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Cannabis consumption and development of psychosis: state of the art

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Cannabis is the most widely used illegal drug in Spain. Currently, its use is on the rise as risk perception is decreasing, primarily among young people. It is well known that cannabis negatively influences course and prognosis in schizophrenic patients. However, the relationship between cannabis use and development of a psychotic or schizophrenic disorder remains controversial. The study of this topic has been approached using longitudinal cohort studies, which study cannabis use and psychotic or schizophrenic disorders. In addition to the classic Swedish conscript study published by Andreasson et al. 1987, during the past years, six more longitudinal cohort studies have been published. The data demonstrate that there are both temporal and dose-response relationships, and that early initiation of cannabis use is highly correlated with the development of psychotic symptoms. Cannabis consumption can increase the risk of developing schizophrenia in a vulnerable population two-fold, to the extent that some studies suggest a causal relationship. The current knowledge base makes it necessary to warn the population about the relationship between cannabis use and the development of psychosis.

Key words:
Cannabis. Psychosis. Dependence. Vulnerability.

Actas Esp Psiquiatr 2007;35(3):182-189

Consumo de cannabis y desarrollo de psicosis: estado actual

El cannabis es la droga ilegal más consumida en España. La disminución de la percepción de riesgo y el aumento del consumo, principalmente en la población adolescente, son fenómenos emergentes en la actualidad. Es conocida la influencia negativa del uso de cannabis sobre el curso y pronóstico de la enfermedad en los pacientes esquizofrénicos consumidores. Sin embargo, es controvertida la relación entre el consumo y el desarrollo de psicosis esquizofrénica o síntomas psicóticos prolongados. Su estudio ha sido abordado mediante la evaluación de cohortes en las que se realiza un seguimiento de muestras de la población y se evalúa la influencia del consumo de cannabis en el desarrollo de psicosis o esquizofrenia. Además de la clásica cohorte sueca, descrita por Andreasson et al. en 1987, en los últimos años han aparecido seis trabajos de seguimiento. Con los datos aportados por todos estos estudios se confirma que el consumo de cannabis es un factor de riesgo para el desarrollo de psicosis, ya que hay una relación temporal y de dosis-respuesta y se confirma que existe gran influencia en el desarrollo de síntomas psicóticos del inicio del consumo en edades tempranas. El consumo de cannabis puede duplicar el riesgo de desarrollar esquizofrenia en población vulnerable, e incluso hay trabajos que apuntan su contribución como factor causal. Con los conocimientos actuales es necesario alertar a la población acerca de la relación entre el consumo de cannabis y el desarrollo de psicosis.

Palabras clave:
Cannabis. Psicosis. Dependencia. Vulnerabilidad.

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INTRODUCTION

Cannabis is a product with more than sixty active substances and is the most widely used illegal drug in Spain. Its use is currently an important subject since its consumption is increasing according to the data provided by the observatory of the National Plan on Drugs[1] (table 1). Use grew significantly during the period 1995-2001. Consumption increased in all age groups and in both genders. The greatest relative increases were observed in the 40-64 year old group, where it increased 4.6 times and in the 15-19 year old group with a 1.8 times greater increase.

There is an increase in the prevalence of consumption when all the time intervals are assessed. In relationship with accumulated consumption, defined as sometime in the lifetime, it is seen that the highest prevalence appears in the

Table 1 Prevalence of cannabis consumption in the years 1997 and 2001, in 15 to 64 year old population

Consumption frequency	1997	2001
Lifetime	13.5%	24.4%
In the last 12 monts	6.8%	9.9%
In the last 30 days	3.1%	6.5%
Daily consumption (in the last 12 months)	0.7%	1.6%
Weekly consumption	2.8%	4.5%

Source: National Plan on Drugs (2003).

20-24 year old group (40.1% in 2001). If the 15 to 64 year old population is assessed, consumption is greater in men, although the present differences of gender (table 2) are less than those detected in the past. These differences decrease in the adolescent and young population, since the lowest ratio between consumption prevalence in men and women is detected in the 15-24 year old group (1.4 times). Inequality between genders decreased in the 1995-2001 period, because the consumption increase was greater in women (where it increased 1.9 times) than in men (1.7 times).

