



Relationship between cannabis use in adolescence and the incidence of psychosis in adulthood – Literature Review

Związek między stosowaniem marihuany w wieku dojrzewania a występowaniem psychoz w wieku dorosłym – przegląd literatury

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Abstract

Introduction and Objective. Cannabis is one of the most widely used illegal stimulants in the world. With a worldwide usage rate of about 4% of the population, it definitely exceeds the use of other drugs. Currently, there is an upward trend in the use of cannabis which is most visible in the adolescent and young adult age groups. Earlier onset of cannabis use may be associated with psychiatric side-effects in adulthood.

Review Methods. PubMed, PubMed Central and Google Scholar online databases were searched using phrases related to the topic. After reviewing the abstracts, articles in English, French and Polish presenting the latest knowledge were selected. The types of articles reviewed were original papers, and review papers. Finally, a total of 62 items of literature and websites were selected.

Brief description of the state of knowledge. Cannabis psychoactive compounds, mainly Δ -9-tetrahydrocannabinol, act by binding to cannabinoid receptors. This mainly affects the mental sphere leading to memory lapses, abnormal sense of time or perceptual impact. Long-term use can result in psychosis or schizophrenia. Studies prove that in addition to the dose of cannabis used, the main risk factor for psychosis is the early age of initiation occurring, usually in adolescence. Cannabis use during the most intensive brain development can result in abnormal cognitive functions with resulting exposure to psychosis in adulthood.

Summary. Cannabis use in adolescence is unanimously considered unsafe and may lead to mental disorders in adulthood. The illegal status of cannabis in Poland, additional environmental influences and comorbidities can only exacerbate the prognosis. People in adolescence should be exposed to psychoactive substances as minimally as possible.

Key words

cannabis use in adolescence, cannabis and psychosis, environmental factors and psychosis, cannabis and mental disorders, genetic predisposition to psychosis

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Streszczenie

Wprowadzenie i cel pracy. Marihuana w skali globalnej jest jedną z najczęściej stosowanych przez ludzi nielegalnych używek. Biorąc pod uwagę, że ok. 4% światowej populacji pali marihuanę, należy stwierdzić, iż zdecydowanie pozostawia w tyle inne narkotyki. Obecnie obserwuje się tendencję wzrostową w zakresie używania marihuany, co widać najbardziej w grupach nastolatków i młodych dorosłych. Rozpoczęcie stosowania marihuany przez osoby z tych grup wiekowych może wiązać się z psychiatrycznymi efektami ubocznymi u tych osób w życiu dorosłym.

Metody przeglądu. Przeszukano internetowe bazy danych PubMed, PubMed Central i Google Scholar, używając fraz i terminów związanych z tezą niniejszej pracy. Po analizie abstraktów zostały wybrane artykuły w języku angielskim, francuskim i polskim prezentujące najnowszą wiedzę, wsparte artykułami i materiałami internetowymi. Ze wstępnego wyszukania wyodrębniono 62 pozycji, które poddano przeglądowi w tej pracy. Podsumowanie badań przedstawiono w tab. 2.

Opis stanu wiedzy. Związki psychoaktywne zawarte w marihuanie, głównie delta-9-tetrahydrokannabinol, działają poprzez wiązanie się z receptorami kannabinoidowymi. Długotrwałe stosowanie marihuany może zatem prowadzić do psychoz lub schizofrenii. Oprócz dawki tej używki, głównym czynnikiem ryzyka psychozy jest wczesny wiek rozpoczęcia jej stosowania, przypadający na okres dojrzewania. Palenie marihuany podczas najintensywniejszego rozwoju mózgu skutkuje nieprawidłowymi funkcjami poznawczymi, z czego wynika narażenie na psychozy w wieku dorosłym.

Podsumowanie. Stosowanie marihuany w wieku dojrzewania jest zgodnie postrzegane jako niebezpieczne i może prowadzić do schorzeń mentalnych w wieku dorosłym. Nielegalny status tej używki w Polsce, dodatkowy wpływ środowiska oraz choroby współistniejące mogą tylko pogorszyć rokowanie. Osoby w wieku dojrzewania powinny być w jak najmniejszym stopniu narażone na substancje psychoaktywne.

