning (e.g., paranoia, auditory/visual hallucinations, doctor visits/mental health concerns etc.). Nuanced responses and qualitative data captured via this format will provide insight into participant experiences. All participants will be compensated $15 for the completion of every survey.

Baseline assessments will consist of psychometrically sound measures to confirm eligibility and medical history. A neurological assessment will be performed by a trained clinician to assess mental status, sensory skills, and motor function. Individuals with any deficits in these areas will be excluded from the study. Participants will be screened before and after the five-year period using the Positive and Negative Syndrome (PANSS), and the Brief Negative Symptom Scale (BNSS).

The Positive and Negative Syndrome Scale (PANSS) is a widely accessible schizophrenia 30-item rating scale that provides a comprehensive evaluation of the positive and negative symptoms associated with schizophrenia [27]. The total scores are generated from three subscales to provide clinicians with a reliable measurement tool for tracking changes in symptomatology over time. The inclusion of a third dimension was implemented to enhance inter-rater reliability [28]. Internal consistency is reported as (a = .77-.89) [29, 30].

The Brief Negative Symptom Scale (BNSS) is a contemporary 13-item psychometric instrument used to measure negative symptomatology in schizophrenia such as anhedonia, asociality, and blunted affect [31]. According to Kirkpatrick and researchers[31], the scale is suitable for large psychological studies and for tracking change in patients' psychological health status. This scale has a strong construct validity and internal consistency, underscored by a Chronbach's alpha of (a = .88 - .93). Administration of the BNSS typically takes approximately 15 minutes (PsycTests Database Record (c) 2021 APA, all rights reserved).

An additional cognitive examination, the Addenbrooke's Cognitive Examination (ACE – III), will be performed by a trained clinician before the five-year trial period and at the end of the study. ACE-III is a cognitive screening tool with 21 questions that takes approximately 15 minutes to administer. Five domains of cognitive function are assessed: memory, attention, visuospatial function, verbal fluency, and language with a total score of 100 [32]. The ACE-III is highly sensitive and accurate for detection of patients who are at-risk of cognitive decline and mild cognitive impairments [32].

Questionnaires centering cannabis use and strain analysis will be statistically analyzed to quantify the magnitude of differences in THC potency, as well as the reported symptom profiles for individuals who sought out medical treatment and emergence of schizophrenia-associated psychotic symptoms.

Results

Individuals in the experimental group CAN-HIGH will exhibit a higher incidence and severity of psychotic symptoms compared to the CAN-LOW and control group suggesting a potential link between high potency cannabis use and exacerbation of schizophrenia-related symptoms [33, 34].

The CAN-HIGH group and CAN-LOW group are expected to demonstrate diminished cognitive function over the five-year period, with the CAN-HIGH group showing the lowest scores on the ACE-III when contrasted with the scores from the control group [35, 36].

Lastly, it is anticipated individuals in the CAN-HIGH group with higher scores on the PANSS will report more frequent hospitalizations and a greater incidence of positive symptoms associated with schizophrenia after the 24-month marker [23, 42].

Discussion

In keeping with prior studies, Di Forti and co-authors[4] found an onset of psychotic symptoms in individuals that consumed high-potency cannabis daily typically emerged around the sixth year period. It is estimated there is a sixfold risk for the development of schizophrenia and psychosis among cannabis users that consume high concentration (15-30%) THC [33, 34]. The presence of severe psychotic symptoms in the CAN-HIGH cohort will affirm the hypothesis that high potency cannabis usage is a robust predictor for the development of schizophrenia.

Regarding the relationship between THC and cognition, one study examining response latency among chronic cannabis users found both low and heavy THC dose groups were slower in decision-making and less apt to making accurate judgments compared to a placebo group [35]. Long-term cannabis use is associated with a smaller hippocampal volume in middle adulthood, IQ decline, and attention problems, creating concern for the risk of developing dementia [36]. The Harvard medical school cautions the average amount of THC in smokable products available in dispensaries is now roughly in the 30% range, a sharp increase from 4% in the 1970's [37]. A measurable decline in cognition indicated by lower ACE III scores would corroborate the theory that high potency usage precipitates both overt and covert cognitive dysfunction during the prodromal stage of schizophrenia that often go unnoticed.

