RESEARCH

Cannabis and schizophrenia: characterisation of a risk factor in a sample of Moroccan patients hospitalised for psychosis

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Abstract

Background: In addition to the biological plausibility widely described through a very large number of studies, the causal link between cannabis uses and schizophrenia disorders has become illicit internationally and given the scarcity of similar studies in Morocco. Our study consists of a prospective descriptive study in the psychiatric department of the Moulay ben Abdallah Hospital in Essaouira. The sample consisted of 95 patients diagnosed with schizophrenia according to the DSM5 criteria. The diagnostic assessment included the Positive and Negative Syndrome Scale to assess the severity of positive and negative symptoms of schizophrenia as well as the patient's general psychopathology, the Clinician-Rated Dimensions of Psychosis Symptom Severity to assess the symptom severity of the psychotic dimensions according, and the Cannabis Abuse Screening Test to assess the extent of cannabis use.

Results: The mean age of the patients recruited in the study was 33.7 ± 9.37 years with a clear male predominance ($p < 0.0001$). Cannabis users compared to non-users were younger and comprised only men. Cannabis users also have a lower educational and economic level than non-users. Furthermore, a clear dose effect of cannabis uses on the onset of positive and negative symptoms of schizophrenia. The temporality criterion is clear in our study, since the predictivity of the parameter: "age of onset of cannabis use" is highly significant ($p = 0.000$). These results suggest that cannabis use can be considered as the most illicit risk factor for the development and/or onset of schizophrenia.

Conclusions: These results suggest that there is a causal relationship between cannabis use and/or dependence (problematic use) and the onset and/or worsening of schizophrenic disorder. This means that problematic cannabis use can be considered as a real risk factor for the emergence and development of schizophrenic disorder.

Keywords: Addiction, Cannabis users, Schizophrenia, Disorder and predictivity

Background

Whether it is occasional use or dependence, the association between problematic cannabis use and schizophrenia is the rule rather than the exception. Indeed, epidemiological studies have confirmed for the last twenty years that addictive comorbidities in schizophrenia concern most patients [1, 2]. One of the first large-scale studies, the Epidemiologic Catchment Anea (ECA) survey published in 1990, estimated that this comorbidity affected 47% of people with schizophrenia, compared to 13.5% in the general population, and more than half of people with schizophrenia have a history of substance abuse [3]. In a cohort of 45,570 Swedes, Anderson 1987 et al. showed that increased cannabis use was associated with a sixfold increased risk (OR = 6.09; 95% CI 4.0–8.9) of developing schizophrenia [4]. This association between the development of schizophrenia and cannabis use is dose-dependent [5]. In 2002, in a 6-year prospective study of 14–15-year-old students, Patton

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et al. showed that daily cannabis use increased the risk of developing anxiety-depressive mood disorders (negative schizophrenia disorders) by five times (OR = 5.6; 95% CI: 2.6–12). This risk is only twice as high for weekly users [6]. This would suggest that these are predisposed individuals with a certain vulnerability to mood disorders, where cannabis use is the triggering factor [7].

Several factors have been identified to explain the mechanisms of this high comorbidity. The hypothesis of a common genetic vulnerability to both disorders has been proposed. This is supported by the observation of a shared heredity; on the one hand, a high rate of addiction problems in non-psychotic relatives of schizophrenic patients and on the other hand a high rate of schizophrenia in relatives of addicted patients [8]. Many social and economic factors are also shared by addicted and psychotic patients (precariousness, isolation, acculturation, etc.) [9]. Psychological vulnerability is the subject of numerous studies on the links between schizophrenia and cannabis. Early cannabis use considerably increases the risk of schizophrenia. The risk is four times higher when use begins before the age of 1 5[10], suggesting the need to consider the developmental dimension in interaction with the genetic and environmental mechanisms involved in vulnerability to schizophrenia. Cannabis use at age 16 increases the risk of emergence of psychosis at age 19 and, conversely, the emergence of psychosis at age 16 predicts cannabis use at age 19 [11]. Certain cognitive and affective disturbances could be predictive of later psychotic and addictive pathologies [12]. Unfortunately, follow-up studies show the stability of addictive behaviours acquired during adolescence in patients suffering from schizophrenia, which may explain the switch to other products, particularly alcohol, which is easier to access than cannabis.

