MEDICINA CLÍNICA Y SOCIAL
Med. clín. soc. 2022;6(2):65-79. e-ISSN: 2521-2281
MAYO – AGOSTO. https://doi.org/10.52379/mcs.v6i2.249

ORIGINAL

Cannabis use and the development of psychosis or schizophrenia, analysis of current legislation and regional mapping: A systematic review

Consumo de cannabis y desarrollo de psicosis o esquizofrenia, análisis de la legislación actual y mapeo regional: una revisión sistemática

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ABSTRACT

Objective: This systematic review aims to summarize the findings of studies that investigated the risk, precocity and intensity of psychosis in cannabis users, taking into account the status of legalization and/or decriminalization of cannabis use in different countries. **Methodology**: Articles published up to May 2018 were included, in English, Portuguese and Spanish, all extracted from the PubMed and SciELO databases, respecting the inclusion and exclusion criteria. **Results**: 19 studies from 18 countries were included. The relationship of cannabis use and the onset of psychotic symptoms was sufficiently substantiated. However, there was no data that supported an increase in the risk, precocity or intensity of psychosis in cannabis users from countries with higher levels of legalization/decriminalization of cannabis use to the date of the present study. **Conclusion**: The use of cannabis is associated with the development of psychosis. So far, there is no data pointing to an increase in the precocity, risk or intensity of psychosis in cannabis users, due to the legalization or decriminalization of the use of cannabis. However, the absence of data to date does not exclude these possibilities, since none of the studies analyzed in this review specifically assessed the effects of legalization/decriminalization policies on those outcomes. Therefore, prospective studies focused on the effects of legalization or decriminalization policies should be conducted in countries such as Canada, Spain, the United States of America (some states), the Netherlands, and Uruguay.

Keywords: Psychosis; Cannabis; Legalization; Decriminalization

RESUMEN

Objetivo: esta revisión sistemática pretende resumir los hallazgos de los estudios que investigaron el riesgo, la precocidad y la intensidad de la psicosis en los consumidores de cannabis, teniendo en cuenta el estado de legalización y/o despenalización del consumo de cannabis en diferentes países. **Metodología**: fueron incluidos artículos publicados hasta mayo de 2018, en lengua inglesa, portuguesa y española, todos extraídos de las bases de datos PubMed y SciELO, respetando los criterios de inclusión y exclusión. **Resultados**: se incluyeron 19 estudios de 18 países. La relación entre el consumo de cannabis y el inicio de síntomas psicóticos estuvo suficientemente fundamentada. Sin embargo, no hubo datos que respaldaran un aumento en el riesgo, la precocidad o la intensidad de la psicosis en los consumidores de cannabis de países con niveles más altos de legalización/despenalización del uso de cannabis hasta la fecha del presente estudio. **Conclusión**: el consumo de cannabis está asociado con el desarrollo de psicosis. Hasta el momento, no hay datos que indiquen un aumento en la precocidad, el riesgo o la intensidad de la psicosis en usuarios de cannabis, debido a la legalización o despenalización del uso de cannabis. Sin embargo, la ausencia de datos hasta la fecha no excluye estas posibilidades, ya que ninguno de los estudios analizados en esta revisión evaluó específicamente los efectos de las políticas de legalización/despenalización en esos resultados. Por ello, los estudios prospectivos centrados en los efectos de las políticas de legalización o despenalización deben llevarse a cabo en países como Canadá, España, los Estados Unidos de América (algunos estados), los Países Bajos y Uruguay.

Palabras clave: Psicosis; Cannabis; Legalización; Despenalización

Received: 03/03/2022
Revised: 15/03/2022
Accepted: 24/04/2022

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Conflicts of interests

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

How to cite this article: Alves da Silva Zunini PA, Passamani Borges G, Almeida Tonon JH, Nishumura R, Barrios I, O'Higgins M, et al. Cannabis use and the development of psychosis or schizophrenia, analysis of current legislation and regional mapping: A systematic review. Med. clín. soc. 2022;6(2):65-79

INTRODUCTION

Cannabis is the most widely consumed illicit drug in the world (1). It is mostly first experienced during adolescence, either as a peer integration factor or as a rite of passage (2). The acceptance of cannabis by the world society, based on its medicinal use to treat nausea, pain or other ailments, was quickly followed by a desire to legalize the drug for recreational use (3). The seemingly innocuous side effects helped open new avenues to make its trade legal (4). Despite the expansion of its use, knowledge about its effects on human health is still limited (5). On the other hand, the potentially detrimental impact on adolescent brain development remains a focal point for research, particularly because of the possibility that users in this age group may face an increased risk of psychosis (6).

Although the controversy over cannabis has already taken place in the past, it is now taking on different characteristics because of the new genetically modified high potency varieties (7). For this reason, the current discussion is not comparable to earlier ones (8). In the last two decades, the acceptance and significant increase in consumption worldwide have led to the development of policies in this regard (9). In this sense, the debate has become politicized and polarized between different positions on its regulation or legalization. On the other hand, there are those who defend increased penalties, the continuation of the current prohibition, and even the persecution of users as well as dealers and distributors (10).