Points of considerable interest are increased hospitalizations and frequent psychotic relapses [38, 39], while Henquet and associates [40] found a dose-dependent relationship among youth who reported cannabis use at baseline and psychotic symptoms during follow up. For these reasons, the expectation of a dose-dependent relationship appearing after 24 months is grounded in the hypothesis that increased exposure to products with elevated levels of THC escalates the risk and severity of both positive and negative symptoms found in schizophrenia. Overall, this suggests that high-potency THC can exacerbate symptoms in individuals predisposed to schizophrenia.

This study has several strengths. First, the sample groups are drawn from different socioeconomic backgrounds and races and are therefore representative of Canada's diverse population. Second, this study illuminates the various cannabis strains that adolescents have access to, in addition to the initial negative and positive symptoms that manifest in the prodrome. Studying the onset of cognitive decline in schizophrenia also has the potential to reveal protective

factors, warranting further research into the relationship between cannabis use and schizophrenia. Notwithstanding, causal inference cannot be inferred as this study did not account for genetic risk factors.

Conclusion

This longitudinal analysis seeks to establish a dose response relationship between the development of schizophrenia and frequent usage of high potency cannabis in early adulthood. Considering earlier initiation of high potency cannabis is linked to increased associated risk for schizophrenia, this inquiry aspires to provide insights for campaigns aimed at reducing harm and enhancing the cognitive well-being of adolescents. As cannabis is becoming more accessible and legalized, it is important to provide education and support evidence-based research that addresses the complexities of cannabis use and its neuropsychiatric implications.

List of Abbreviations Used

ACE-III: Addenbrooke's cognitive examination-III
BNSS: brief negative symptom scale
CBD: cannabidiol
D9-THC or THC Δ-9 : tetrahydrocannabinol
GABA: Gamma-aminobutyric acid
IQ: Intelligence quotient
PANNS: positive and negative syndrome scale
PFC: prefrontal cortex

Conflicts of Interest

The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

This is a proposed research study. Ethics approval has not been obtained, nor has recruitment commenced.

Authors' Contributions

MP: made contributions to the design of the study, drafted the manuscript, and gave final approval of the version to be published.

Acknowledgements

A thank-you to Youssef, M. for their expertise and assistance throughout all aspects of creating this research protocol.

Funding

This study was not funded.

References

[1] Fergusson, D. M., Horwood, L. J., & Swain-Campbell, N. R. (2003). Cannabis dependence and psychotic symptoms in young people. Psychological Medicine, 33(1), 15–21. https://doi.org/10.1017/S0033291702006402

[2] Wainberg, M., Jacobs, G. R., di Forti, M., & Tripathy, S. J. (2021). Cannabis, schizophrenia genetic risk, and psychotic experiences: a cross-sectional study of 109, 308 participants from the UK Biobank. Translational Psychiatry, 11(1), 211–211. https://doi.org/10.1038/s41398-021-01330-w

[3] Casadio, P., Fernandes, C., Murray, R. M., & Di Forti, M. (2011). Cannabis use in young people: the risk for schizophrenia. Neuroscience and Biobehavioral Reviews, 35(8), 1779–1787. https://doi.org/10.1016/j.neubiorev.2011.04.007

[4] Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S. A., Marconi, A., La Cascia, C., Reis Marques, T., Pariante, C., & Dazzan, P. (2014). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophrenia Bulletin, 40(6), 1509–1517. https://doi.org/10.1093/schbul/sbt181

[5] Godin, S., & Shehata, S. (2022). Adolescent cannabis use and later development of schizophrenia: An updated systematic review of longitudinal studies. Journal of Clinical Psychology, 78(7), 1331–1340. https://doi.org/10.1002/jclp.23312

[6] Mealer, R. G., Williams, S. E., Daly, M. J., Scolnick, E. M., Cummings, R. D., & Smoller, J. W. (2020). Glycobiology and schizophrenia: A biological hypothesis emerging from genomic research. Molecular Psychiatry, 25(12), 3129–3139. https://doi.org/10.1038/s41380-020-0753-1