In Morocco, the national survey on the prevalence of mental disorders in the general population aged 15 years and over (ENPTM, 2003–2006) revealed that 5.6% suffer from psychotic disorders and that more than 200,000 Moroccans aged 15 years and over suffer from schizophrenia [13], which is 0.5% in a recent study conducted by our laboratory in a town in Taza (eastern Morocco) with 1.5% drug addiction in a sample of 3803 patients [14]. On the other hand, the Mediterranean survey on the use of alcohol and other drugs in schools [15], conducted on 7000 Moroccan students, found that 9.0% of 15–17-year-olds use cannabis. In the general population, cannabis is the most used drug (3.94%) after tobacco. In Morocco, a study dealing with this comorbidity in a sample of 106 schizophrenic patients showed that 9.4% of patients were dependent on cannabis [14]. In addition, the psychiatric sector is a public health problem, and the Moroccan Ministry of Health in its "Health Plan 2025"

[15] has stated that it wants to change the situation by announcing that the mental health sector will be a priority of the Moroccan government to better respond to the expectations of patients and their families. In Morocco, few studies have focused on the co-morbidities between the use of active substances such as cannabis and schizophrenia; indeed, a study done in the hospital of the city of Fez showed that the prevalence of substance use is 60.2% including cannabis and that early identification of risk factors for substance use in patients with schizophrenia could improve the prognosis of patients by reducing the number of relapses and promote adherence to care [16]. Given the lack of official data on addictive comorbidities in schizophrenic patients and the scarcity of studies on this subject, our study aims firstly to draw up a socioeconomic profile of schizophrenic patients in the study area and secondly to assess the role of cannabis as a "risk factor" in the development of schizophrenic disorder or the emergence of psychotic symptoms related to schizophrenia.

Methods

Type of study

This is a prospective study of two groups of schizophrenic patients hospitalised at the Moulay ben Abdallah Hospital in Essaouira (HMBAE): a group that had never used cannabis and another that had used it.

Recruitment of the sample

The sample of participants was exhaustive including all patients with schizophrenia according to the diagnostic criteria of the fifth version of the Diagnostic and Statistical Manual of Mental Disorders DSM-5, consecutively admitted to the psychiatry department of the HMBAE over a period of 12 months (between 1 January and 31 December 2017) for psychotic break. Data collection is done in the morning to ensure the presence of the head doctor and nurses, and patients are calmer in the morning and can interact well with the proposed scale questionnaires.

The data were collected using an anonymous self-administered questionnaire distributed to the department and the CMS by the investigators (2 nurses from the psychiatry department of the Moulay Mohamed ben abdallâh Hospital in Essaouira, given their experience with schizophrenic patients). For each patient, we filled in an exploitation form and the questionnaires evaluating the severity of the psychiatric disorders were filled in and questioned by our team.

The study exclusion criteria for both groups were the presence of a confusional state, dementia, or age less than 18 years or more than 80 years; the final sample size was 95 patients.

Study variables

The diagnostic assessment included the Positive and Negative Syndrome Scale (PANSS) to assess the severity of positive and negative symptoms of schizophrenia as well as the patient's general psychopathology, the Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS) to assess the symptom severity of the psychotic dimensions according to DSM V criteria, and the Cannabis Abuse Screening Test (CAST) to assess the extent of cannabis use.

On the other hand, patients admitted to the psychiatric department of the HMBAE during the same period for substance use disorders and with a history of cannabis use were interviewed for an underlying schizophrenic disorder.

The comparison between the results of cannabis users and non-users was carried out on the following elements:

- Socio-demographic parameters: age, gender, place of residence, economic level, education level
- Quality of social adjustment: occupation, marital status
- Family and personal history: behavioural disorders, suicidal threat, addictive behaviour, psychotic relapse, somatic complaints, delusions, anxiety, and sudden mutism
- Clinical: symptoms of schizophrenia according to DSM-5, age at diagnosis of the disease; duration and number of hospital admissions
- Use of other psychoactive substances (PAS), including psychotropic drugs
- Cannabis use: amount consumed in number of joints (unit) per use, frequency of use (once/day; once/week; once/2 weeks; once/month; < once/month), date of start and stop of use

