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Cannabis and schizophrenia: impact on onset, course, psychopathology and outcomes

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Abstract *Cannabis* consuming schizophrenic patients are younger at onset, are likely to have started abuse before onset of schizophrenia and show more prominent positive symptoms than nonabusers. It has been suggested that *cannabis* is a risk-factor for schizophrenia. Our aim was to assess prevalence and pattern of *cannabis* use in 125 chronic male schizophrenic subjects and its impact on socioepidemiological and clinical variables as well as which disorder precedes the other in onset. Assessment of consumption was made with a semi-structured clinical interview. Clinical status was assessed by means of the SANS, SAPS, PANSS and BPRS scales. *Cannabis* consumption was found in 54 subjects (43 %), 66.7 % of whom started it at least three years before onset of schizophrenia. Consumers were younger and with lower negative symptoms, specially abusers and polysubstance abusers. Family history positive for psychosis was more frequent in consumers, especially when consumption started before onset of schizophrenia. Subjects whose onset of schizophrenia preceded the beginning of *cannabis* abuse had more positive symptoms than those who started abuse before the onset of schizophrenia. On these grounds, our sample could be subdivided into two main groups, one that uses substances to counter distressing symptoms of schizophrenia and another in which *cannabis* might be one of the factors predisposing to the disease; the former had less negative symptoms than nonabusers. Our data support both heterogeneity of schizophrenia and genetic susceptibility to environmental agents.

Key words *cannabis* · schizophrenia · self-medication · vulnerability · psychopathology

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Introduction

Cannabis sativa is the most abused illicit drug, especially among teen-agers and young adults. *Cannabis* abuse and dependence in the USA is about 4 % in the general population, with a peak in the age range 18–29 years (14 %) (Robins and Regier 1991; Kessler et al. 1994). Similar values were found in Europe (EMCDDA 1995) and, specifically, Italy. Despite the absence of a nationwide registration system (EMCDDA and IFT 1999), regional data available show similar figures for various Italian regions of North and Central Italy (10 % of non-opiate addicts among young adults [Italian Health Ministry 1999]). This pattern of abuse remained substantially stable across the years since 1975, with a trend towards reduction since the late 1980s (Arnao 1993).

Prevalence appears to be even higher in psychiatric populations, particularly in psychotic patients (Mueser et al. 1992). Substance abuse was found to be 4.6 times higher in a population of schizophrenic subjects than in the rest of the population (Regier et al. 1990). *Cannabis* (41 %) was the most abused illicit drug (Mueser et al. 1990). In the literature, comorbid schizophrenia and substance abuse ranges from 15 % to 65 % (Kovasznay et al. 1993).

While it is accepted that *cannabis* may cause acute psychosis (Hollister 1988), its role in onset, course and clinical expression of chronic psychoses, like schizophrenia, is less clear.

Younger age of schizophrenic onset and first hospitalization (Mueser et al. 1990), better pre-morbid adjustment (Arndt et al. 1992) and the fact that *cannabis* use tends to occur prior to onset of schizophrenia (Linszen et al. 1994) suggest an etiological role for this drug

(Kosten et al. 1997; McDonald and Murray, 2000). The most convincing evidence comes from Andréasson et al. (1987, 1989), who found the relative risk for developing schizophrenia to be 2.4- to 6.0-fold higher in subjects with *cannabis* use/abuse, as compared to nonconsumers and that *cannabis* was the third best predictor for schizophrenia (Andréasson et al. 1987).

The extent to which substance abuse might alter the clinical course of schizophrenia is still debated. Some investigators suggest that cannabis is related to poorer outcome, to higher hospitalization rates and to behavioral dyscontrol (Linszen et al. 1994; Owen et al. 1996; Barry et al. 1996), but others do not support this (Zisook et al. 1992; Cantor-Graae et al. 2001).