[7] D'Souza, D. C., DiForti, M., Ganesh, S., George, T. P., Hall, W., Hjorthøj, C., Howes, O., Keshavan, M., Murray, R. M., Nguyen, T. B., Pearlson, G. D., Ranganathan, M., Selloni, A., Solowij, N., & Spinazzola, E. (2022). Consensus paper of the WFSBP task force on cannabis, cannabinoids and psychosis. The World Journal of Biological Psychiatry, 23(10), 719–742. https://doi.org/10.1080/15622975.2022.2038797

[8] D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., Braley, G., Gueorguieva, R., & Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology, 29(8), 1558–72. https://doi.org/10.1038/sj.npp.1300496

[9] Hudson, R., Renard, J., Norris, C., Rushlow, W. J., & Laviolette, S. R. (2019). Cannabidiol counteracts the psychotropic side-effects of Δ-9-Tetrahydrocannabinol in the ventral hippocampus through bidirectional control of ERK1-2 phosphorylation. The Journal of Neuroscience, 39(44), 8762–8777. https://doi.org/10.1523/JNEUROSCI.0708-19.2019

[10] Stark, T., Iannotti, F. A., Di Martino, S., Di Bartolomeo, M., Ruda-Kucerova, J., Piscitelli, F., Wotjak, C. T., D'Addario, C., Drago, F., Di Marzo, V., & Micale, V. (2022). Early blockade of CB1 receptors ameliorates schizophrenia-like alterations in the neurodevelopmental MAM model of cchizophrenia. Biomolecules, 12(1), 108-. https://doi.org/10.3390/biom12010108

[11] Murphy, M., Mills, S., Winstone, J., Leishman, E., Wager-Miller, J., Bradshaw, H., & Mackie, K. (2017). Chronic adolescent Δ 9 -tetrahydrocannabinol treatment of male mice leads to long-term cognitive and behavioral dysfunction, which are prevented by concurrent canna bidiol treatment. Cannabis and Cannabinoid Research, 2(1), 235–246. https://doi.org/10.1089/can.2017.0034

[12] Krebs, M., Kebir, O., & Jay, T. M. (2019). Exposure to cannabinoids can lead to persistent cognitive and psychiatric disorders. European Journal of Pain, 23(7), 1225–1233. https://doi.org/10.1002/ejp.1377

[13] Luzi, S., Morrison, P. D., Powell, J., Di Forti, M., & Murray, R. M. (2008). What is the mechanism whereby cannabis use increases risk of psychosis? Neurotoxicity Research, 14(2–3), 105–112. https://doi.org/10.1007/BF03033802

[14] Starzer, M. S. K., Nordentoft, M., & Hjorthøj, C. (2018). Rates and predictors of conversion to schizophrenia or bipolar disorder following substance-induced psychosis. The American Journal of Psychiatry, 175(4), 343-. https://doi.org/10.1176/appi.ajp.2017.17020223

[15] Addington, J., Liu, L., Buchy, L., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., Bearden, C. E., Mathalon, D. H., & McGlashan, T. H. (2015). North American Prodrome Longitudinal Study (NAPLS 2): The Prodromal Symptoms. The Journal of Nervous and Mental Disease, 203(5), 328–335. https://doi.org/10.1097/NMD.0000000000000290

[16] Giuffrida A., Leweke F. M. , Gerth C. W., Schreiber D., Koethe D., Faulhaber J., Klosterkötter J., Piomelli D. (2004). Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacology, 29, 2108–2114. https://doi.org/10.1038/sj.npp.1300558

[17] Leweke, F. M., Giuffrida, A., Koethe, D., Schreiber, D., Nolden, B. M., Kranaster, L., ... & Piomelli, D. (2007). Anandamide levels in cerebrospinal fluid of first-episode schizophrenic patients: impact of cannabis use. Schizophrenia research, 94(1-3), 29-36. https://doi.org/10.1016/j.schres.2007.04.025

[18] Di Forti, M., Morgan, C., Dazzan, P., Pariante, C., Mondelli, V., Marques, T. R., Handley, R., Luzi, S., Russo, M., Paparelli, A., Butt, A., Stilo, S. A., Wiffen, B., Powell, J., & Murray, R. M. (2009). High-potency cannabis and the risk of psychosis. British Journal of Psychiatry, 195(6), 488–491. https://doi.org/10.1192/bjp.bp.109.064220