Słowa kluczowe

stosowanie marihuany w wieku dojrzewania, marihuana i psychoza, czynniki środowiskowe i psychoza, marihuana i choroby psychiczne, genetyczne predyspozycje do psychoz

INTRODUCTION

Marijuana – the dried product extracted from *Cannabis* plants – is the most widely used illegal narcotic substance not only in Europe and Poland, but worldwide. According to 2021 data, the number of annual cannabis users globally was more than 219 million (4.3% of the population) [1, 2]. Cannabis use in 2021 among people aged 15–34 in the European Union is estimated at 15%, and increases to 19% when only the 15–24 age group is considered [3]. In Poland in the same age group, the level is 7.8%, and 9.6% among 15 – 24-year-olds. Meanwhile, in the country's population, cannabis use ever in life is declared by 12.1% [4]. The prevalence of cannabis use has remained at a similar level since the 1990s with a tendency to increase, although it fluctuates from decade to decade, or under the influence of various global circumstances, e.g. the COVID-19 pandemic [1, 5].

There has been interest in cannabis for its psychoactive properties since the first century AD. Cannabis owes these properties to a number of compounds, particularly Δ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [6]. The component that mediates most of the psychoactive and mood-related effects also has addictive properties in the form of THC which acts as an agonist of cannabinoid receptors – CB1 and CB2. This activates presynaptic CB1 receptors, resulting in functional effects by decreasing cAMP synthesis, and consequently reducing neural transmission [7]. Physiological effects include general mental and perceptual impact, difficulty in concentrating, temporary short-term memory lapses, impaired sense of time, motor disturbances, and decreased or increased appetite [8]. A comparison of cannabinoid receptors is presented in Table 1.

According to the NASEM (National Academies of Sciences, Engineering, and Medicine), significant health risks associated with cannabinoid intake include addiction among the same age group, respiratory disease, traffic accidents, decreased birth weight in offspring, schizophrenia, and other psychoses [8]. For this reason, the legal status of the possession and use of cannabis products is the subject of public debate in all parts of the world. Over the past two decades, the position of some countries has changed significantly, e.g. in Canada, cannabis was legalized in 2018 (as it had been a few years earlier in Uruguay); Thailand became the first country in South-East Asia to legalize the medical use of cannabis in 2019, and in 2022 also for recreational use. Similar legislation is also being drafted by other countries, including Mexico, Malta and Luxembourg. In the United States, cannabis has a non-uniform status depending on the State, ranging from illegal through decriminalized to legalized [9, 10]. Currently, cannabis for recreational use is illegal in 142 countries, in

50 it has been decriminalized under certain conditions, and only in 8 countries it is finally declared legal – Uruguay, Georgia, South Africa, Canada, Mexico, Malta, Thailand and Luxembourg. The legal aspects of the pharmacological use of marijuana for medical purposes are quite different – in 130 countries it is illegal, legal in 51, while in 19 the possibility to use it is limited to a product containing only CBD. The patient is often required to have an appropriate medical certificate [11] (Fig. 1).

In Poland, possession of marijuana for non-medical purposes is legal only with THC concentrations below 0.3% [12]. For medical purposes (pharmaceutical material for preparing prescription drugs), cannabis became legal in Poland in November 2017 [13]. Proponents of medical marijuana opt for its use in a wide range of medical conditions. It is most commonly used in the treatment of pain of various origins, and multiple sclerosis, although it is also included in the treatment or relief of symptoms of dystonia, epilepsy, Tourette's syndrome, tic disorders, cancer, rheumatic diseases, post-traumatic conditions, AIDS, dementia, or certain psychiatric conditions [14–16]. It is estimated that in the United States more than 3.5 million people use medical marijuana [16]. In Poland, medical cannabis has mostly been prescribed for cancer-related pain, chronic pain and neuropathic pain [17]. From 1 January 2019 – 13 June 2023, prescriptions were issued to more than 100,000 Polish patients, and the amount of cannabis sold for medical use exceeded two tons [18].

