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Cannabis and Premonitory Symptoms of Schizophrenia: What Is the Time Sequence?

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Summary

Nowadays, cannabis is the most widely used illegal drug in France. Epidemiological studies have shown that in schizophrenic patients the risk of developing cannabis dependence is six times what it is in the general population. However, debates on the real chronology of the appearance of psychiatric disorders and addictive cannabis behaviour are ongoing. The aim of this article is to try to find out how best to interpret the association of cannabis and premonitory symptoms through a review of the literature. Some recent longitudinal studies suggest a potential role for pre-existing troubles, taking the view that cannabis would only aggravate them and turn them into schizophrenic symptoms. By contrast, other studies propose a causal linkage as well as a dose-effect relationship between cannabis consumption and the appearance of schizophrenia. Conclusion: The methodology of these studies limits the possibility of a reverse causality. In addition, it must be noted that some research teams excluded from their cohort subjects who presented psychiatric disorders at entrance. Cannabis appears to be a risk factor for psychotic disorders, because it interacts with a pre-existing vulnerability. Neuroimaging research will make it possible to clarify the common cerebral mechanisms of cannabis and schizophrenia.

Key Words: Schizophrenia, premonitory symptoms, cannabis, vulnerability

Nowadays, cannabis is the most widely used illegal drug in France. Over the last decade, the number of consumers has continued to increase. The study carried out by Bersani et al. [4] revealed that in schizophrenic patients the frequency of cannabis consumption is 4.6 times the figure for the general population. 15 to 40% of schizophrenic patients have experienced at least once in their life an episode of cannabis dependence or abuse according to CIM-10 criteria.

Epidemiological studies show that cannabis abuse prevalence is markedly higher in psychotic persons than in those who are free of symptoms of that type [5], and that in schizophrenic patients the risk of developing cannabis dependence is six times what it is in the general population [10].

The high frequency of this comorbidity brings us back to multiple etiopathogenic hypotheses connected with the sequence of this association: we need to inquire: 'Is cannabis a cause or a consequence of a psychotic disorder?'

It is difficult to distinguish the outset of a schizophrenic disorder in the early stages of a cannabis-related intoxication, all the more so since these diseases tend to develop insidiously. Schizophrenic disorders are frequently preceded by unspecific premonitory symptoms such as withdrawal from society, loss of interest in usual activities, temper, body neglect or peculiarities in behaviour that may, by themselves, tend to encourage cannabis consumption. The chronology of the disorders does not seem to be clearly defined: It seems that cannabis abuse often comes prior to the psychiatric disorder, but that its onset comes after the premonitory symptoms in as many as two-thirds of these cases [6, 12].

Diachronic evolution of these disorders: Some patients who present signs of 'vulnerability' ('non-pathological' characteristics) will reveal premonitory symptoms that precede the transition phase to the first psychotic episode (profile a). None of these transitions is ineluctable. In particular, most of the 'vulnerable' subjects will never evolve into a pathological state. Likewise, some subjects

who show premonitory signs will never evolve into a constituted psychotic state (profile b). Consequently, it is preferable to use the notion of a mental state with a higher risk of psychotic transition than that conveyed by the term 'premonitory symptoms' (figure 1).

The 2003 Consensus conference on early schizophrenia notably recommended "rapidly making a diagnosis so as to promote the rapid setting up of a treatment, guaranteeing a better prognosis". According to our review of the literature, some studies have taken these premonitory