In recent years, the complications of cannabis use have again attracted the attention of researchers, although they no longer focus on the cannabis-psychosis relationship as they once did (11). Despite the existence of several indicators of increased use, there is still no evidence that fully proves the relationship between the first psychotic crisis or schizophrenia and cannabis use (12). Despite this, it is now accepted and virtually established that the younger the age of onset of use, and the higher the potency of cannabis, the earlier the onset of psychosis (13). Evidence shows that cannabis may be related to psychotic disorders, especially in regular users, in addition to potentiating symptoms in those already diagnosed with a psychiatric disorder (14). Cannabis use has not yet been fully linked to the development of psychosis, although there is evidence of a cause-effect relationship, and a large number of articles establish some kind of statistical correspondence between its use and the first psychotic crisis (15).

Considering that the legalization and/or decriminalization of cannabis could increase the frequency and quantity of its use, the present systematic review aims to summarize the findings of studies that investigated the risk, precocity, and intensity of psychosis in cannabis users.

METHODOLOGY

The PRISMA statement (16) (minimum set of evidence-based elements to assist in the reporting of systematic reviews and meta-analyses) was chosen as the methodological reference for the present systematic review.

Eligibility criteria

Clinical studies, comparative studies, data sets, legal cases, multicenter studies, observational studies, and twin studies, published in English, Spanish, or Portuguese, dealing with cannabis use and the development of psychosis or schizophrenia were included in this review. Excluded were animal studies, autobiographies, biographies, books, case reports, classic articles, clinical conference proceedings, commentaries, congress abstracts, dictionaries, editorials, historical articles, interactive tutorials, interviews, conferences, letters, meta-analyses, news, newspaper articles, patient education booklets, personal narratives, technical reports, audio and video media, and webcasts, studies of previously schizophrenic patients and unrelated affective psychoses, or articles that did not focus on only one aspect of the topic of interest, as well as studies without statistical information.

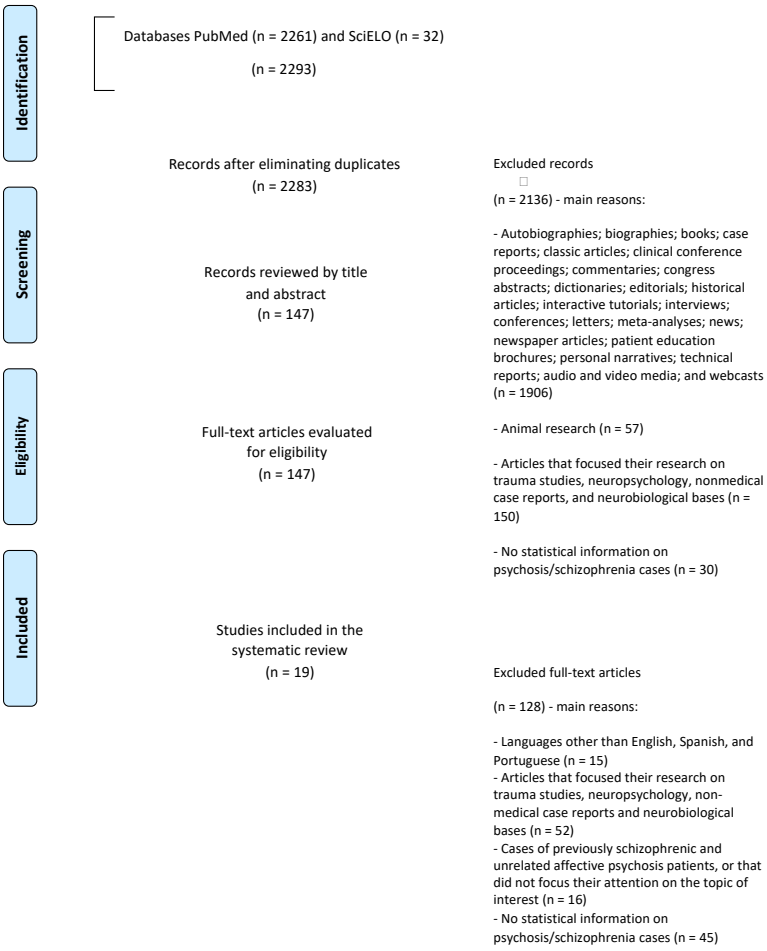
Sources of information

The search in PubMed and SciELO databases used the following terms: (marijuana OR marihuana OR cannabis OR THC OR tetrahydrocannabinol OR hashish OR pot) AND (psychotic OR psychosis OR schizo* OR delusional), in English, Spanish or Portuguese.

Literature search

Figure 1 shows the flow diagram for the identification, selection, eligibility, and inclusion of studies in the present systematic review, after using the PRISMA methodology (16). A database search was performed by the first and last author (PASZ and JMCM, respectively) to identify relevant articles for the present review. The first search was completed in February 2018 and duplicate citations were removed from the various databases. A second search was conducted in December 2018, using the same terms and databases. A total of 2293 studies were identified.