If consumption in the last 12 months is considered, the highest prevalence was observed in the 15-19 year old group (21.5%). Gender difference decreases with age and is minime in the 15-19 year old group, being only 1.4 times greater in men. Prevalence of recent consumption, in the last 30 days, also increased, going from 3.1% (1995) to 6.5% (2001). The increase occurred in all age groups and in both genders, being greater in women and in the 40-64 and 15-19 year old groups. Gender difference clearly decreased with age.

According to the above appears that there has been a significant increase of experimenting with cannabis in Spain in recent years, mainly among youth and women. As has been pointed out in the different use indicators, relative gender difference decreases with age. In cases of clear adverse effects related with consumption of this substance have been described[2]. Increase in consumption and its consequences are also reflected when treatment indicators are studied, since an increase is detected in health care demand related with cannabis[1], a phenomenon that has also been described recently in other European countries[3]. In Spain, when only the cases without previous treatment are considered, cannabis accounts for 16.9% of hospital admisions. In addition to consumption, it should be stated that the active substance concentration may be increasing[4,5]. In Europe, this could be related with its production with intensive hydroponic techniques[6].

Table 2 Prevalence of consumption in 15-64 year old population, according to gender

	Men	Women
Lifetime	31.9%	16.9%
Last 12 months	13.8%	5.9%

Source: National Plan on Drugs (2003).

Risk perception, especially in the younger population, is much lower than with other drugs[1]. Furthermore, increased consumption in this population has been evident for years[7]. These factors may explain why the consumption of cannabis in our society is increasinly common, which may be favored by the potent sales industry of products related with it.

It is known that cannabis consumption has health consequences on health, such as the production of dysphoria, behavioral disorders and that continued consumption produces substance dependence, poor cognitive development, psychopathological disorders and antisocial behavior. It has been related to educational deterioration, reduction of productivity and increased risk of use of other substances[5]. Acute consumption of Delta 9-THC in healthy volunteers, with no history of cannabis abuse, produces symptoms similar to the positive and negative ones of schizophrenia, perception alterations, increased anxiety, euphoria, decrecises in immediate and deferred recall of words and worsens execution in distractibility test, verbal fluency and work memory in recognition tasks. These data indicate that Delta-9-THC produces a wide range of transitory and behavioral symptoms as well as cognitive deficits, which in healthy volunteers mimic some aspects of endogenous psychoses[8]. There is no doubt that psychotic symptoms may appear in intoxication[8,9] and that cannabis consumption produces relapses and worsens the course in already diagnosed schizophrenic patients[10,11]. It has also been related to the onset of this disease at an earlier age[12]. In Spain, it has been described that cannabis consumption is a good predictive factor for relapses in schizophrenics[13].

RELATIONSHIP OF CANNABIS AND PSYCHOSIS

The controversial question concernine the relationship between cannabis consumption and the occurence of psychosis has not been resolved. It is possible that the relationship between both should be included within a polyfactorial model in which there is a genetic-environmental interaction[14,15]. Experimental demonstration would consist in administering cannabis, or different doses of this substance, in a group of subjects and comparing it with another

similar group that does not receive it, maintaining the rest of the setting exactly the same. However, this is not viable and is ethically unacceptable. Thus, the only means available to explain the nature of the relationship are correlational studies that detect the relationship between its consumption and the appearance of psychosis or permanent psychotic symptoms. Different strategies have been proposed to explain this question (table 3), although the most frequent and fundamental one is the follow-up of cohorts over prolonged periods, from the first stages of birth[16,17], childhood[18], adolescence[19] or the onset of youth[20,21]. Follow-up of representative stratified samples of the population[22] or the follow-up of cohorts at risk of developing psychosis and assessing the influence of cannabis in its appearance has also been proposed[23], although defining what risk or vulnerable groups that should be studied is controversial. However, longitudinal studies of follow-up of cohorts are not exempt methodological problems, since confounding factors, such as consumption of other substances, urbanicity, sociodemographic characteristics, ethnic characteristics, existence of other psychopathological disorders or of other risk factors, etc., must be controlled.