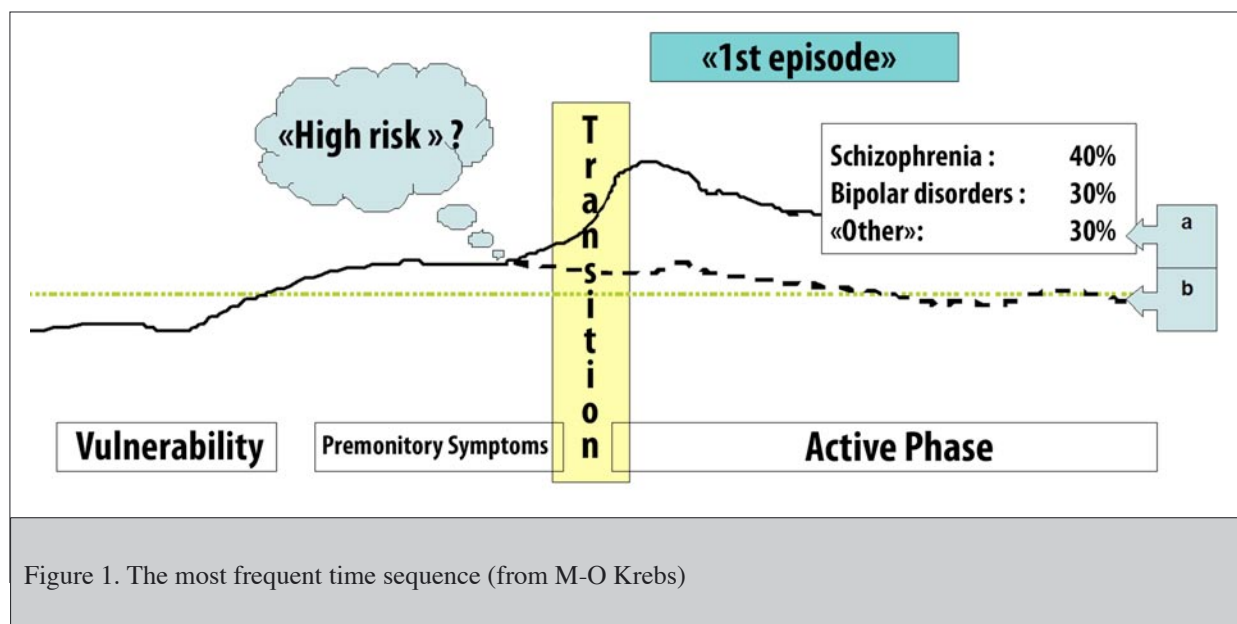


Figure 1. The most frequent time sequence (from M-O Krebs)

Table 1 : Longitudinal studies suggesting the potential role of preexisting premonitory symptoms.

Study	Population	Age/Gender	Follow up	Evaluation of the psychiatric becoming	Results
Fergusson et al. (2005)	1055	18, 21,25 Male and female	25 years	Prospective study	Early and repeated Cannabis use; as well as premonitory symptoms increase the development of psychiatric symptoms.
Henquet et al. (2005)	2437	14 et 24 years Male and female	4 years	Prospective study	The existence of premonitory symptoms and teenage consumption increase the risk of contracting a psychosis.
Degenhardt et al. (2003)	Patients born between 1940 and 1979	15 et 60 years. Male and female	30 years	Pooling the analysis of 8 cohorts	Cannabis precipitates the appearance of premonitory symptoms and aggravates the prognosis of vulnerable patients. No causal relation.
Verdoux et al. (1996)	79 Students	?	?	Questionnaires	Cannabis precipitates or emphasizes psychotic experiences in vulnerable patients.

Table 2: Longitudinal studies that have verified and rejected the impact of pre-existing premonitory symptoms.

Van Os et al. (2002)	4045	18- 64 years Male and female	3 years	Structured diagnostic interview at entrance, 1 year and 3 years of follow-up.	Causal relation Dose/Effect relation Cannabis influence is higher in persons presenting heavy psychiatric disorders during the study but the results are not significantly different from people devoid of psychiatric symptoms.
Andréasson et al. (1987)	45570	18-20 years	15 years	Auto-Questionnaire	Causal relation Dose/Effect relation The relation Cannabis/Schizophrenia is independent of the premonitory symptoms.
Arsenault et al. (2002)	Cohorte de 759 born	15- 18 years	26 years	Structured diagnostic interview. Premonitory symptoms existence evaluated at 11 years.	Teenage Cannabis use boosts the emergence of psychiatric symptoms at adulthood. Causal relation Dose/Effect relation The relation Cannabis/Schizophrenia is independent of the premonitory symptoms.
Zammit et al. (2002)	50000	12- 20 years	27 years	Auto-questionnaire	Causal relation Dose/Effect relation. Subjects that become schizophrenic presented a personality disorder at entrance but the study revealed that the relation Cannabis/Schizophrenia was independent of the premonitory symptoms.

symptoms into account and drawn a conclusion as to whether or not they have any influence on the consumption of cannabis (Table 1).