FIGURE 1: FLOW DIAGRAM ACCORDING TO PRISMA STATEMENT.



Selection of studies

In the selection phase, the first (PASZ) and last author (JMCM) read the abstracts of all the studies found in the search (n = 2293), independently. Inclusion and exclusion criteria were applied, and 1956 articles were excluded. Articles that were recommended for exclusion by only one of the two authors at this stage were further evaluated in a later phase. In the eligibility phase, the first (PASZ) and last (JMCM) author evaluated the full-text articles (n = 327), independently. The second author (GPB) made an inclusion or exclusion decision in cases of disagreement between the first (PASZ) and last (JMCM) author. Three hundred and eight articles were excluded based on the inclusion/exclusion criteria. Finally, 19 studies were included in the present systematic review.

Data collection process

The first (PASZ) and last (JMCM) authors read all 19 included studies independently. The first author (PASZ) tabulated the data from the studies.

Collected data

From the 19 included studies, the following data were collected: authors; year of publication; type of study; number of participants and mean age of participants; city, country, and time period in which the study was conducted; methodology; and main results. No method was conducted to combine the results of the studies due to the high heterogeneity of the studies: different types of studies; non-similar measures; heterogeneity of the intervention; and heterogeneity of sampling and design.

Cannabis legalization in countries

Taking into consideration the countries that had at least one study included in the present systematic review, the first (PASZ) and last (JMCM) author conducted a secondary review on cannabis legalization in those countries, looking for the following variables: country; legislation on cannabis use; legislation on cannabis cultivation; legislation on cannabis sale; year of legalization; source.

RESULTS

Characteristics of the studies

Table 1 shows the main results found in the present systematic review. Finally, 19 articles (17-35) were selected that possessed the necessary characteristics and dealt with the research topic in a sufficiently specific manner. All the studies were related to the use of cannabis prior to the first psychotic crisis and its evolution, varying the time studied and the characteristics of each study. Since the sample was varied, it is understood that cultural, legislative and temporal characteristics may have had a different influence in each case. Of the 19 articles included, 9 were comparative studies, 4 multicenter studies, 1 observational study, 1 randomized multivariate study, 3 longitudinal studies (of these, 1 was a prospective cohort, and 2 were prospective longitudinal studies), and 1 was a retrospective case-control study. Most of the studies were conducted in Europe (Netherlands, United Kingdom, Norway, Spain, Italy, Germany, Austria, Poland, Czech Republic, France, Belgium, Bulgaria). Other articles came from the United States of America (New York, New Jersey), Canada, New Zealand, India, Australia and Israel. No studies were found from Latin America, the Caribbean or Africa.

Sample sizes ranged from less than 30 patients to more than 1500 in some cases, with the vast majority of studies containing between 100 and 800 patients. The focus was to study the relationship between cannabis use and the onset of psychotic symptoms. It should be noted that all the studies included women and that the mean age of the participants was between 17 and 35 years approximately (although in some studies there were patients under 16 years of age and even patients aged 78 years in others). The year in which the studies were conducted was between 1978 and 2015.

TABLE 1: ANALYZED STUDIES

Author(s); year of publication; type of study	Number of participants; average age of participants	City(s); country; period in which the study was conducted	Methodology	Main results
Barnes et al. (19); 2006; prospective longitudinal	152; average age not specified	West London; United Kingdom; period not specified	The study recruited 152 people with a first episode of schizophrenia, who reported the use of psychoactive substances. Their age, symptom onset, IQ, mental and cognitive status, as well as executive and social functions were analyzed.	A strong association was found between cannabis use and psychotic symptoms. It was estimated that cannabis may influence the onset of the first psychotic crisis in predisposed individuals. Cannabis was identified as a risk factor.
Barnett et al. (17); 2007; comparative study	139; 25	South Cambridge; United Kingdom; 2002-2005	A sample of patients was taken from a referral center for the early care of patients with a first psychotic episode, and then compared with the general population not using psychoactive substances.	Cases of psychosis in users of psychoactive substances were twice as high as in the general population (mostly in the male sex). Fifty-one percent were users of cannabis, 43% of alcohol, more than half were users of class A drugs and 38% of multiple substances. The age of onset of drug use was directly associated with an early onset of psychotic symptoms.
Basu et al. (34); 1999; retrospective case-control study.	1950; <30	Chandigarh; India; 1978-1996	A sample of patients hospitalized for psychotic symptoms in a drug addiction care center was used.	In the group of cannabis users, psychotic symptoms were twice as long and more prolonged. There were no significant differences in past and family histories of mental illness, nor in the pre-morbid personality pattern.
Bhavsar at al. (20); 2015; comparative study.	750; average age not specified	No city specified; United Kingdom; 2014	This study evaluated the association between known risk factors for schizophrenia (genotypic markers, cannabis, urban residence and birth, psychological trauma, perinatal brain injury, and migration) with a set of important variables (age at onset and prodrome, symptom expression, and socioeconomic status). The data set analyzed contained male patients with a diagnosis of schizophrenia, according to DSM 5.	Cannabis use was associated with earlier age of onset of schizophrenia. Very similar inferences were drawn from the data for age of onset and prodrome.