Another possible strategy, complementary to those previously mentioned, to adequately approach the relationship between cannabis use and the development of psychotic disorders is the study of the incidence and prevalence of psychosis over different decades. A study using this approach[24] has been used. It has also been criticized, given that it was necessary to compare administrative data of disease registries made with decades apart. This could thus influence the reliability of the registries made in pre-computer times. Furthermore, the data are not concordant and there are discrepancies since some studies state that the incidence and prevalence of schizophrenia remain stable[24] and others, however, state they are increasing[25].

Table 3 Strategies used in the study of the relationship of cannabis consumption and psychosis

Specific studies
General population
Conscripts
Stratified samples
Children
At risk population
Adolescents
Young persons
Students
Non-specific studies
Conscript sample

Table 4 Possible biases in cohort studies

Consumption of other substances
Presence of other psychiatric disorders
Consumption evaluation system: mostly self-reports
Time sequence
Selection of sample
Confounding factors: personality traits

Different causal criteria are used to define the causal relationship between exposure to a substance and development of a disease[14]. Hill's criteria (1965)[26] should be mentioned. They included consistency, specificity, biological gradient, temporality, coherence, plausibility and force. However, temporality is the *sine qua non* condition and the biological gradient, or influence of the dose, seems fundamental. There are several biases that may influence the detection of the causal relationship (table 4) and it is presently difficult to speak only of necessary or sufficient causes, but rather it should be proposed as a combination of component causes.

SPECIFIC STUDIES OF COHORT FOLLOW-UPS

Different patient cohorts have been studied to attempt to resolve some of these problems, especially that of temporality and substance use prior to developing psychosis. The first one, published in the 1980's[20], studied a Swedish cohort. In recent years, there have been six cohort follow-up studies designed to evaluate the development of psychosis or psychotic symptoms in cannabis consumers (table 5): a new report on data from the Swedish cohort[21] and studies on five other new cohorts, one from Holland[22], two different cohorts from New Zeland[16,18], one Greek cohort[17] and one German one[27]. In addition, papers with samples of pa-

Table 5 Specific recent studies of cohort follow-up

Author	Country	Year	Persons included	Persons finishing	Years of follow-up
Zammit et al.	Sweden	2002	50,087	45,570	27
Van Os et al.	Holland	2002	7,076	4,848	3
Arsenault et al.	New Zealand	2002	1,037	995	15
Fergusson et al.	New Zealand	2003	1,265	1,053	21
Stefanis et al.	Greece	2004	11,048	3,500	19
Henquet et al.	Germany	2005	3,021	2,434	4

tients not specifically designed for this purpose have been published[19].

The first study to systematically assess the appearance of psychotic disorders in relationship with cannabis consumption was conducted in Sweden with a cohort of conscripts[20]. In the years 1969 and 1970 all the Swedish conscripts born between 1959 and 1961, 50,465 subjects in all, were evaluated. Of these, 2%-3% were excluded, since they were exempt from recruitment. Those who were recruited were administered a questionnaire on general epidemiological and psychosocial data and a second questionnaire on the use of drugs, types of consumption, etc. Seven percent refused to answer it. The cohort was followed up for 15 years until 1983. Data on all psychiatric admissions were obtained. A total of 274 subjects with a diagnosis of schizophrenia were detected. Eleven endpoints were controlled when analyzing the data. The endpoint that best predicted the development of psychosis was the existence of a psychiatric diagnosis on recruitment. Cannabis consumption was also identified as a predictor and the amount consumed was related with the risk of developing schizophrenia. Relative risk of developing schizophrenia in the group that used cannabis was 2.4. However, risk increased with the consumption level, the OR (Odds Ratio) being 3.0 (95% CI: 1.6-5.5) in those consuming 11 to 49 times and 6.0 (4.0-8.9) in those consumers of more than 50 times over their lifetime.

The authors conclude that there is an association between cannabis consumption and schizophrenia and that cannabis increases the risk of developing schizophrenia, an increased based on the amount consumed. They consider cannabis as a risk factor within a multifactorial model.