Cannabis also seems to affect the clinical course of schizophrenia. Despite negative results (Brunette et al. 1997), an association between *cannabis* and positive symptom worsening was found (Negrete et al. 1986; Caspari 1999). Negative symptoms were variously found to be worsened (Cleghorn et al. 1991), unaffected (Kovasznay et al. 1997), or even improved by *cannabis* (Peralta and Cuesta 1992; Buckley et al. 1994; Kirkpatrick et al. 1996). These differences may be due to sample heterogeneity and methodological differences, since the above studies involved patient populations from different countries and various designs (Table 1).

Four hypotheses were formulated to account for the direction of causality between substance abuse and schizophrenia (Allebeck et al. 1993; Silver and Abboud, 1994): 1) the causation hypothesis, according to which substance abuse may precipitate or cause schizophrenia, at least in vulnerable subjects (Mueser et al. 1990); 2) the common factor hypothesis, which suggests genetic vulnerability to determine an overlap of biological mechanisms between psychosis and substance abuse (Tsuang et al. 1982; Ziedonis and George 1997); 3) the self-medication hypothesis, which views substance abuse as the patient's effort to counter distressing symptoms or treatment side effects (Schneier and Siris 1987; Dixon et al. 1991); 4) the independent occurrence hypothesis, according to which these disorders are independent and just share similar onset age peaks and prevalence (Hambrecht and Häfner 1996).

Recently, Mueser et al. (1998) proposed a somewhat more elaborate model of comorbidity, the etiology of which appears to be heterogeneous, with antisocial personality disorder and supersensitivity to low levels of substance abuse as contributing factors. Younger age, male gender, and lower educational level also predicted substance abuse in schizophrenia (Mueser et al. 2000).

We expected to find a high rate of *cannabis* abuse/consumption in our population of patients, for both the putative etiological role of *cannabis* and the self-medication hypothesis. In the former case, we would expect drug abuse/consumption to precede disease onset and a higher rate of familial occurrence of psychotic disorders, whereas, in the latter case, an opposite trend would be more likely. Our goals were to 1) determine the prevalence of *cannabis* use and abuse in a relatively large sample of chronic schizophrenic inpatients; 2) compare *cannabis* consumers patients *vs.* nonconsumers on socioepidemiological and clinical variables, to monitor for possible differences at onset, course and outcome, also according to the amount of consumption (use and abuse); 3) examine the temporal relationship between the onset of *cannabis* consumption and of schizophrenia; 4) compare schizophrenic patients who started the consumption before with those

Table 1 Studies of schizophrenia and cannabis abuse from 1990[a] to 2001

Reference	Type and patients (N)	Cannabis	Method	Time relation	Follow-up	Country
Mueser et al. 1990	Acute relapses (101)	42 %	Retrospective	N. I.	No	USA
Dixon et al. 1991	Acute and chronic (68)	31 %	Retrospective	N. I.	No	USA
Cleghorn et al. 1991	Acute and chronic (63)	60 %	Retrospective	N. I.	No	Canada
Peralta & Cuesta 1992	Acute and chronic (95)	24 %	Retrospective	N. I.	No	Spain
Zisook et al. 1992	Chronic (65)	< 52 %	Retrospective	N. I.	No	USA
Allebeck et al. 1993[b]	Chronic (112)	100 %	Longitudinal	69 % CbS	12 years	Sweden
Kovasznay et al. 1993	Chronic (76)	< 37 %	Retrospective	95 % CbS	No	USA
Soyka et al. 1993	Chronic (183)	< 11 %	Retrospective	N. I.	No	Germany
	Chronic (447)	< 25.7 %				
Silver & Abboud 1994[b]	Acute and chronic (42)	98 %	Retrospective	78 % CbS	No	Israel
DeQuardo et al. 1994	Chronic (67)	28 %	Retrospective	N. I.	No	USA
Linszen et al. 1994	Acute (93)	26 %	Prospective	N. I.	1 year	Holland
Buckley et al. 1994	Chronic (118)	< 25 %	Retrospective	N. I.	No	USA
Kirkpatrick et al. 1996	Nondeficit chronic (80)	31.3 %	Retrospective	N. I.	No	USA-Mexico
	Deficit chronic (43)	17 %				
Hambrecht & Häfner 1996	1st episode (232)	13 %	Retrospective	27.5 % CbS	No	Germany
Owen et al. 1996	Chronic (135)	< 42 %	Prospective	N. I.	6 months	USA
Kovasznay et al. 1997	Acute (96)	69 %	Prospective	N. I.	6 months	USA
Caspari 1999[b]	Chronic (39)	100 %	Prospective	N. I.	68 months	Germany
Mueser et al. 2000	Acute and chronic (89)	26 %	Retrospective	N. I.	No	USA
Cantor-Graae et al. 2001	Chronic (87)	17 %	Retrospective	88 % CbS	No	Germany