Donoghue et al. (18); 2011; comparative study.	371; 23-26	Nottingham; United Kingdom; 1992-1994 and 1997-1999	Schizophrenia prevalence study, which classified etiology and ethnicity of schizophrenia and other psychoses. It included all individuals with a first episode of psychosis between 1992 and 1994 and 1997 and 1999, respectively. Individuals with a comorbid diagnosis of problematic substance use, according to ICD-10, were identified.	An increasing (but not statistically significant) trend was found for all substance use disorders in the first psychotic episode population as a whole (11.9% and 18.2%, in each cohort, respectively). When analyzed by age, a significant increase in cannabis-specific substance use disorders was seen for all first psychotic episode cases in 16–29-year-olds (3.2% and 10.6% in each cohort, respectively). When analyzed by age and sex, a significant increase in all substance use disorders was seen in female patients with a first psychotic episode, aged 16-29 years (6.1% and 24.2% in each cohort, respectively). This increase was not observed in male patients.
Ferdinand et al. (21); 2005; comparative study (randomized controlled trial).	1580; average age not specified	Rotterdam; The Netherlands; 1983-1997	A 14-year follow-up study was conducted on 1580 patients, initially aged 4 to 16 years, who were randomly selected from the general Dutch population. At the first evaluation, psychopathology was assessed with the Child Behavior Checklist (CBCL). Throughout the 14 years of follow-up, cannabis use and psychotic symptoms were assessed with the Composite International Diagnostic Interview (CIDI).	Survival analyses showed that the association between cannabis use and psychotic symptoms occurred independently of baseline CBCL scores (HR=2.54; 95% CI=1.60-4.04). It was concluded that the link between cannabis use and psychotic symptoms is specific and does not depend on the early presence of other types of psychopathology. This shows that research aimed at unraveling the mechanisms that are responsible for this specific association is useful. Furthermore, since cannabis use appears to be a specific risk factor for future psychotic symptoms, prevention directed against cannabis use may prevent the onset of psychotic symptoms in vulnerable individuals.
Fergusson et al. (31); 2003; longitudinal study.	1265; average age not specified	No city specified; New Zealand; 1977	Data were collected during the course of the Christchurch Health and Development Study (CHDS). The CHDS is a longitudinal study of a birth cohort of 1265 children who have been studied from birth to age 21 years. As part of this study, data were collected on cannabis dependence and psychotic symptoms at ages 18 and 21 years.	Young people who met DSM-IV criteria for cannabis dependence had elevated rates of psychotic symptoms at age 18 (rate ratio 3.7; 95% CI 2.8-5.0; p<0.0001) and 21 (rate ratio 2.3; 95% CI 1.7-3.2; p<0.0001). These associations were adjusted for prior psychotic symptoms and for a range of other confounders using a generalized estimating equation model. This analysis showed that after adjusting for confounders, those who met criteria for cannabis dependence still had an increased rate of psychotic symptoms (rate ratio 1.8; 95% CI 1.2-2.6; p<0.005). The results showed that the development of cannabis dependence is associated with increased rates of psychotic symptoms in young people, even considering pre-existing symptoms and other antecedents.

Foti et al. (22); 2010; comparative study	229; average age not specified	Suffolk County (NY); United States of America; 1989-1995	A total of 229 patients with a schizophrenia spectrum disorder were evaluated five times: at first admission, at 6 months, 2 years, 4 years, and 10 years later. At each evaluation, cannabis use and psychiatric symptoms (psychotic, negative, disorganized and depressive) were measured.	Lifetime cannabis use was associated with earlier onset of psychosis. Rates of current use ranged from 10% to 18% across all assessments. Mixed-effects logistic regression revealed that changes in cannabis use were associated with changes in psychotic symptoms over time, even after controlling for potential confounders (sex, age, socioeconomic status, use of other drugs, use of antipsychotic medications, and other symptoms). Structural equation modeling showed that the association with psychotic symptoms was bidirectional. It was concluded that cannabis use was associated with an adverse course of psychotic symptoms in schizophrenia, and vice versa, even after accounting for other clinical, substance use, and demographic variables.
González-Pinto et al. (23); 2009; comparative study	92; 30	No city specified; España; 1997-1999	Patients were studied after their first admission for psychosis, being interviewed at the first, third and fifth years. At follow-up (8 years later), functional outcomes and alcohol and drug abuse were recorded. Patients were classified according to cannabis use: 25 used cannabis before their first psychotic episode and had continuous use during follow-up (CU); 27 used cannabis before the first episode but stopped using it during follow-up (CUS); and 40 had never used cannabis (NU).	The 3 groups did not differ significantly in symptoms or functional outcome either at baseline or during short-term follow-up. The CUS group showed better long-term functional outcome compared with the other 2 groups and had fewer negative symptoms than the CU group, after adjusting for potential confounders. For the CUS group, the effect size was 1.26 (95% CI 50.65 - 1.86) for functional outcome and 20.72 (95% CI 521.27 - 20.14) for negative symptoms. All patients experienced improvements in positive symptoms. It was concluded that the harmful effect of cannabis is evident: even the improvement of the CUS group may be due to a lower genetic load than those in the NU group, as they have better recovery power. However, those in the CU group (despite this supposed lower genetic load) had a negative prognosis.
Helle et al. (26); 2016; multicenter study	1119; 30	Oslo, Stavanger, and Bergen; Norway; 2000-2013	Patients were recruited from catchment areas in Oslo, Stavanger and Bergen (Norway), diagnosed according to DSM-IV and examined according to their history of substance use. Linear regression analysis was used to examine the relationship between substance use and age at disease onset.	Patients with substance use (n=627) presented psychotic symptoms (23.0±7.1 years) about 3 years earlier than the non-drug using group (n=492, 25.9±9.7 years). It was concluded that cannabis use was associated with 3 more years of psychosis in the individual's lifetime. Only cannabis had a significant relationship compared to other factors such as sex or family pathological history.
Kelley et al. (28); 2016;	247; 24	No city specified; United	A total of 247 patients with a diagnosis of first episode psychosis were	Escalation of pre-morbid substance use in the 5 years prior to onset was highly predictive of increased risk of psychosis