Data collection

Data collection was carried out under the guidance of a medical specialist and two experienced nurses using two methods, a chart review coupled with an interview with the same patient and a closed questionnaire targeting the risk factors sought. Data collection was carried out with respect to anonymity and confidentiality. All included patients were informed about the principles and objectives of the study and gave their consent to participate. The data was collected by our team and the nurses either through direct contact with the patients or from information in their medical records

Statistical analysis

Descriptive statistics regarding the demographic and clinical characteristics of the participants and the cannabis use patterns of the users were calculated and reported in terms of means and proportions. The analytical study used Student's *t* test for the comparison of continuous variables between the user and non-user groups, and the chi-squared test for categorical variables. A correction by the Fisher exact method was made for categorical variables with small numbers. The multivariate analysis was based on logistic regression of cannabis use parameters potentially predictive of schizophrenic disorder. ORs with 95% confidence intervals (CIs) and *p*-values were reported for each predictor. A *p*-value < 0.05 was considered significant. The analysis was performed on the SPSS 20 software.

Results

Over a 12-month period, we recruited 95 schizophrenic patients, 69 of whom had a history of cannabis use. Of these 69 patients, 21 were admitted for substance use disorders and were included in the study after a diagnosis of schizophrenia. Twenty-three patients approached by the evaluators could not be included in the study due to lack of criteria for schizophrenic disorder or refusal to participate.

Socio-demographic characteristics

The average age of the 95 schizophrenic patients included in the study was 33.7 ± 9.37 years with a clear male predominance (Table 1). Cannabis users compared to non-users were younger and comprised only men. Cannabis users also have a lower level of education and a lower economic level than non-users. On the other hand, we did not find any significant difference between the two groups concerning the place of residence and marital status.

Characteristics of cannabis users

Seventy-two out of one hundred patients admitted to the study had used cannabis at least once in their lifetime (Table 2). Of these, 55.1% were still using. The average age of onset of use was 14.4 years. The average frequency of use was 13.9 times/month, and the average number of joints smoked per use was 3.3 joints. Patients had a mean CAST score of 12.4 (SD = 7.9). Among the cannabis users, 43.4%, 23.1%, and 5.7% were at high, medium, and low risk for cannabis addiction, respectively. About 74% of cannabis users used at least one other substance of abuse. Among these substances, tobacco (86%), kif (75%), maâjoun (street drug) (53%), and alcohol (47%) are the most common among cannabis users.

A multivariate analysis of demographic variables predictive of cannabis use was conducted. Male gender, low education level, and young age were more associated with cannabis use than female gender, high education

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Table 1 Comparison of sociodemographic characteristics between cannabis users and non-users

	Non-users of cannabis	Cannabis users	P
Gender,*n*(%)			< 0.0001
Male	21 (80.7)	69 (100)	
Woman	5 (19.2)	0 (0)	
Economic level,*n*(%)			0.0052
Top	2 (7.6)	4 (5.7)	
Medium	16 (61.5)	28 (40.5)	
Bottom	8 (30.7)	37 (53.6)	
Residence,*n*(%)			0.3201
Urban	14 (53.8)	42 (60.8)	
Rural	12 (46.1)	27 (39.1)	
Marital status,*n*(%)			0.6203
Single	16 (61.5)	37 (53.6)	
Married	8 (30.7)	20 (28.9)	
Divorced	2 (7.6)	12 (17.3)	
Level of education,*n*(%)			0.0121
Illiterate	2 (7.6)	28 (40.5)	
Primary	3 (11.5)	18 (26.1)	
College	6 (23.1)	15 (21.7)	
Secondary	10 (38.4)	8 (11.5)	
Academic	5 (19.2)	0 (0)	
Age, average (SD)	41 (10.6)	32.6 (8.2)	0.0012
Total,*n*(%)	26 (27.3)	69 (72.6)	0.0023