[a] For studies before 1990, see Mueser et al., 1990; [b] Only abusers were included in the study group. *CbS* Cannabis onset before schizophrenia; *N. I.* not investigated. < should be understood as cannabis use not specified.

who started after psychotic onset on the above-mentioned variables; 5) compare pure *cannabis* consumers *vs*. polysubstance abusers and nonconsumers, in the attempt to control for any additional effect of the various drugs.

Materials and methods

The study was based on data collected from 125 male inpatients, consecutively admitted to the ward of the III Psychiatric Clinic of the University of Rome, "La Sapienza". All patients were affected by DSM-IV (American Psychiatric Association 1994) chronic schizophrenia and were on stabilized neuroleptic treatment. Diagnoses were based on clinical interview and were all made by the treating clinical psychiatrist, who was blind as to the aims of the study, and were confirmed by the senior investigator (G. B). All subjects were able to give informed consent to enter the study and did not present either a clear organic etiology for psychosis or a diagnosis of any mental retardation and neurological disease. Mean age was 32.44 ± 8.53 at recruitment; mean age at onset of schizophrenia was 22.13 ± 6.99 years and mean disease duration was 10.31 ± 7.44 years.

Illicit substance abuse was assessed by an interviewer who was different from the patient's psychiatrist-in-charge, using a semi-structured clinical interview focusing on use/abuse of *cannabis*, hallucinogens, stimulants (amphetamines and cocaine) and opiates, and the contemporary misuse of alcohol and minor tranquilizers. Particular attention was paid to properly define the onset of drug consumption, the connection with psychotic onset and the modality, frequency and duration of the use/abuse. DSM-IV criteria for substance abuse were also considered.

The sample was then subdivided into three groups on the basis of *cannabis* consumption: group 0, nonconsumers; group 1, occasional *cannabis* users, with use duration less than three years, irregular and sporadic modality and monthly or annual frequency of consumption; group 2, *cannabis* abusers, with a continuing abuse pattern, at least weekly and lasting at least three years. The latter group, moreover, fulfilled DSM-IV criteria for substance abuse.

Recorded were socioepidemiological (age at recruitment, age at onset of schizophrenia, years of education, number of school failures) and clinical (hospital admissions, months of neuroleptic treatment, prevalence of alcohol and minor tranquilizers abuse/dependence and family history for psychiatric diseases [nonpsychotic mood, anxiety and substance abuse disorders, and mental retardation] and for psychosis [schizophrenia, schizoaffective, psychotic mood and delusional disorders]) parameters. Family history was recorded using both a research interview with the patient and an interview with the relatives. To study the effect of *cannabis* use/abuse on symptoms of schizophrenia, the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) were used (Andreasen 1983; Andreasen 1984). Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al. 1987) and the 18-item version of the Brief Psychiatric Rating Scale (BPRS), a scale developed in 1962 (Overall and Gorham 1962) and was later incorporated in the PANSS, were administered to assess the overall severity of the clinical picture at baseline.

We first compared nonconsumers (group 0) with consumers (groups 1 and 2) on these variables. Since illness duration may be a confounding factor, we then corrected results for this variable.

Subsequently, to better evaluate the effects of use intensity, we compared each group [0, 1, 2] with all others. Thereafter, to test at least some of the postulates of the vulnerability and self-medication models, we compared patients who started substance abuse at least three years before the onset of schizophrenia (N = 36) with those who started it after (N = 18) on the same variables, and in a second time, with nonconsumers.