The intake of cannabis can occur by ingestion, smoking, vaporization, rectal or sublingual administration. The clinical use of cannabis and artificial cannabinoids balances the therapeutic effect benefitting the patient against other harmful – sometimes long-term – effects. Common effects of medical cannabis include short-term memory loss, drowsiness or dizziness. More serious adverse effects can also occur, e.g. anxiety, abstinence syndrome, risk of infection, paranoia or psychosis [19]. According to an extensive meta-analysis involving more than 12,000 patients from 39 clinical trials, adverse effects are common, affecting about 26% of patients [20]. In particular, cannabis use before the age of 15 may significantly increase the risk of psychotic episodes in later life. It is also known to have a dose-response relationship, where more frequent use of especially high doses correlates positively with a decrease in the age of first episode onset [21]. However, a distinction must be made between patients suffering from psychosis after cannabis use and patients who have developed schizophrenia. Psychoses are a group of mental disorders involving loss of contact with reality, occurring with disturbed perception of self and surroundings and disorganization of thoughts and behaviour, with hallucinations and/or delusions.

Table 1. Cannabinoid receptor comparison. CNS – central nervous system, AD – Alzheimer disease

Feature	Receptor Type CB-1	CB-2
Localization	mainly CNS	immune system cells
Expression in liver	poor	absent
Structure	G-protein-coupled receptor, 7 transmembrane domains, heterodimer A _{2A}	G-protein-coupled receptor, 7 transmembrane domains, heterodimer D ₂
Action	appetite, emesis, memory, mood control, motor activity	immunomodulation, anti-inflammatory, analgesia
Role in metabolism	food intake, insulin resistance, lipogenesis	inflammation, fibrogenesis, ischaemia
Therapeutic use examples	weight reduction, smoking cessation	AD, cardiovascular, autoimmune, gastrointestinal, psychiatric diseases