The same cohort of patients was reanalyzed by Zammit et al. (2002)[21]. They assessed all the admissions of this group until the year 1996. Thus, the follow-up was superior to 25 years. Up to the date of the analysis, 362 cases of schizophrenia had been detected. Only five of the 11 confounding endpoints studied in this analysis had influence. Relative risk of developing schizophrenia among the consumers was 2.2. A dose-response relationship was detected. Once again, the patients who reported using cannabis on more than 50 occasions during their lifetime had an OR of developing schizophrenia of 6.7 relative to an OR of 3.1 for those who did not consume when adjusted by the confounding factors. The association persisted when the data were adjusted by the use of tobacco, alcohol and other drugs (especially stimulants) and by personality traits. It was superior in the patients who reported consumption five years following recruitment than in the group that consumed it after five years, thus with older age. There was no relationship with disease onset time from recruitment.

Cannabis may increase risk of schizophrenia by 30%, which would imply that 13% of the schizophrenia cases could be prevented if cannabis was eliminated. The authors state that cannabis is associated with the increased risk of developing schizophrenia, that the relationship is causal and that it cannot be explained by the consumption of other drugs or personality traits. The statements on the relationship of cannabis and psychosis, with more years of follow-up of the cohort, have been confirmed and the data also indicate the influence of the relationship of risk with consumption age.

Van Os et al. (2002)[22] have made the follow-up of a stratified sample of the Dutch population, from 90 municipalities. They selected 7,076 persons who were evaluated on three occasions, baseline, T1, one year later T2, and three years after the first visit. 4,848 completed the study. The CIDI Interview (Composite International Diagnostic Interview) and the structured interview SCID (Structured Clinical Interview for DSM) were used with all the subjects with psychotic symptoms at the baseline interview and in T2. Those who had any psychotic experience were defined as vulnerable to psychosis. The BPRS (Brief Psychiatric Rating Scale) was used in the T2 evaluation. Those having a score of 1 to 3 were assigned to the group of some psychotic symptoms and those who had 4 or more were assigned to the group of pathological level of psychosis. A group of four experts decided if it was necessary for them to receive treatment for their psychotic symptoms. When consumption was evaluated, the rate of use in the period prior to the study and during the same period was examined. The subjects were classified according to on amount consumed.

Those persons who used cannabis versus those who did not at baseline had an adjusted OR of 2.76 of presenting psychosis. The group of persons who had psychotic symptoms had an OR of 24.17 and among those requiring treatment for the symptoms, the OR was 12.01. The results of the OR were adjusted by age, gender, ethnic group, civil status, education level, urbanicity and level of social discrimination. The effect of cannabis was much greater in persons with a psychosis diagnosis in the baseline evaluation. The effect of consumption of other substances was reduced or disappeared when studied jointly with the use of cannabis. It was found that the effect of cannabis consumption at baseline on the evolution to psychosis was much greater than consumption at T1 and T2, so that the effect is more distal than proximal.

The authors conclude that evolution to psychosis could be reduced, if cannabis consumption was eliminated, by 67% in the group with a pathological level of psychosis and by 50% in the group requiring treatment due to psychotic symptoms. Thus, it is verified that use of cannabis increases the risk of the incidence of psychosis persons without a history of psychosis, with a dose-response relationship between exposure to cannabis and development of psychosis and worsens the prognosis of those vulnerable to suffering psychotic disorder.

Henquet et al. (2005)[27] studied the Munich population. They included a representative sample of 3,021 persons from this area. A total of 2,434 of them completed the 4 year

study. They were evaluated at baseline, at two years follow-up and at four years follow-up. They used the Munich version of CIDI (M-CIDI) and SCL-90 (Symptom Check List-90). Predisposition was considered present in those who score above the 90th percentile in paranoid ideation and psychoticism on the SCL-90 and psychosis was defined as the presence of two positive detections of items in the M-CIDI interview. Exposure to cannabis was defined as lifetime use on more than five occasions. Interaction between cannabis consumption and vulnerability is very important, since the difference in the risk between those who are vulnerable and those who are not in the non-consumption group is 6.3% while the same difference in the consumption group is 23.8%.

These authors conclude that frequent use of cannabis doubles the possibility of developing psychotic symptoms and thus that it is a risk factor, confirming the findings of the Dutch study[22]. The authors conclude that the contribution of this substance to the presence of psychosis in the population is between 8%-13%. The self-medication hypothesis is excluded since predisposition for psychosis does not predict the use of cannabis at the follow-up.