Finally, we separated the pure *cannabis* (N = 21) from the polysubstance consumers (N = 33) (*cannabis*, hallucinogens, stimulants and opiates) and we matched these new two groups on socioepidemiological and clinical variables and then each group against the nonconsumers, in the attempt to assess the real impact of *cannabis* on schizophrenic symptoms.

The SPSS-PC+ package was used for statistical analysis. The impact of *cannabis* consumption on socioepidemiological and clinical variables was evaluated using one-way ANOVA and Student's *t* test for quantitative variables and the chi-square test for qualitative variables. The significance cut-off point was set at $p < 0.05$. When necessary, correction for multiple statistical tests was performed with Bonferroni's post hoc multiple comparisons test. Correction for illness duration was conducted with Wilks' Lambda multivariate test. Moreover, to investigate the effects of intensity of *cannabis* abuse on schizophrenic symptoms, Pearson's *r* correlational analysis was performed.

Results

Illicit drug abuse was present in 43 % of schizophrenic patients (54 out of 125 patients); all these patients were *cannabis* consumers (users, N = 21, 17 %; abusers, N = 33, 26 %). After *cannabis*, the most abused illicit drugs were hallucinogens (N = 24; 19 %), followed by stimulants (N = 23; 18 %) and opiates (N = 10; 8 %). Alcohol and minor tranquilizer consumption was present in 26 % and 11 % of the substance consumer sample and in 27 % and 13 % of nonconsumer sample, respectively, without any differences in prevalence among groups ($\chi^2 = 0.11$, df = 1, p = 0.541; $\chi^2 = 0.71$, df = 1, p = 0.508).

Substance consumers were younger at the start of the study (p < 0.000) and scored lower on the SANS total (p = 0.001); *cannabis* consumers showed significant levels of positive family history both for general psychiatric and psychotic disorders (Table 2). On the other epidemiological variables, the groups did not differ.

Table 2 Family occurrence of general psychopathology and psychosis in our sample of 125 chronic schizophrenics, taking into account cannabis consumption and its temporal association with onset of disease

	Yes	No	χ^2	DF	Significance *p* (two-sided)
General					
NC (n = 71)	13	58			
C (n = 54)	26	28	12.7	1	0.000
NC (n = 71)	13	58			
CBS (n = 36)	17	19	9.9	1	0.002
NC (n = 71)	13	58			
CAS (n = 18)	09	09	7.7	1	0.005
CBS (n = 36)	17	19			
CAS (n = 18)	09	09	0.1	1	0.847
Psychotic					
NC (n = 71)	07	64			
C (n = 54)	13	41	4.6	1	0.000
NC (n = 71)	07	64			
CBS (n = 36)	10	26	5.7	1	0.000
NC (n = 71)	07	64			
CAS (n = 18)	03	15	0.7	1	0.414
CBS (n = 36)	10	26			
CAS (n = 18)	03	15	0.8	1	0.368

C Consumers, *CBS* Beginning of consumption before onset of schizophrenia, *CAS* Beginning of consumption after onset of schizophrenia, *DF* degrees of freedom, *NC* Non-consumers

To assess the real impact of *cannabis* on schizophrenic symptoms, we split the consumer group into a pure *cannabis* consumption subgroup (N = 21) and a polysubstance consumption subgroup (N = 33). In both groups *cannabis* played an important role; in fact in all cases but one it was the most abused drug either for length of time or intensity, modality and frequency of consumption. All the polysubstance consumers but 9 were *cannabis* abusers, and 8 of these 9 subjects were regular *cannabis* users and only occasional consumers of other substances. Moreover, when opiate use/abuse was present (N = 10), this referred to the past and ended at least two years before entering this study. None of these subjects was on substitutive treatment with methadone or other drugs.