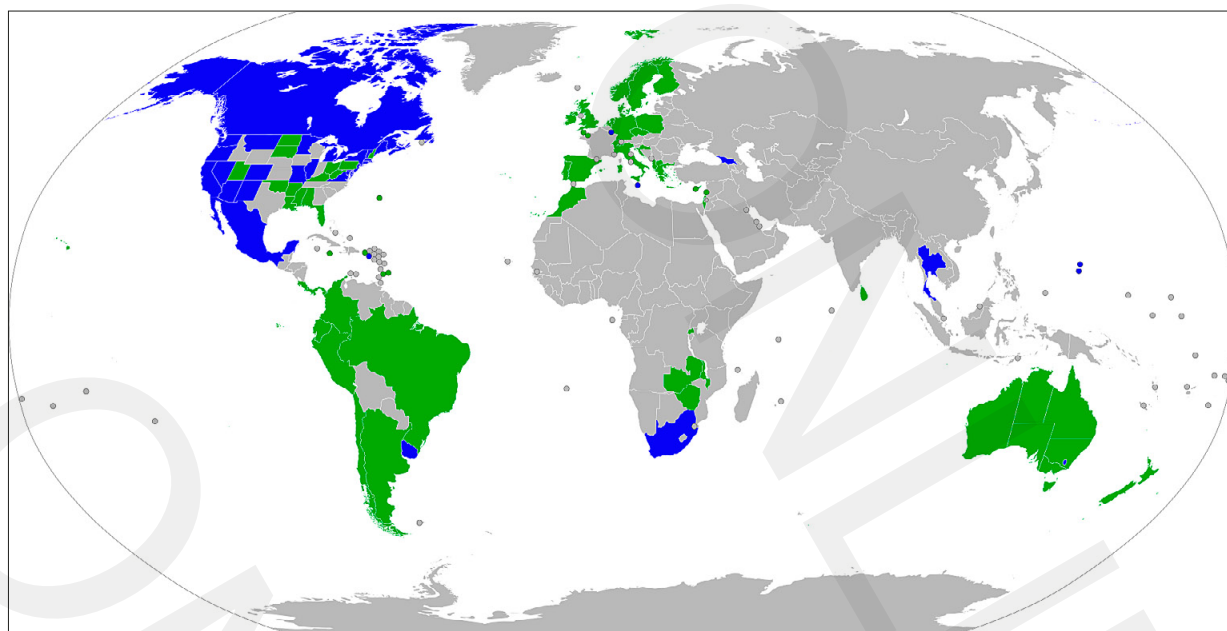


Figure 1. Legal status of cannabis for medical use. Legend: blue – legal for recreational use, green – legal for medical use, grey – illegal or unknown. Source: Wikimedia Commons. Map showing legal status of medical cannabis across the world. Under the license Jamesy0627144, CC BY-SA 4.0 via Wikimedia Commons [62]

They can result from factors such as stress, trauma, physical illness, mental illness or psychoactive substances, and are a temporary condition that can resolve once the cause is eliminated. In contrast, schizophrenia is a complex, chronic disorder whose etiology consists of a combination of genetic, neurochemical and environmental factors, and its symptoms are more specific [22, 23].

When taking into consideration the social impact of cannabis, it is important to note that the global trend is towards relaxing the law on its legality. For the purposes of this study, the impact of cannabis legalization on the prevalence of its use among the youth population is worth considering. This topic was raised by Lachance et al. in a 2022 review article [24] which analyzed 32 studies of cannabis use before and after legalization among populations living in places where it has been legalized. The largest increase in cannabis intake among the study groups was observed among adolescents. However, the authors point out that the results should be interpreted with caution due to the wide variation in the study groups, which only underscores the complexity of the topic of legalization and its impact on global usage. Nevertheless, education is important in terms of minimizing the risks associated with cannabis consumption. A 2023 study suggests an inverse correlation between the level of knowledge about cannabis, knowledge of the risks of cannabis use, and the frequency of use among adolescents [25]. The results of the analysis highlight the relevance of the problem of educating adolescents in the context of preventing the negative consequences of cannabis consumption.

The topic of education seems to be particularly important in the face of global trends toward the legalization of cannabis. When analyzing the correlation between cannabis use in adolescence and the occurrence of psychotic episodes or schizophrenia in adulthood, it should be noted that most of the studies are retrospective. The data on cannabis intake comes mostly from the declarations of patients already affected, therefore caution should be taken in inferring cause-and-effect relationships based on this data.

The aim of this study is to provide an overview of recent knowledge regarding the impact of cannabis use by adolescence on the occurrence of psychosis in adulthood. In today's world, the impact of environmental factors on health is becoming increasingly negative. Unhealthy lifestyles, often associated precisely with the use of stimulants, such as cannabis, will decrease the quality of health and life the earlier it is initiated.

REVIEW METHODS

PubMed, PubMed Central and Google Scholar online databases were searched using phrases related to: 'cannabis use in adolescence', 'cannabis and psychosis', 'environmental factors and psychosis', 'cannabis and mental disorders', and 'genetic predisposition to psychosis'. After reviewing the abstracts, articles in English, French and Polish presenting the latest knowledge were selected. The types of articles reviewed were original papers and review papers. Items from Polish printed literature were also used to correctly explain certain medical definitions. Additionally, Web articles and reports supplemented the review with the latest data from institutions directly dealing with cannabis use. A simple summary of the research is presented in Table 2. Finally, a total of 62 items of literature and from websites were selected, and the review divided into relevant paragraphs on the impact of cannabis on psychosis, early onset of cannabis use, environmental factors, and genetic predisposition to psychosis.

STATE OF KNOWLEDGE

Physiology of adolescence and onset of mental disorders.