[19] Morgan, C. J. A., & Curran, H. V. (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. British Journal of Psychiatry, 192(4), 306–307. https://doi.org/10.1192/bjp.bp.107.046649

[20] Rømer Thomsen, K., Callesen, M. B., & Feldstein Ewing, S. W. (2017). Recommendation to reconsider examining cannabis subtypes together due to opposing effects on brain, cognition and behavior. Neuroscience and biobehavioral reviews, 80, 156–158. https://doi.org/10.1016/j.neubiorev.2017.05.025

[21] Vergara, D., Bidwell, L. C., Gaudino, R., Torres, A., Du, G., Ruthenburg, T. C., deCesare, K., Land, D. P., Hutchison, K. E., & Kane, N. C. (2017). Compromised external validity: Federally produced cannabis does not reflect legal markets. Scientific Reports, 7(1), 46528–46528. https://doi.org/10.1038/srep46528

[22] Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. Schizophrenia Bulletin, 42(5), 1262-1269. https://doi.org/10.1093/schbul/sbw003

[23] Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Ajnakina, O., Gayer-Anderson, C., Colizzi, M., Quattrone, D., Behlke, I., Shetty, S., McGuire, P., David, A. S., Murray, R. & Bhattacharyya, S. (2016) Effects of continuation, frequency, and type of canna bis use on relapse in the first 2 years after onset of psychosis: An observational study. Lancet Psychiatry 3(10), 947–953. https://doi.org/10.1016/S2215-0366(16)30188-2

[24] Di Forti, M., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., Rodriguez, V., Jongsma, H. E., Ferraro, L., La Cascia, C., La Barbera, D., Tarricone, I., Berardi, D., Szöke, A., Arango, C., Tortelli, A., Velthorst, E., Bernardo, M., Del-Ben, C. M., Menezes, P. R., Selten, JP., Jones, P. B., Kirkbride, J. B., Rutten., B. P., de Haan, L., Sham, P. C., van Os, J., Lewis, C. M., Lynskey, M., Morgan, C., Murray, R. M. (2019). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): A multicentre case-control study. The Lancet Psychiatry, 6(5), 427–436. https://doi.org/10.1016/S2215-0366(19)30048-3

[25] Kujala, S., Miron-Shatz, T., & Jokinen, J. (2024) The cross-sequential approach: A short-term method for studying long-term user experience. The Journal of User Experience, 14(2), 105-116. https://uxpajournal.org/cross-sequential-studying-long-term-user-expereice/

[26] Bidwell, L. C., Ellingson, J. M., Karoly, H. C., YorkWilliams, S. L., Hitchcock, L. N., Tracy, B. L., Klawitter, J., Sempio, C., Bryan, A. D., & Hutchison, K. E. (2020). Association of naturalistic administration of cannabis flower and concentrates with intoxication and impairment. JAMA Psychiatry (Chicago, Ill.), 77(8), 787–796. https://doi.org/10.1001/jamapsychiatry.2020.0927

[27] Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1989). The Positive and Negative Syndrome Scale (PANSS): Rationale and Standardisation. British Journal of Psychiatry, 155(S7), 59–65. https://doi.org/10.1192/S0007125000291514

[28] Lefort-Besnard, J., Varoquaux, G., Derntl, B., Gruber, O., Aleman, A., Jardri, R., Sommer, I., Thirion, B., & Bzdok, D. (2018). Patterns of schizophrenia symptoms: hidden structure in the PANSS questionnaire. Translational Psychiatry, 8(1), 237–10. https://doi.org/10.1038/s41398-018-0294-4

[29] Edgar, C. J., Blaettler, T., Bugarski-Kirola, D., Le Scouiller, S., Garibaldi, G. M., & Marder, S. R. (2014). Reliability, validity and ability to detect change of the PANSS negative symptom factor score in outpatients with schizophrenia on select antipsychotics and with prominent negative or disorganized thought symptoms. Psychiatry Research, 218(1), 219–224. https://doi.org/10.1016/j.psychres.2014.04.009