SD Standard deviation, *p p*-value

Table 2 Characteristics of cannabis users

	Average (DS)
Age of onset (years)	14.4 (5.3)
Age of cessation (years,*n* = 31)	32.1 (3.4)
Consumption period (years)	13.5 (5.8)
Frequency of consumption (/month)	15.1 (13.9)
Number of joints per episode	3.3 (4.5)
CAST score	12.4 (7.9)
	n (%)
Current cannabis user	38 (55.1)
Cannabis addiction (CAST score > 7)	45 (65.2)
Consumption of other PPS	51 (73.9)
Tobacco	60 (86.9)
Kif	52 (75.3)
Maâjoun (street product)	37 (53.6)
Organic solvents	18 (26.0)
Alcohol	33 (47.8)
Psychotropic drugs	17 (24.6)
Cocaine	7 (10.1)
Other	6 (8.6)
Total,*n*(%)	69 (100.0)

Psychotropic drugs: sedatives, hallucinogens, stimulants, benzhexol (Trihexyphenidyl), gamma hydroxybutyrate (GHB)

SD Standard deviation, *SPA* Psychoactive substance

level, and older age. There was also a linear relationship between education level and cannabis use.

Characteristics of schizophrenic disorder
The mean age at diagnosis of schizophrenic disorder among the total population was 25.8 years, and the mean number of previous hospitalisations was 4.4 hospitalisations or 0.5 hospitalisations per year since diagnosis of the disorder (Table 3). Cannabis users compared to non-users started their disorder at a younger age (21.2 vs 30.5 years; $p = 0.0026$). They had more previous hospitalisations (4.3 vs 3.7; NS). In total, 67% of the schizophrenic patients included in the study were hospitalised for a manic episode, 2% for a hypomanic episode, 23% for a major depressive episode, and 8% for substance abuse intoxication. Of the admissions for major depressive episode, 73.9% of the patients were female.

Predictors of schizophrenia
Multiple regression analysis was performed to identify predictors of schizophrenic disorders among the collected data (Table 4: only significant **$p < 0.05$ or highly significant ***$p < 0.001$).

The multiple linear regression study revealed a strong interdependent relationship between the different variables and the onset of schizophrenia symptoms as evidenced by the PANSS score; age of onset and frequency of cannabis use were highly associated with the emergence of schizophrenic disorder (***$p = 0.000$ and **$p = 0.001$ respectively). The same was true for the rest of the parameters studied.

Dose-effect relationship
Our study shows the existence of a dose-effect relationship between the frequency of cannabis use and the onset of schizophrenic disorder in our patients. Indeed, this risk is 2.5 times higher if the CAST score is higher than 7 as shown in Fig. 1.

The dose effect also seems to be very clear in our study; Fig. 2 shows that the PANSS score increases considerably if the dose of cannabis use is high; indeed, it increases from 51 to 185 when the frequency of use increases from once a month to several times a day (Fig. 2).

Discussion
The rush of governments to exploit the positive effects of cannabis should not hide the reality that cannabis appears to be a risk factor for many diseases other than psychiatric ones. This study shows some relationship

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Table 3 Clinical characteristics of schizophrenia and psychiatric history in cannabis users and non-users