Mané at al. (27); 2015; comparative study	119; 24	No city specified; Spain; 2008-2014	The study analyzed patients in their first psychotic episode. The inclusion criteria were adult patients (18-35 years), with a DSM IV diagnosis, without a history of severe head trauma or any neurological disease, with an IQ of approximately 80, and who did not use substances other than cannabis or tobacco (users were considered to be those who had consumed between the last weeks and the previous 6 months). The sociodemographic variables considered were age, onset of psychosis, sex, cannabis use, weekly amount, age of onset of use. Symptoms were assessed by the PANSS scale. Participants were divided into two groups: cannabis users and non-cannabis users.	The findings showed that cannabis use is related to an earlier age of onset of psychosis. In addition, patients with first episode psychosis reported using cannabis to alleviate hallucinations, suspiciousness, and to organize their thoughts. These findings are consistent with the self-medication hypothesis and the secondary psychosis hypothesis.
Pencer et al. (24); 2005; comparative study.	138; 17	No city specified; Canada; period not specified	Symptomatic and functional outcome and cognitive functioning were examined in adolescents who experienced their first episode of psychosis. Sixty-nine adolescents were evaluated and compared with 69 adults. All were enrolled for the first time in a specialized psychosis treatment program. Assessments were conducted at baseline, 1-year and 2-year follow-up. Assessments included positive and negative symptoms, depression, number of relapses, substance use, cognitive functioning, age-appropriate productivity (employment or being in school), and quality of life.	Functional and symptomatic outcome after a first episode of psychosis in adolescents was generally similar to that in adults. The only robust difference found was increased cannabis use. In adolescents, the most important predictor of treatment outcome was residual symptoms, both positive and negative, which were maintained at 1 and 2 years. In addition, the level of cannabis use at program admission was predictive of the likelihood of being gainfully employed and school performance.

Schoeler et al. (30); 2016; prospective cohort study	220; 29	No city specified; United Kingdom; 2012-2013	A follow-up of at least 2 years after the first episode of psychosis was conducted for 220 patients attending psychiatric services. Longitudinal modeling (fixed-effects analysis, cross-path analysis) was used to examine whether the association between changes in cannabis use and risk of relapse over time is the result of shared vulnerability between psychosis and cannabis use, or conversely whether psychosis increases the risk of cannabis use (reverse causation).	Fixed-effects models adjusting for variables (other illicit drug use, adherence to antipsychotic medications) and time-invariant confounders (e.g., genetic or pre-morbid environment) revealed that there was an increased odds of experiencing a lapse in psychosis during periods of cannabis use, relative to periods of no use (odds ratio =1.13; 95% CI; 1.03-1.24). The change in continuation pattern significantly increased the risk (odds ratio = 1.07; 95% CI; 1.02-1.13), suggesting a dose-dependent association. Crossover analysis confirmed that this association reflected an effect of cannabis use on later risk of relapse (Ct1 → Rt2: β = 0.44; p = 0.04), rather than an effect of relapse on subsequent cannabis use (Rt1 → Ct2: β = -0.29; p = 0.59).
Schoeler et al. (32); 2016; observational study	256; 28	South London; United Kingdom; 2002-2015	In this study, patients aged 18 to 65 years who presented with their first episode of psychosis to psychiatric services in South London were prospectively recruited and followed. Relapse of psychosis within 2 years of psychosis onset was defined as the risk of later hospital admission. Patients were classified according to different patterns of cannabis use: continuity of use after the onset of psychosis; potency of cannabis use; and frequency of use after the onset of their illness. Multiple regression analysis (logistic or binomial) was used to compare the different cannabis use groups and propensity score analysis was used to confirm the results.	Between April 12, 2002, and July 26, 2013, 256 patients presented with a first episode of psychosis. Follow-up evaluations were done for these patients until September 2015. Simple analyses showed that former regular cannabis users who had stopped after the onset of psychosis had a more favorable disease course with respect to relapses. In multiple analysis, continuous high-frequency users (i.e., daily use within 24 months) of high-potency cannabis (similar to a skunk) had the worst outcome, evidenced as a higher risk of subsequent relapse (odd ratio = 3 - 28, 95% CI; 1 - 22-9 - 18), more relapses (odds ratio = 1 - 77; 95% CI; 0 - 96-3 - 25), fewer months to relapse (b -0 - 22; 95% CI; -0 - 40 to -0 - 04), and more intense psychiatric care (odds ratio = 3 - 16; 95% CI; 1 - 26-8 - 09) after psychosis onset.
Sevy et al. (35); 2010; multivariate randomized study	100; average age not specified	New York; United States of America; 1998-2004	Forty-nine patients with a first episode of schizophrenia and cannabis use disorder and 51 subjects with a first episode of schizophrenia without cannabis use disorder were compared. Multivariate logistic regression was	It was determined that 74% of subjects with cannabis use disorder initiated use prior to positive symptoms. Subjects with cannabis use disorder were predominantly male, younger at baseline, had an earlier age of onset of positive symptoms, lower educational attainment, lower socioeconomic status, better pre-morbid childhood social adjustment, a tendency toward poorer