Adolescence is an important stage of human growth, usually described as initiated by the onset of sexual maturation and completed by the achievement of the roles and responsibilities

Table 2. Research summary

CATEGORY	NUMBER OF ITEMS	
Total	62	
Web materials	11	
Articles	48	
Language	English	46
	French	1
	Polish	1
Database / search engine used (including duplicates)	PubMed	43
	PubMed Central	46
	Google Scholar	48
Year of publication	2023	4
	2022	2
	2021	4
	2020	2
	2019	6
	2018	8
	2017	3
	2016	6
	2015 and before	13

of adult life. The process of adolescence is dynamic and is influenced by social and environmental factors [26]. One of the main purposes of adolescence is the formation of interpersonal relationships and managing increasingly complex group situations. It is understandable that many of the changes in the brain are related to cognitive skills relevant to social functioning. Although the exact structure of the brain network is not precisely defined, it usually includes areas such as the dorsal prefrontal cortex, temporal-occipital gyrus, inferior occipital gyrus, and the anterior temporal cortex [27]. The first signs of mental illness often appear during adolescence, and almost 50% of adults with mental disorders have the onset of their illness before the age of 14, and about 75% before the age of 25 [28]. Mental health problems adversely affect school performance and family relationships, which can increase the risk of substance abuse. A particular concern is that in recent years the number of adolescents with mental health problems appears to be increasing significantly [29].

Cannabis in adolescence. One of the most commonly abused psychoactive substances is cannabis. In the context of a possible increase in the availability of cannabis to adolescents, reduced perception of its harmfulness through medical marijuana and pro-legalization legislation, the link between early cannabis use and early onset psychosis is a significant public health concern [30]. According to estimates, the annual prevalence of cannabis use among adolescents in United States aged 12–17 is about 13.4%, and more than 25% of them meet the criteria for the diagnosis of cannabis use disorder [31]. There is evidence suggesting that cannabis use can cause temporary experiences of a psychotic and emotional nature. The findings also show that cannabis can increase the risk of later psychosis two-fold, with a relative risk 2–4 times greater for single use, and 6 times greater for those who have used cannabis 50 or more times, compared to those who have never tried the substance.

Continued cannabis use may increase the risk of persistence of subclinical psychotic symptoms [32]. Individuals with schizophrenia show greater sensitivity to the effects of THC, while adolescents who use cannabis are more likely to present higher rates of schizophrenia [33].

Cannabis and schizophrenia. The relationships observed between cannabis and schizophrenia are well described in many studies, but determining whether there is a cause-and-effect relationship between them is a much more complicated challenge [34]. Gage SH et al. attempted to answer the aforementioned problem. They performed bi-directional 2-sample MR, using summary-level genome-wide data from the International Cannabis Consortium and the Psychiatric Genomics Consortium. The authors inferred that starting cannabis use can increase the risk of schizophrenia, but that the magnitude of the estimated causal relationship is low. In contrast, they found much stronger evidence that schizophrenia risk predicts the initiation cannabis use. This is probably because the genetic factors for schizophrenia are stronger than these for starting cannabis use [34].

Early onset of cannabis use affects the earlier onset of psychosis and worse cognitive function. Two large studies conducted in the USA and UK found an association between concurrent cannabis smoking and the onset of psychosis [35, 36]. Davis GP et al., after analyzing the scientific literature observed that cannabis use was associated with the onset of schizophrenia/psychosis in a dose-dependent manner [37]. However, it is worth noting that the authors did not take into account potential variables, such as cigarette smoking, alcohol, and the use of many other harmful substances. The consideration of simultaneous use of these substances is crucial, as many people who start using cannabis in early adolescence tend to use other stimulants as well [38]. Stefanis NC et al. observed a relationship between the age of cannabis use onset, age of psychosis onset, and the average time from first cannabis use to diagnosis of a psychotic disorder. Of 7,955 people eligible for the study, 1,825 randomly sampled individuals with psychosis were selected. The study showed a linear relationship between the age of onset of cannabis use and the age of onset of psychosis. The average time between first exposure to cannabis and the development of psychotic disorders was 7–8 years. However, the researchers noted that during the period of first exposure to cannabis – adolescence, young people had access to a variety of psychoactive substances or other stimulants that may also have influenced the onset of psychosis later in life. This could have affected the study results. The authors suggest that the relationship between early age of cannabis use onset and first psychotic symptoms is direct, as evidenced by the relatively constant mean time between the first exposure to cannabis and the onset of first symptoms of psychosis across age groups, with people starting cannabis use between the ages of 12 and 21 [39].