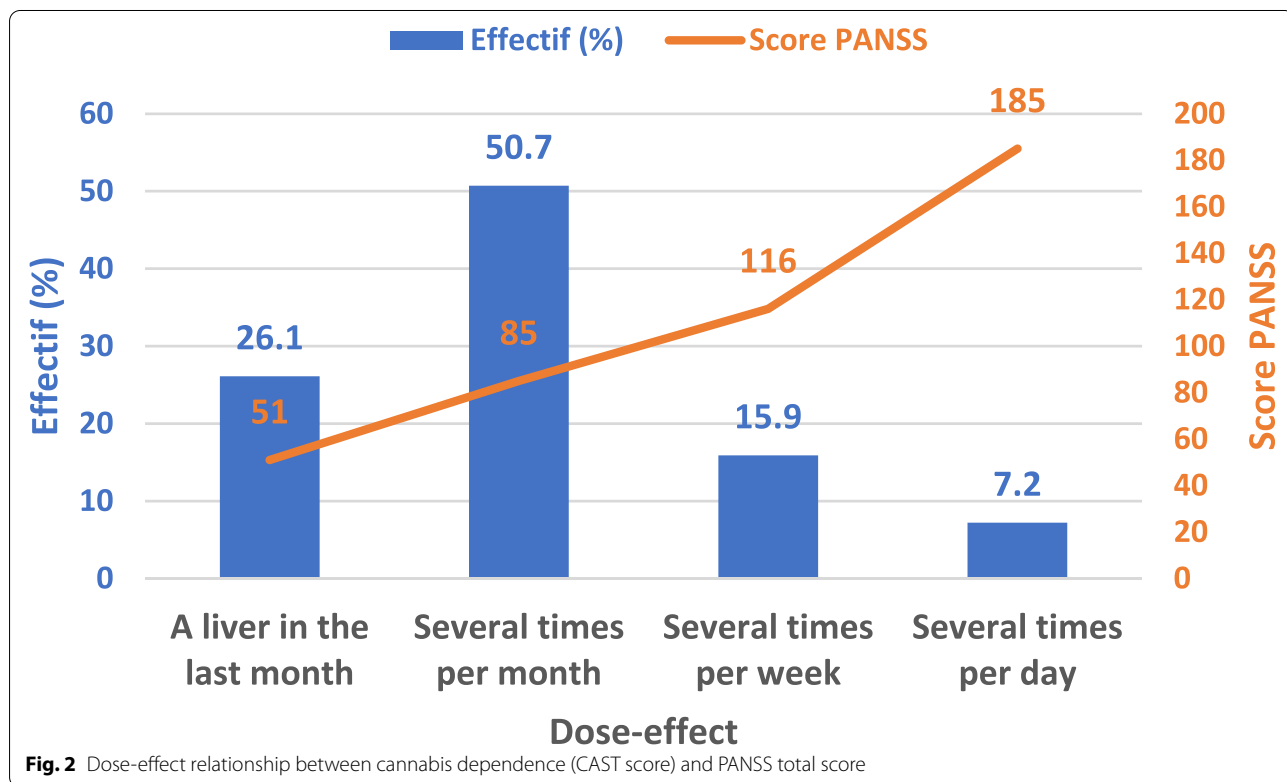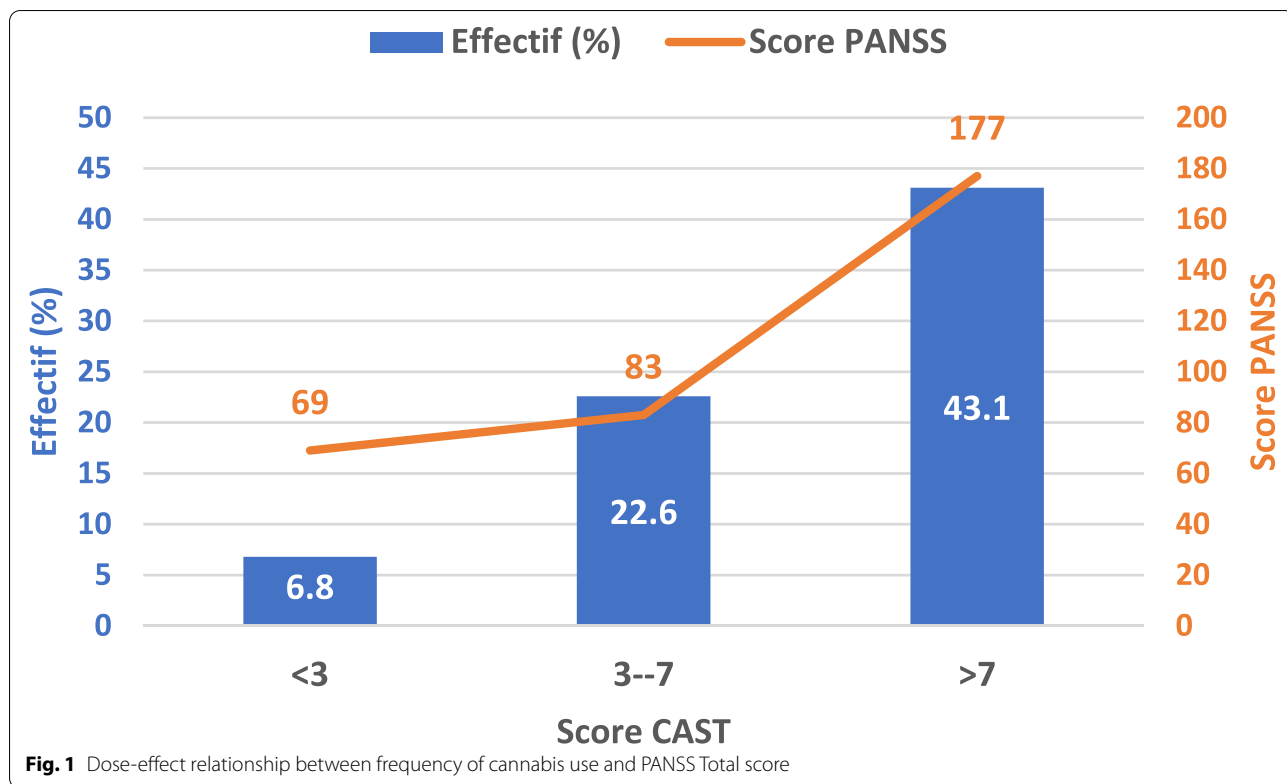|	Non-users of cannabis	Cannabis users	*P*
Age at diagnosis, mean (SD)	30.5 (6.8)	21.2 (9,3)	0.0026
History of hospitalisation, n (%)	16 (61.5)	46 (66.6)	0.5033
Annual hospitalisations			
Average number (DS)	3.7 (2.5)	4.3 (3.3)	0.6701
Average duration (days ± SD)	31.6 (7.8)	29.2 (6.0)	0.5428
Reasons for hospitalisation, n (%)			0.1037
Behavioural problems	17 (65.3)	31 (44.9)	
Suicidal threat	0 (0)	7 (10.1)	
Addictive behaviour	3 (11.5)	16 (23.1)	
Psychotic relapse	20 (76.9)	58 (84.0)	
Other	10 (38.4)	25 (36.2)	
Family history, n (%)			
PANSS score, average (DS)			
Positive scale	18 (4.3)	39 (6.6)	
Negative scale	29 (7.8)	41 (8.0)	
General psychopathology scale	67 (12.6)	102 (13.1)	
Total score (/210)	104 (8.2)	181 (15.4)	0.0001
CRDPSS score, average (SD)			
Hallucinations	1 (0.0)	3 (1.6)	
Delusional ideas	0 (0.0)	2 (0.7)	
Disorganised speech	1 (1.2)	4 (0.0)	
Abnormal psychomotor behaviour	2 (0.3)	3 (1.2)	
Negative symptoms	2 (1.3)	3 (1.3)	
Cognitive deficit	1 (0.8)	2 (0.8)	
Depression	2 (1.6)	4 (0.6)	
Mania	1 (1.2)	3 (1.2)	
Total score (/32)	10 (3.4)	25 (4.7)	**0.0021**