Tosato et al. (29); 2013; multicenter study	296; 32	City not specified; Italy; 2005-2007	The study was conducted in the framework of the Psychosis Incident Cohort Outcome Study (PICOS), a multicenter investigation of patients with first episode psychosis attending psychiatric services in the Veneto region of Italy. Standardized instruments were used to collect sociodemographic, clinical and drug use data.	Cannabis use was not associated with a higher level of positive symptoms but was correlated with less severe depressive symptoms. No relationship was seen between pre-morbid adjustment or IQ and cannabis use. Patients with a first episode of psychosis who used cannabis had an earlier age of onset than non-using patients, even after adjusting for sex and diagnosis. The results suggest a possible causal role of cannabis in the activation of psychosis in certain vulnerable subjects.
Wobrock et al. (25); 2013; multicenter study	498; 25	Cities not specified; Germany, Austria, Italy, Israel, The Netherlands, Poland, Czech Republic, France, Spain, Belgium, Bulgaria; period not specified	This study was conducted in 11 European countries. Patients with a first psychotic episode were included, analyzing their psychopathology and cognitive performance. The sample was composed of patients with a first psychotic episode, separating them into three groups: drug users, who continued to use drugs; those who were users and then stopped; and those who had never used drugs. These groups were compared at baseline and then at 6 months. The neurocognitive assessment included the Rey Auditory Verbal Learning Test (RAVLT), Trail Test, Purdue Pegboard test and digit-symbol coding.	With respect to cognition, the only significant difference was a slightly better performance in verbal memory in those patients who only abused cannabis compared to those who used other substances. It was also found that psychopathology was slightly worse in cannabis users who started using cannabis before the age of 16 years.

Main results

All the comparative studies analyzed, regardless of the size of the samples selected, related cannabis use to the first psychotic crisis. In the United Kingdom, cannabis was the most commonly used drug in the 30 days prior to the first psychotic crisis, although the result was equivalent in persons who had not used it (17). Likewise, also in the United Kingdom, although not statistically significant, an increase in the specific use of cannabis in the first psychotic crisis was observed, mainly in the age group between 16 and 29 years of age, and mostly in female patients (18). It has been reported that the link between cannabis use and the development of psychosis is specific, so it does not necessarily depend on the early presence of other psychopathologies to manifest itself (19, 20). Likewise, it is reaffirmed that cannabis use is a risk factor to be considered in health promotion (19). When considering other factors throughout the individual's life (e.g., variations in socioeconomic status, age, treatment or not with antipsychotics), a study conducted in the United States of America (22) has reported that cannabis use has been associated with an adverse course of psychotic symptoms and the evolution of schizophrenia.

In Spain, users who stopped using cannabis after the first psychotic crisis showed a better long-term functional outcome and fewer negative symptoms, compared to those who did not stop using (23). In Canada, when studying and comparing (at the functional and somatic levels) adolescents in their first psychotic crisis with adults, similar results were observed. However, it is noted that adolescent cannabis users maintained positive and negative symptoms for a longer period, with lower predictions of access to paid employment and poor school performance (24).

The multicenter studies analyzed showed the existence of an association between cannabis and psychosis, with a worse cognitive evolution (25). In this regard, one of the studies (conducted in Norway) determined that cannabis use brings forward the onset of psychotic symptoms by three years, compared to non-user patients (26). In Spain, a similar result was found in a comparative study (27). In the United States of America, it was also found that pre-morbid use, in the five years prior to the crisis, was highly predictive of the onset of psychosis, increasing up to 2.2 times. These results were independent of sex and family history of the patients (28). On the other hand, in Italy, another study did not associate consumption with a higher level of positive symptoms, although it was associated with less severe depressive symptoms. This study also suggested the role of cannabis as a causal factor in the activation of psychosis in certain vulnerable subjects, recommending that reducing its use may delay or prevent some cases of psychosis (29). The 3 longitudinal studies also reaffirmed the association between consumption and psychotic symptoms (19, 30, 31), in the United Kingdom and in New Zealand.