Another approach that attempts to resolve the question of the existence or non-existence of the relationship between cannabis and psychosis and clarify the question of the existence of the time relationship is the development of studies that follow cohorts from very young ages[16-18].

Fergusson et al. (2003)[16] studied a New Zealand cohort of 1,265 persons born in Christchurch, from the time of birth to 21 years of age. The existence of psychotic symptoms prior to consumption was controlled since the cohort is studied at the time of birth, at 4 months, yearly from 1 year until 16 and again at 18 and 21 years. They evaluated measure of personal, family and social functioning before 18 years and measures of mental disorder and substance use or abuse before 16 years. The presence of psychotic symptoms was evaluated at 18 and 21 years, within the mental examination, using items from the SCL-90, seltreport was use to assess cannabis. Cannabis dependence was evaluated in those subjects who responded affirmatively, using CIDI items. Consumption of other substances was studied, detecting dependence or evaluating for other mental disorders, such as major depression or anxiety disorder.

At 18 years, cannabis dependent patients had a 3.7 times greater incidence of psychotic symptoms relative to those who were not dependent on this substance. At age 21, cannabis dependents had a 2.1 times greater likelihood of having psychotic symptoms than those who were not. The data were adjusted for possible confounding factors, such as the previous psychotic symptoms, cannabis consumption, influence of the use of other substances and mental disorders and individual, social and family characteristics. In spite of this, the association between cannabis dependence and psychotic symptoms continued to be significant. Those who met the criteria for cannabis dependence had rates of psychotic symptom that were 1.8 times greater than those who were not cannabis dependent. However, with this design, it is not possible to exclude the fact that the presence of psychotic symptoms, among the evaluations of the adult life, increases cannabis consumption.

The authors conclude that the development of cannabis dependence is associated with the increase of psychotic symptoms in young subjects, even when the preexistence of psychotic symptoms and other factors are taken into account.

Arsenault et al. (2002)[18] studied another New Zealand cohort of 1,037 persons born between 1972-1973. To attempt to respond to the causality question, they assessed the presence of psychotic symptoms at 11 years and substance consumption at 15 and 18 years and conducted a psychiatric evaluation at 26 years. This approach aims to determine when psychotic symptoms are previous to consumption and when they are subsequent to it. Those who used cannabis at 15 or 18 years, defined as consumption more than three occasions, had more symptoms of schizophrenia than those who did not. These results are still significant when adjusted based on the existence of psychotic symptoms at 11 years. Those using cannabis at 15 years had a 4 times greater likelihood of having a schizophrenia diagnosis at 26 years than the controls. Furthermore, early use, at 15 years, bestows a greater risk than when use is at 18 years. Use of other drugs does not precede evolution to schizophrenia. It is concluded that cannabis use is a risk factor for development of schizophreniform disorders in adult age.

Stefanis et al. (2004)[17] followed-up a Greek cohort where they studied the effect of cannabis use in adolescents with subclinical positive and negative symptoms of psychosis. In this cohort, a total of 11,048 persons born in Greece in April 1983 were studied. A first evaluation was made at 7 years, and was repeated at 18 years. The evaluation includes socio-familial, medical and behavioral aspects. At 18 years, 3,500 questionnaires had been collected. This subsample does not differ from the total sample in regards to sociodemographic characteristics. At 19 years, cannabis consumption was investigated and the patients were classified according to consumption frequency.

Cannabis consumption appears for be associated with the positive symptoms of psychosis and remains significant after adjusting for use of other drugs, depressive symptoms, gender and schooling. The negative symptoms are also associated with the frequency of cannabis use. Furthermore, the large difference between patients who began consumption before 15 years or after, both for positive and negative symptoms, is described.

The authors conclude that cannabis contributes to the occurence of psychosis, especially it's use at early ages, as during adolescence. It also increases the risk of positive and negative symptoms of psychosis. This study confirms the re-

lationship between early consumption and development of psychotic symptoms, identified by Arsenault[18].