Under the term "Other," we have grouped the reasons: somatic complaints, delusions, anxiety, and sudden mutism

SD Standard deviation

Table 4 Summary of the regression of the variable "total score in PANSS" ($R^2 = 0.82$; $F = 7.03$; $p = 0.000$)

Independent variables	BETA	BETA standard error	*t*	*P*
Smoked cannabis alone	0.53	0.06	5.09	0.000
Tobacco consumption	0.80	0.23	6.13	0.000
Frequency of tobacco use	0.42	0.12	3.43	0.001
Age of onset of cannabis use	− 0.91	0.15	− 4.74	0.000
Often smoked cannabis alone	0.91	0.39	7.20	0.000
Perception of risk related to tobacco and cannabis use	0.15	0.21	2.13	0.039
Representations of the unpleasant psychological effects and physical risks of cannabis	− 0.32	0.65	− 3.85	0.000
Representations of positive school effects of cannabis	0.37	0.19	2.53	0.016
Representations of dependency	0.47	0.72	5.31	0.000
Cannabis dependence	− 0.45	0.09	− 3.59	0.001

R^2 Multiple correlation coefficient, *F* F-statistic

Fig. 1 Dose-effect relationship between frequency of cannabis use and PANSS Total score

Fig. 2 Dose-effect relationship between cannabis dependence (CAST score) and PANSS total score

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between cannabis use and the emergence and development of schizophrenic disorders.