In an observational study conducted in the United Kingdom, it was found that patients who stopped using cannabis after the first psychotic crisis had fewer relapses, fewer hospitalizations and less need for medical care. On the contrary, those who continued with a high frequency of use, in this case Skunk-type marijuana, showed an unfavorable evolution with an increase in relapses, hospitalization time and the need for psychiatric care (32). Studies in India found that cannabis users who were hospitalized for a psychotic crisis had a duration of symptoms twice that of non-users, and a higher probability of psychosis than users of other substances (33). However, there were no significant differences when looking at all patients together in relation to their pre-morbid histories, family history of mental illness or personality type (34).

Finally, in the United States of America, a multivariate randomized study attempted to characterize cannabis users with a first psychotic crisis. To this end, they were separated into two groups: those who were users and those who were not, and then compared. The results obtained showed that most of the patients who were users were male, younger than non-users, with an early onset of positive symptoms and lower socioeconomic status; they also presented lower school performance, as well as more severe hallucinations and delusions (35).

Cannabis legislation in different countries

Table 2 shows the situation of legalization/decriminalization (36-40) of cannabis in countries that had studies included in this systematic review. In this regard, considering these countries, it was possible to stratify them into 4 different levels of legalization/decriminalization of consumption. At the first level are countries in which cannabis use is totally illegal: Bulgaria, France, and the United Kingdom. At the second level, there are Israel and Poland, countries that only allow the medicinal use of cannabis. In the third level, which concentrates most of the countries included in this review, medicinal use is allowed and there is tolerance with personal use and/or in small quantities and/or in parts of the country. At this level are Austria, Belgium, the Czech Republic, Germany, India, Italy, Norway, the United States of America and the United States of America. Finally, Canada, Spain and the Netherlands are in the fourth level. In these countries the use of cannabis has been legalized/decriminalized more broadly. In this last level, Spain and the Netherlands stand out with a history of decriminalization/legalization of consumption that is much older than the rest of the countries.

TABLE 2: CANNABIS LEGISLATION IN DIFFERENT COUNTRIES.

Country	Legislation on cannabis use	Cannabis cultivation legislation	Legislation on the sale of cannabis	Year of legalization	Source
Germany	Legal for medicinal purposes. Legal recreational use is considered self-harm. As with all drugs, cannabis-related offences are punishable by up to 5 years imprisonment or a fine. The penalty may be waived in cases of 'insignificant quantities' for personal use.	No information available.	Illegal. However, with a doctor's prescription and federal permission, it can be used medicinally.	No information available.	EMCDDA (36)
Austria	Illegal, although personal use is allowed.	Illegal.	Illegal.	Illegal.	EMCDDA (36)

Belgium	Illegal (decriminalized up to a certain weight). Possession of cannabis for personal use is prohibited, but a person only receives a warning from the police if he/she does not cause public disorder. Individuals causing public disorder to receive 3 months to 1 year imprisonment. The 2003 directive states that the maximum for personal use is 3 g of cannabis or one plant.	Legal (maximum 1 plant).	Illegal.	Law of February 24, 1921, Art 2ter; Arrêté royal of December 31, 1930, Art 28; Directive of April 17, 1998. Ministerial Directive of May 16, 2003; Directive of the Ministry of Justice and Judicial Authorities of January 25, 2005.	EMCDDA (36)
Bulgaria	Illegal.	Illegal.	Illegal.	Illegal.	EMCDDA (36)
Canada	Free consumption and production.	Legal.	Legal.	Law passed in June 2018 (effective as of October 17, 2018).	Hill & George, 2019 (38)
United States of America	Illegal at the federal level. Legal or decriminalized in some states. Legal for medicinal and recreational purposes in Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, and Washington.	Legal or decriminalized in some states.	Legal or decriminalized in some states.	Alaska, 2015; California (1996 medical; 2016 recreational); Colorado, 2012; Massachusetts, 2016 (not yet enforced); Oregon, 2015, Washington, 2015. It is illegal to transport cannabis between states and the law is not enforced in several places despite being approved.	Governing (37)
Spain	Legal, in the private sphere (decriminalized up to a certain amount). As with all drugs, cannabis-related offenses, such as possession and use in public places, are punishable by administrative sanctions.	Article 36, paragraph 18 of the Citizen Security Law. This article states that "only the cultivation of cannabis in places visible to the public is sanctioned". The ambiguity of the law is questioned.	Illegal. Judicial practice suggests that punishable possession includes quantities exceeding 40 g of hashish.	Law 1/1992, art. 25-28.	EMCDDA (36)