[30] Montoya, A., Valladares, A., Lizán, L., San, L., Escobar, R., & Paz, S. (2011). Validation of the Excited Component of the Positive and Negative Syndrome Scale (PANSS-EC) in a naturalistic sample of 278 patients with acute psychosis and agitation in a psychiatric emergency room. Health and Quality of Life Outcomes, 9(1), 18–18. https://doi.org/10.1186/1477-7525-9-18

[31] Kirkpatrick, B., Strauss, G. P., Nguyen, L., Fischer, B. A., Daniel, D. G., Cienfuegos, A., & Marder, S. R. (2011). The Brief Negative Symptom Scale: Psychometric properties. Schizophrenia Bulletin, 37(2), 300–305. https://doi-org.ezproxy.library.yorku.ca/10.1093/schbul/sbq059

[32] Beishon, L. C., Batterham, A. P., Quinn, T. J., Nelson, C. P., Panerai, R. B., Robinson, T., Haunton, V. J., & Beishon, L. C. (2019). Addenbrooke's Cognitive Examination III (ACE-III) and mini-ACE for the detection of dementia and mild cognitive impairment. Cochrane Database of Systematic Reviews, 2019(12), CD013282–CD013282. https://doi.org/10.1002/14651858.CD013282.pub2

[33] Andréasson, S., Engström, A., Allebeck, P., & Rydberg, U. (1987). Cannabis and schizophrenia: A longitudinal study of Swedish conscripts. The Lancet, 330(8574), 1483–1486. https://doi.org/10.1016/S0140-6736(87)92620-1

[34] Cash, M. C., Cunnane, K., Fan, C., & Alfonso Romero-Sandoval, E. (2020). Mapping cannabis potency in medical and recreational programs in the United States. PloS One, 15(3), e0230167–e0230167. https://doi.org/10.1371/journal.pone.0230167

[35] Vadhan, N. P., Hart, C. L., van Gorp, W. G., Gunderson, E. W., Haney, M., & Foltin, R. W. (2007). Acute effects of smoked marijuana on decision making, as assessed by a modified gambling task, in experienced marijuana users. Journal of Clinical and Experimental Neuropsychology, 29(4), 357–364. https://doi.org/10.1080/13803390600693615

[36] Meier, M. H., Caspi, A., R. Knodt, A., Hall, W., Ambler, A., Harrington, H., Moffitt, T. E. (2022). Long-term cannabis use and cognitive reserves and hippocampal volume in midlife. American Journal of Psychiatry, 179(5), 362–374. https://doi.org/10.1176/appi.ajp.2021.21060664

[37] Hill, K., & Hsu, M. (2022). Cognitive effects in midlife on long-term cannabis use. Harvard Health Publishing. Web. Available from: https://www.health.harvard.edu/blog/cognitive-effects-of-long-term-cannabis-use-in-midlife-202206142760

[38] Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ, 325(7374), 1212–1213. https://doi.org/10.1136/bmj.325.7374.1212

[39] Fergusson, D. M., Horwood, L. J., & Swain-Campbell, N. R. (2003). Cannabis dependence and psychotic symptoms in young people. Psychological Medicine, 33(1), 15–21. https://doi.org/10.1017/S0033291702006402

[40] Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H.-U., & van Os, J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ, 330(7481), 11–14. https://doi.org/10.1136/bmj.38267.664086.63

[41] Faul, F., Erdfelder, E., Lang,A.G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods, 39(2), 175-191. https://doi.org/10.3758/BF03193146

[42] Hall, W., & Degenhardt, L. (2008). Cannabis use and the risk of developing a psychotic disorder. World Psychiatry, 7(2), 68–71. https://doi.org/10.1002/j.2051-5545.2008.tb00158.x

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Miray Youssef, Jane Kim
Article Dates: Received Mar 21 24; Accepted Aug 15 24; Published Oct 09 24

Citation
Please cite this article as follows:
Perez M. Examining the relationship between schizophrenia and cannabis use: a research protocol. URNCST Journal. 2024 Oct 09: 8(10). https://urncst.com/index.php/urncst/article/view/590
DOI Link: https://doi.org/10.26685/urncst.590