Our sample comprises a young population with an average age of 33.7 ± 9.37 years. Therefore, negative public opinion can have serious consequences on them and their families; it prevents social integration, interferes with the performance of social roles, and reduces expectations and quality of life. These factors can be major barriers to recovery, impact on long-term prognosis, and lead to disability [17]. It is also noted that the percentage of single people is higher, which is probably due to the socio-cultural context, where the man often has the financial responsibility for his family. Consequently, the repercussions of stigmatisation such as lack of work and lack of housing limit the resources of these subjects and hinder their autonomy [18]. Finding a job in these conditions is often difficult, and they are considered less intelligent, with limited abilities, or simply unable to carry out the tasks assigned to them. These results are confirmed by the literature [19]; in Spain, 95% of the general population and 69% of the families of patients think they cannot study, 33% think they have limited abilities, and 81.1% of employers in Germany would not hire a former psychiatric patient. Thus, the working life of patients is affected, not only by the nature of the disorder, but above all by the prejudices and the fragility of the social support it encounters, which are all barriers to the integration and development of patients [20]. The rate of urbanicity found in both groups is quite high, which is consistent with the result of the national survey [21]. The work of Penn et al. [22] on 20 populations showed the dominance of psychiatric disorders in urban settings. In addition, a study conducted in rural and urban Canada concluded that urban origin was a risk factor for psychiatric disorders. This study implicated the lack of social support in urban settings as opposed to rural settings [23].

The interrelationships revealed by our study suggest that the risk of emergence of schizophrenic symptomology increases with several parameters related to cannabis use, (age and history of use, duration, ...). Indeed, this risk is 2.5 times higher if the CAST score is higher than 7 as shown in Fig. 1; the same result was found by another study [24].

The dose effect also seems very clear in our study; Fig. 2 shows that the PANSS score increases considerably if the dose of cannabis use is high; indeed, it increases from 51 to 185 when the frequency of use increases from once a month to several times a day (Fig. 2). This result is supported by the result of a pioneering study in 2004 by DC D'Souza et al. [25], showing a clear dose effect of cannabis use on the onset of positive and negative symptoms of schizophrenia [26], in a population of non-schizophrenic volunteers. The temporality criterion is clear in our study,

as the predictivity of the parameter: "age of onset of cannabis use" is highly significant ($p = 0.000$), which means that there is probably a causal relationship between cannabis use and the onset of schizophrenia, that is, exposure to cannabis use precedes the emergence of the schizophrenic disorder. According to a study in France [27] cannabis use is a risk factor, with two consistent data: a high level of use and an age of use below 15 years. Still in France in 2014, another study of patients suffering from schizophrenia in hospital found a prevalence of cannabis use of 33.6%, 88% of whom were dependent patients [26]. In other studies, the effect of reciprocal reinforcement of the pathology and the use of cannabis is still accepted [27]. This reproducibility of results indicates a possible causal relationship between cannabis use and the onset of schizophrenia.

Conclusions

The link between substance abuse and the emergence of psychotic disorders has become illicit, particularly for schizophrenia, which now represents a heavy burden internationally as well as nationally.

Our study aims to add to the scientific repertoire and to further explore the existence of causal links (or risk factors) between cannabis use and the emergence and development of schizophrenia. Our results show that:

- The strength of the relationships revealed by the study of the prediction of the parameters studied is quite significant
- Temporality, which suggests the importance of age at onset of cannabis use
- The frequency of use which indicates a clear dose-effect relationship
- The reproducibility of the results proved by a multitude of studies having given similar results

These results suggest that there is a causal relationship between cannabis use and/or dependence (problematic use) and the onset and/or worsening of schizophrenic disorder. This means that problematic cannabis use can be considered as a real risk factor for the emergence and development of schizophrenic disorder. On the other hand, our results recommend more vigilance towards the exploitation of the positive effects of cannabis and to give the necessary importance to the careful practice of this substance in pharmaceutical fields.

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Declarations

Ethics approval and consent to participate
The procedures followed were in accordance with the ethical standards of the competent commission for human experimentation and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants and authorisation from the ethics committee of the CED (CENTRE D'ETUDES DOCTORALES-FSK) of the Faculty of Science in Kenitra and the provincial delegation of the Ministry of Public Health 09/2015 to continue the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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