France	Illegal.	Illegal.	Illegal.	Illegal.	EMCDDA (36)
The Netherlands	Legal in coffee shops and decriminalized up to a certain quantity	Legal up to 5 plants (more than 5 cannabis plants carry penalties of up to 6 years imprisonment)	Legal in coffee shops	Legal. It came into force in 1928 and was fundamentally amended in 1976.	EMCDDA (36)
India	Illegal/legal or decriminalized in some regions.	Illegal/legal or decriminalized in some regions.	Illegal.	No information available.	Room (40)
Israel	Legal for medical purposes.	No information available.	Illegal.	Illegal.	EMCDDA (36)
Italy	Illegal (decriminalized/legal for medicinal use). As with all drugs, cannabis-related offenses (such as possession for personal use) are punishable by administrative sanctions after the second offense.	Illegal.	Illegal.	Illegal. THC 1 g; DPR309 / 90. Art. 72-75; Decree of the Ministry of Health of April 11, 2006.	EMCDDA (36)
New Zealand	Illegal.	Illegal.	Illegal.	Illegal	Rychert & Wilkins, 2016 (39)
Norway	Illegal (decriminalized/legal for medical use)	Illegal.	Illegal.	No information available.	EMCDDA (36)
Poland	Legal for medical purposes only	Illegal.	Illegal / legal for medical purposes.	No information available.	EMCDDA (36)
United Kingdom	Il Illegal. Cannabis-related offences, such as possession, are punishable by up to five years' imprisonment. For adults, police may warn or issue a penalty notice for disorderly conduct rather than prosecute, as part of a three-point escalation process for possession of cannabis for personal use.	Illegal.	Illegal.	Not legalized. In January 2009, cannabis was reclassified to Class B.	EMCDDA (36)
Czech Republic	Illegal (legal for medicinal use). Small quantities of up to 15 grams of dried marijuana and 5 grams of hashish are not penalized. Government Decree n. 467/2009	Illegal.	Illegal / legal for medical purposes.	Illegal. Prior to January 2010, the old Penal Code did not distinguish between cannabis and other substances.	EMCDDA (36)

DISCUSSION

The aim of this systematic review was to summarize the findings of studies that investigated the risk, precocity and intensity of psychosis in cannabis users in countries with different legislation regarding the legalization/decriminalization of this drug. Based on the 19 studies conducted in 18 different countries, it was verified that there is no data to support an increase in the earliness, risk, or intensity of psychosis in cannabis users in countries with a higher level of legalization/decriminalization of cannabis to date. However, it should be noted that several countries have still recent legislation about the recreational and/or free use of cannabis, in comparison with the legislation of the Netherlands or Spain.

In this sense, the studies by Ferdinand et al. (21), in the Netherlands, González-Pinto et al. (23) and Mané et al. (27), both in Spain, present results influenced by legalization/decriminalization in those countries. However, in these studies, the findings of risk, precocity and intensity of psychosis among cannabis users do not present data that differ from the findings obtained in the other studies included in this review. With respect to the studies of the third level countries (Austria, Belgium, Czech Republic, Germany, India, Italy, Norway, United States of America and the Czech Republic), no discrepant data with the other levels were found either.

Nevertheless, it is possible to confirm that the relationship between cannabis use and the onset of psychotic symptoms is sufficiently substantiated. It should also be noted that the impact of cannabis-specific legislation on the health of the population should be evaluated longitudinally over the years. None of the articles makes specific reference to the legislative situation in the countries during the development of the research, nor how patients had access to cannabis. It was not possible to know what influence these factors had on the development of psychosis. Obviously, it cannot be overlooked that there are other factors that influence the development of psychosis, such as genetic, biochemical or environmental factors, and that THC is related to the increase of psychotic symptoms.

The present review had several limitations. First, only studies in English, Spanish and Portuguese were included. In addition, the included studies had different designs and measures of exposure and there were also sample differences. However, it was possible to perform a review with 19 studies, with a total of 7641 patients from various countries included. Pooling and analysis of the results of the different investigations was not performed, due to the heterogeneity of the included studies (e.g., different types of studies, non-similar measurements, very heterogeneous sampling and design). Future cross-national studies should be conducted with standardized measures to investigate what effect cannabis legalization/decriminalization has on cases in which psychosis develops. The present review does not intend to conclude with a statement about the potential effect of cannabis legalization/decriminalization on the incidence of psychosis cases but highlights the evidence.

In conclusion Cannabis use is associated with the development of psychosis. However, so far, there are no data showing an increase in the precocity, risk or intensity of psychosis in cannabis users due to the legalization or decriminalization of cannabis use. The absence of data to date does not exclude these possibilities, as none of the studies analyzed in this review specifically evaluated the effects of legalization/decriminalization policies on these outcomes. Therefore, prospective studies focusing on the effects of legalization or decriminalization policies should be conducted in countries such as Canada, Spain, the United States of America (some states), the Netherlands, and Uruguay.

AUTHOR'S CONTRIBUTIONS

PASZ and JMCM have taken part in the conception and design of the work, data collection, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript and approval of its final version. GPB, JHAT, RN, IB, MO, NRD, JA-S, RN, AV, JT, and ASMdS have taken part in the drafting of the manuscript, critical revision of the manuscript and approval of its final version

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