The analysis by Ryan JE et al. presents several important findings. While this study did not provide significant evidence of a direct link between cannabis and the incidence of schizophrenia/psychosis in adults aged 18–34, it presents other noteworthy correlations, e.g. a higher prevalence of drug-related problems in the families of those with schizophrenia/psychosis (53% versus 42%), and that those with schizophrenia/psychosis were significantly more likely

to report cannabis use (38% vs. 22%), cigarettes (36% vs. 22%) and alcohol (37% vs. 28%), as well as other drugs before the age of 16 (21% vs. 8%). Cannabis use in adolescents was associated with a twofold greater probability of developing schizophrenia/psychosis. However, after adjusting for other variables, such as gender, race, education, income, history of trauma, sexual orientation and family history of drug problems, the association lost its statistical significance [40]. The majority of people (78%) who reported that they smoked cigarettes before the age of 16 and suffered from schizophrenia/psychosis, also declared cannabis, alcohol, and the use of other drugs. After a more thorough analysis, the researchers found that only cigarette smoking showed a significant association with schizophrenia/psychosis. In addition, the authors' findings consistently showed an association between the use of other drugs and the occurrence of schizophrenia/psychosis [40]. Bearing in mind the fact that the age of initiation for cigarettes smoking is decreasing, it can be concluded that the compounding effects of such stimulants are beginning to be a serious problem from the adolescent years [41]. Ringen PA et al. published a paper that emphasizes that cannabis use before the onset of psychosis has a noticeable impact on progression of the disease. Moreover, it is associated with a younger age of onset of psychosis. The study was conducted on individuals with schizophrenia, and the findings indicate that cannabis use prior to the onset of schizophrenia was associated with more severe psychotic symptoms and dysfunction among those with schizophrenia spectrum disorders. In addition, the more cannabis the patients used before developing the illness, the more severe were the psychotic symptoms. Starting cannabis use before the age of 17 was associated with an earlier age of onset of psychosis, regardless of potential variables affecting the time of onset [42]. Batalla A et al. proved that starting cannabis use at a young age is associated with impaired cognitive performance and the formation of brain structural abnormalities [43]. Dervaux A et al. also found that adolescents who started cannabis use at a young age showed noticeable deterioration in various cognitive functions, such as attention skills, episodic and working memory [44].

In contrast, a study by Hanna RC et al. focused on the age of onset of cannabis use and its effect on cognitive function in people already suffering from psychosis or schizophrenia, produced entirely different results. The authors noted that patients diagnosed with schizophrenia who started cannabis use at a younger age showed more efficient brain function, including higher information processing speed, and better verbal and working memory, compared to patients who started at a later age. In terms of cognitive function, they performed similarly to those who did not use cannabis [45]. In 2018 Setien-Suero E et al. conducted a study involving 349 patients who experienced a first episode of non-affective psychosis. 135 patients reported cannabis use. Patients were divided into 2 groups based on the age of onset of cannabis use. This study showed no significant differences in cognitive brain function based on age of onset of cannabis use [46]. Di Forti M et al. also examined the relationship between age of cannabis use onset and the onset of psychosis. The study was conducted among 461 patients aged 18–65 who had a confirmed diagnosis of psychosis according to ICD-10 criteria; organic causes of the disorder were excluded. Patients answered questions related to the age of first cannabis use,

Table 3. THC and CBD similarities and differences. SM – sclerosis multiplex, HR – heart rate

THC	CBD
Δ -9-tetrahydrocannabinol	cannabidiol
psychoactive	not psychoactive
addictive effect	no addictive effect
binds to CB-1 and CB-2 receptors	binds to CB-1 and CB-2 receptors
muscle relaxant, appetite stimulant, analgesic, euphoric, paranoid effects	neuroprotective, anticonvulsant, antipsychotic, anti-inflammatory effects
can be used in: chronic pain, SM, glaucoma, chemotherapy side-effects	can be used in: schizophrenia, seizures, depression, chemotherapy side-effects
side- effects: memory impairment, dry mouth, confusion, elevated HR, red eyes	side- effects: drowsiness, dry mouth, diarrhoea

its frequency, repetition, and the type and strength of the cannabis used. It turned out that the highest potency cannabis (so-called 'skunk') contained the highest amount of THC, which resulted in greater psychogenic potential due to containing less CBD. Patients taking a substance with a high THC concentration had a significantly earlier onset of psychosis than those smoking cannabis containing more CBD [47]. Table 3. compares the effects of THC and CBD.