STUDIES IN RISK POPULATION

Another strategy is the study of populations at risk of psychosis. Phillips et al. (2002)[23] conducted a study with 100 young Australians with high risk of psychosis. The authors define risk as the presence of family background of psychosis, presence of schizotypal traits and, during the last year, decrease in functionality, subclinical symptoms or presence of self-limiting psychotic symptoms (less than one week). The patients were followed-up for a period of 4 to 1,051 days.

The authors conclude that there are no differences in the percentage of patients who develop psychosis in the consumers versus non-consumers. The study, however has been criticized becouse it does not follow the patients after the onset of the episode and beginning of treatment. The subjects showed very low consumption levels, and consumption is not controlled at follow-up. Furthermore, consensus has not been reached on the concept of vulnerable population since there are authors who propose including not only those who have a personal background of psychosis or first grade relatives with psychosis but also youth with symptoms of anxiety or depression as risk population[28].

OTHER STUDIES OF NON-SPECIFIC COHORTS

Cohort studies of the general population that are not specifically designed for the study of the development of psychosis in cannabis consumers, can they contribute interesting data. The results obtained are less conclusive and should be interpreted with greater precaution, due to greater risk of biases. This is because, on the contrary to the previous ones, they do not collect the possible confounding factors as systematically.

Studies with adolescents

Weiser et al. (2002)[19] conducted a study of a general population cohort not designed to assess the influence of cannabis consumption and development of psychosis. They describe the follow-up of Israel adolescents who are forcibly assessed at 16 or 17 years, within the selection process prior to military recruitment. Data on 270,000 adolescents who were evaluated in the 1980's and 1990's were gathered, so that the follow-up time varied from 4 to 15 years.

Initial evaluation included intelligence measures, an interview in which personality traits were studied and behavior evaluation in which social functioning, personal autonomy, social skills and physical activities were studied. All the adolescents identified as problematic, about 15%-20% (50,413 persons), were given extensive psycho-social evaluations. Psychiatric disorders, including the detailed study of substance consumptions in those who answered affirmatively was evaluated. Frequency of substance use and its influence on their life was investigated.

The type of substance used is not specified, but the authors know from previous epidemiological studies that the main drug used in this age group is marijuana. Subsequently, the registry of psychiatric admissions, that collects all the hospitalizations made in their country, is investigated. Adolescents who had been hospitalized in psychiatry previous to the evaluation or during the following year were excluded in order to not include patients who were already diagnosed or those who were developing the prodromes at the time of evaluation.

The prevalence of substance abuse assessed via self-report is more than double in those who are later hospitalized due to schizophrenia. A higher presence of mental disorders other than psychosis during adolescence in patients who subsequently develop this disorder is also detected. This association persists after controlling for the effects of intelligence quotient, social functioning or presence of non-psychotic disorders at the time of evaluation. The authors conclude that drug abuse, especially that of marijuana, is a risk factor for the development of schizophrenia, the previously described cohort follow-up studies agreeing with the data obtained.

The paper has several limitations, since it only studies men within a forensic psychiatric evaluation process that tries to discriminate the group of persons not suitable for military service. Furthermore, the study has not been designed specifically to detect psychotic symptoms. Thus, some persons who did not have any type of psychopathology in the first phase may not have been studied thoroughly and it is difficult to understand what criteria are followed to determine who is a problematic adolescent. In addition registry of hospital admissions, not specifically designed for the investigation and which, thus, only collect the most serious cases, are used as a measurement of outcome.

Studies with university students

Within the general population cohort study, Verdoux et al. (2003)[29] used a different approach, since they studied a sample of 685 fourth year French university students. Of these, they selected 79 who reported significant consumption of cannabis and null consumption. This authors tried to avoid the problems of retrospective collection and aimed to study vulnerability to the present of psychotic symptoms associated to cannabis consumption.