Debates on the real chronology of the appearance of psychiatric disorders and behaviour showing cannabis addiction are still ongoing; to date, the time sequence cannot be precisely determined. Moreover, contradictory data have emerged, depending on the studies and their methods of investigation [3].

The interpretation to be given to the association between cannabis and premonitory symptoms appears to be a very difficult question; the aim of this article is to find out if subjects with psychiatric disorders use THC (tetrahydrocannabinol) as an automedication, which might convert the premonitory symptoms into psychosis or if, conversely, the use of THC is a risk factor in developing a psychosis.

Retrospective studies showed that THC consumption precedes the beginning of psychotic disorders [8]. Nonetheless, the limit is that the retrospective dating of premorbid disorders is often a very complicated matter [1, 12, 13].

1. Cannabis induces psychotic disorders

The cohort studies (table 2) drew the conclusion that there is a causal relationship between THC consumption and psychosis development, as well as a dose-effect relationship. The cohort led by Van Os in 2002 [11] found the same results: There is a causal relationship that is independent of the premorbid disorders; evaluated by the diagnostic interview at entrance, and during the follow-up. Its principal limit was the low number of entrances and the short length of the follow up.

The Arsenault cohort [2] turned out to show similar outcomes. Teenage cannabis consumers (15-18 years old) had more psychotic symptoms in adulthood than non-consumers. The main strength of this study is that it took into account the existence of morbid disorders at the age of 11 and concluded that adulthood psychosis was closely related to cannabis consumption, but was independent of pre-existing premonitory symptoms. Its limit was the lack of memorization (retrospective evaluation through auto-questionnaires).

2. Premorbid disorders induce and precede cannabis consumption

A prospective study carried out by Miller et al. in 2001 on a population of 'high risk' selected patients pointed out that there is a positive temporal relationship between THC consumption and the existence of psychotic disorders. They showed that, in subjects presenting early forms of schizophrenia, toxic consumption was twice what it was in the control population. Cannabis appears to be temporally linked to psychotic disorders.

Longitudinal studies (Table 1) highlighted the fact that the existence of premorbid disorders is a risk factor in increased cannabis consumption, which might make the premonitory symptoms evolve into schizophrenic psychosis.

Fergusson (New Zealander cohort) [7] showed that prolonged and premature cannabis use contributes to the development of psychoses, particularly when premonitory symptoms pre-exist. In 18-year-old cannabis using patients, the relative risk was assessed as being 3.7 times what it is in non-consumers. That same risk ratio falls to 2.3 for 21-year old patients.

Henquet [9] came to the same conclusions when leading a prospective study on 2,437 patients followed up over a period of 4 years: Precocious cannabis consumption and the presence of premorbid disorders precipitate the schizophrenia symptoms in patients with premonitory symptoms.

A 2003 Australian analysis pooled the results of eight cohorts [5] selected from a population of male and female patients aged between 15 and 60; the follow-up lasted as long as 40 years. The authors concluded that cannabis turns the psychotic symptoms into schizophrenia and have proposed a time sequence in which the consumption of cannabis comes after premonitory symptoms and before schizophrenia.

3. Concluding remarks

Cannabis appears to be a risk factor for psychotic disorders, as it interacts with a pre-existing vulnerability.

Considering this undeniable link, regardless of its actual direction, the screening of the teenager population turns out to be essential and to be of major interest, when it comes to public health and prevention.

High performance prospective studies based on an effective methodology, taking into account staggering factors, environment and family history need to be carried out. We will definitely find far more new information when neuroimaging makes it possible to clarify the common cerebral mechanisms of cannabis and schizophrenia, especially those involving the endocannabinoid system.

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Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present review.

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