It is noteworthy that a correlation was also shown between an increased risk of psychosis at a young age in people who reported cannabis use, than those who never used the substance. The study also indicated that those who start cannabis use before the age of 15 were at risk of developing psychosis faster than those who started later [47]. A study by Hosseini S et al. also concluded that patients reporting cannabis use before the age of 15 were at increased risk of developing symptoms of schizophrenia by the age of 26, compared to those who first used the drug before the age of 18. It is also known that males are more likely to exhibit symptoms of psychosis than females who use the same amount of cannabis [48]. Hahn B. points out in a review the anti-psychogenic effects of CBD. It has properties that moderate cognitive deterioration and shows the opposite effect to THC, which is an inducer of psychosis. Using cannabis that contains more CBD than THC is associated with a lower probability of developing psychosis-like symptoms, as well as psychosis itself [49]. CBD may also exhibit a protective effect against those who are at risk of developing psychosis. A single oral dose of 600mg of CBD has been proven to normalize brain structures, the disturbed functioning of which has been linked to the development of psychosis [50]. Other studies also note the existing correlation between cannabis and the occurrence of psychosis. Gage SH et al. noted the exacerbation of psychosis by concurrent cannabis use and smoking, and Wainberg M et al. described the onset of psychosis in cannabis users as being earlier, more intense, and causing greater distress [51,52].

Genetic predisposition and environmental conditions also interact with cannabis on the onset of psychosis.

Ksir C et al. indicate the complexity of the impact of cannabis use and the environment during adolescence on the occurrence of psychotic episodes and schizophrenia in adulthood. They contrast the 'marijuana in young adulthood causes schizophrenia' hypothesis with the 'marijuana in

young adulthood and schizophrenia have a common cause' hypothesis. The authors conclude that there are other risk factors that predispose young people to behaviours that collectively affect the onset of psychosis in later life. In addition to early and excessive cannabis use, they cite early alcohol use, early onset of sexual intercourse, poor school performance, reduced religiosity, and a higher incidence of behaviours, such as lying, stealing, fighting and truancy. It should be mentioned that although there is a clear correlation between cannabis use and the occurrence of psychotic episodes, it should be noted that the presented data originates from retrospective studies, and information about using marijuana comes from patients' declarations. Patients with a first diagnosed psychotic episode or with schizophrenia are significantly more likely to admit that they use or have used cannabis in the past, compared to the general population. Considering this, the link between cannabis and the occurrence of psychosis seems to be undeniable. The problem is to assess the severity of this correlation, since in the vast majority of cases, cannabis use is accompanied by other risk factors, exposure to toxins, infections *in utero*, month of birth, or genetics [53]. The topic is also complex from a genetic perspective. Power RA et al. suggest that people with an increased genetic predisposition to schizophrenia are more prone to cannabis use, moreover, at higher rates. The authors do not rule out the possibility that cannabis use is a risk factor for schizophrenia by itself, instead they point to the existence of at least a partial inverse correlation between the presence of schizophrenia and susceptibility to cannabis use. Researchers also indicate that the possession of schizophrenia risk alleles does not indicate that cannabis would be the only risk factor for the disease [54]. Hiemstra M. et al. in a 2018 study, reach similar conclusions. A genetic predisposition to schizophrenia correlates with increased cannabis use between the ages of 16 and 20. This study found no such correlation for cigarette smoking or alcohol. In fact, the authors tend to conclude that genes predisposing to schizophrenia, or psychiatric conditions in general may also influence young people's propensity to use cannabis, but they also suggest that consideration should be given to whether cannabis use itself is a risk factor for schizophrenia [55].