Psychiatric interviews were done to determine the presence of psychotic symptoms in absence of consumption. To do so, the CAPE-42 (Community Assessment of Psychic Experiences-42) scale was used. All the students selected had

to periodically fill out a survey on presence of symptoms several times a day (5). Furthermore the existence of consumption or not of cannabis at this time was controlled. Perceived hostility decreases after cannabis consumption, there is a friendlier perception of people and unusual perceptions increase. This relationship occurs up to three hours after consumption. However, in those with high vulnerability to psychosis, perception of hostility and presence of rare impressions and unusual perceptions are more likely. Thus, the authors suggest that the interaction between consumption and vulnerability as a modulator of the appearance of psychotic symptoms. On the other hand, it is seen that psychotic symptoms are not only related to acute cannabis use, but that the repeated consumption of cannabis in vulnerable patients may produce permanent psychotic symptoms.

It is concluded that vulnerability and cannabis use are independent predictors of the presence of rare impressions and unusual perceptions. Within the limitations of this study, it must be stressed that the group is made up of students, mainly females. The «vulnerability» measurement has been expressly designed for this study and it is impossible to distinguish the spontaneously produced symptoms from those related with cannabis.

Incidence and prevalence studies

Using a retrospective study, Degenhardt et al. (2003)[24] assess the number of schizophrenia cases in different cohorts of Australian patients. The cohorts include patient data from the year 1940-1944 to 1975-1979. No increase in the incidence of schizophrenia is detected in this study. It is stated that schizophrenics consume more cannabis than the general population and that the disorder onset age is decreasing. The authors conclude that consumption may precipitate the disorder in vulnerable patients and worsen the disorder course.

NEUROBIOLOGICAL HYPOTHESES

Several explanations that justify the interaction between cannabis consumption and appearance of psychotic symptoms from the neurobiological point of view, have been hypothesized. It is known that THC increases dopamine release[30] and greater presence of cannabinoid receptors in the dorsolateral prefrontal cortex in schizophrenic subjects have been described when compared with controls[31]. This increase of the receptors could explain the increased risk since if they are exposed to precipitating substances, they will more likely have psychotic symptoms[19]. The long term effect of cannabis use may be due to the deregulation of the endogenous anandamide cannabinoid system[22]. Cannabis use may initially increase synaptic dopamine, which could produce maintained changes in the cannabinoid system[27]. It would interact with vulnerability or previous deregulation, which would explain that the effect was especially intense in those vulnerable to psychosis. Another possible explanation is that the alterations in neurodevelopment in the hippocampus and prefrontal pathways contribute to the development of schizophrenia and vulnerability for substance dependence by the dysfunctional interactions with the nucleus accumbens[19].

CONCLUSIONS

Longitudinal studies that examined the relation were reviewed. These types of studies best able to clarify these questions. However, it must be remembered that they may have different biases, such as consumption of other substances, presence of other psychiatric disorders, or the method used to evaluate drug use, which in this type of follow-up studies should mostly be based on patient self-reports. Other methodological problems are the difficulty to establish time sequence, selection bias and influence of personality. Most of the reviewed studies are consistent and most of the authors mention consumption as a risk factor, although there are studies that point out that cannabis consumption is a causal factor for the development of schizophrenic disorders[21] or psychotic symptoms[16]. The importance of relevant factors, such as dose-response ratio and consumption age onset of has been described by the cohort studie. In relationship with the amount consumed, it has been stated that repeated use of cannabis may increase risk of suffering from psychosis[21,22]. It has even been described that the risk is clearly increased when the number of consumptions is greater than 50 over the lifetime[20,21] and others relate it to the existence of cannabis dependence[16]. The relationship between cannabis consumption and psychosis is not restricted to a poor course of the psychotic symptoms, but rather there is a relationship both with the production of psychotic symptoms and with the appearance of psychosis and need to receive treatment[22]. The other important factor described is age onset of consumption, since consumption, before 15 years, is associated with greater risk of developing psychosis and greater riskiness[17,18]. Furthermore, the sooner the dependence develops, the greater the possibility of having psychotic symptoms[16].

The studies reviewed clearly suggest that the use of cannabis constitute risk factor constitute the onset of schizophrenia, and that cannabis is a causal factor for psychosis. It is calculated that around 10% of schizophrenias could be prevented by elimination of cannabis consumption[14,27]. Cannabis consumption doubles the risk of developing psychosis, in vulnerable persons. There is a relationship with the dose and early onset of consumption. Thus it is necessary to transmit the known risks of continued consumption of cannabis to the population by the mental health care professionals.

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