There are also factors that modify the effect of cannabis use in adolescence on the occurrence of psychosis in adulthood, a topic addressed in a 2021 meta-analysis. The first of these factors is the age of cannabis use at onset. Most studies suggest that a younger age of onset correlates with a shorter age of psychotic symptoms, and shorter periods between episodes. In addition, patients who started cannabis use under the age of 15, present more psychotic symptoms compared to the control group. The second factor is the frequency of cannabis use, which seems to be directly proportional to the frequency of psychosis in later life. The experience of trauma in childhood is also an important factor. One study cites a 20 times higher risk of psychosis in people who experience trauma in childhood, and smoked cannabis in adolescence. Higher rates of psychotic episodes are also seen in people experiencing sexual or emotional abuse in combination with cannabis use at a young age. Other stimulants, such as alcohol or cigarettes in combination with cannabis, also may increase the risk of psychosis [56]. Cannabis significantly affects the risk of schizophrenia and psychotic symptoms, especially in genetically predisposed people. The onset of schizophrenia is influenced by gene-environment interactions [57]. Sarris

M. et al. indicate several genes that may increase the risk of schizophrenia after cannabis use. These include such genes as BDNF, CNR1, COMT, AKT1, DRD2, SETD1A, with COMT and BDNF genotypes appearing to be the most relevant. If a combination of these genes is present along with childhood trauma in the patient, then susceptibility to the disease can also be increased [58]. Klimkiewicz A et al. in their 2018 study indicate that cannabis use in adolescence negatively affects the reward system, which can lead to more frequent use of other psychoactive substances. Cannabis may also be an inducer of an amotivational syndrome [59].

As quoted earlier, schizophrenia is one of the most inheritable neuro-psychiatric disorders, and classic studies on twins have estimated the heritability of this disease to be as high as 80%. In addition to the COMT and BDNF genotypes mentioned above, variants in other genes also influence the development of schizophrenia. Some of the first identified mutations affecting the onset of schizophrenia were a 22q11.2 deletion and a mutation in the SETD1A gene. In recent years, many new loci potentially affecting the development of schizophrenia have been identified. These include dopamine pathway genes, glutamate pathway genes, genes responsible for the function of ion channels, and genes involved in the immune response system [60]. The thesis that cannabis is a cause of persistent psychotic episodes is also favoured by Bechtold J. et al., whose study was designed to test whether one-year abstinence from cannabis in patients between the ages of 13–18 would result in a decrease in the frequency of psychotic symptoms. In patients who regularly used cannabis, the frequency of subclinical psychotic symptoms increased by 21%, subclinical paranoia by 13%, and hallucinations by 92%. These effects persisted after a one-year period of abstinence [61].

Exposure to cannabis and its effect on the onset of psychotic symptoms and schizophrenia is also important in the prenatal period, a topic addressed in a study from 2021. The authors demonstrated an indirect negative effect of prenatal cannabis use on the quality of the adult memory. This was related to earlier memory deficits and early onset of cannabis use [62].

CONCLUSIONS

The study focused on discussing the impact of early cannabis use and the occurrence of psychosis in adulthood by citing the results of a number of recent clinical studies. It can be noted that the topic is complex and requires in-depth analyses to draw the correct conclusions. It is important to point out that due to the multiplicity of risk factors, genetic factors, the susceptibility of cannabis abusers to also use other substances in the group of risk factors for schizophrenia, it is difficult to isolate a study group exposed only to cannabis in the period before the onset of a psychotic episode or schizophrenia. Conclusions about an unequivocal cause-and-effect relationship between cannabis use in adolescence and schizophrenia in adulthood, and the strength of this correlation, should therefore be cautious. Cannabis is particularly dangerous for people who are predisposed to mental illness, therefore these patients especially should reconsider before using this substance. There are many individuals who use cannabis for multiple years, but do not develop psychosis. Thus, it is possible that many variables

act as mediators in triggering a psychotic episode, but their influence on the process is not precisely known.

The potency of the interaction of marijuana with other stimulants in the context of the development psychosis is not fully understood. Further prospective controlled studies are needed to improve our understanding of other risk factors, and to determine how dangerous cannabis can be for inducing episodes of psychosis in the general population.

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