Cannabis consumers scored lower on each single SANS item (Affective flattening, p = 0.013; Alogia, p = 0.002; Avolition-apathy, p = 0.005; Anhedonia-asociality, p = 0.001; Attention, p = 0.018), on PANSS Negative scale (p = 0.049) and on the SAPS thought disorder item (p = 0.023) (Table 3). These results remained significant for *cannabis*, even after correction for illness duration. *Cannabis* consumption correlated inversely with negative symptomatology (SANS and PANSS) (Table 4).

Cannabis users showed fewer positive symptoms when compared to nonusers (Thought disorder, p = 0.009; only a positive trend at SAPS total). They were younger (p = 0.034) and had lower levels of negative symptoms than nonconsumers, although only at a trend level (SANS, p = 0.054; Affective flattening, p = 0.053). Negative symptoms were, on the contrary, more prominent in nonconsumers, if compared to *cannabis* abusers (Alogia, p = 0.007; Avolition-apathy, p = 0.004; Anhedonia-asociality, p = 0.002; SANS, p = 0.007).

The comparison between schizophrenic consumers according to temporality showed differences on positive symptomatology (Hallucinations, p = 0.000; Delusions, p = 0.040; SAPS, p = 0.049), which was more represented in schizophrenic patients who started *cannabis* consumption before the onset of the psychotic disorder (N = 36, 67 %) than in patients whose onset of schizophrenia preceded the beginning of *cannabis* consumption (N = 18, 33 %). *Cannabis* consumers, moreover, were younger (p = 0.005), had significantly positive family history for both psychiatric and psychotic disorders (Table 2), lower levels of negative symptomatology and more hallucinations (Alogia, p = 0.029; Avolition-apathy, p = 0.018; Anhedonia-asociality, p = 0.004; Attention, p = 0.037; SANS, p = 0.009; Hallucinations, p = 0.042) when compared to nonconsumers. When *cannabis* use/abuse started after the onset of schizophrenia, posi-

Table 3 Sociodemographic, clinical characteristics and significant differences between cannabis consumers and non-consumers

	Non-consumers (N = 71)	Consumers (N = 54)	p
Sociodemographic			
Age	35.0 (8.7)	29.1 (7.1)	0.000
Age at onset	22.5 (8.0)	21.6 (5.4)	Ns
Education (years)	10.1 (3.9)	10.7 (2.9)	Ns
School failures	0.4 (0.5)	0.5 (0.9)	Ns
Hospitalization	2.5 (3.0)	2.3 (2.4)	Ns
Treatment (months)	65.9 (70.7)	47.0 (46.7)	Ns
SANS			
Affective flattening	15.2 (22.0)	11.6 (7.2)	0.013
Alogia	9.8 (5.7)	6.9 (4.4)	0.002
Avolition-Apathy	10.7 (3.9)	8.7 (4.1)	0.005
Anhedonia-Asociality	15.0 (5.5)	11.8 (5.3)	0.001
Attention	3.5 (3.2)	2.2 (2.4)	0.018
Total	54.5 (23.6)	41.5 (19.9)	0.001
SAPS			
Hallucinations	9.3 (6.0)	10.2 (7.4)	Ns
Delusions	16.3 (8.9)	15.2 (9.3)	Ns
Bizarre behavior	9.9 (4.8)	9.1 (3.7)	Ns
Thought disorder	15.7 (8.2)	12.6 (6.8)	0.023
Total	51.2 (22.0)	47.2 (19.5)	Ns
PANSS			
Positive	21.1 (7.3)	21.8 (6.8)	Ns
Negative	22.9 (8.3)	20.1 (7.7)	0.049
General	49.4 (11.0)	49.4 (7.6)	Ns
Total	92.8 (19.8)	91.3 (14.9)	Ns
BPRS			
Anergia	10.4 (4.5)	9.8 (3.9)	Ns
Thought disturbance	12.8 (4.1)	13.5 (3.6)	Ns
Activation	9.1 (2.9)	8.9 (2.3)	Ns
Paranoid-belligerence	9.5 (3.1)	10.1 (2.6)	Ns
Depression	10.1 (3.2)	10.2 (3.4)	Ns
Total	51.7 (10.9)	52.4 (8.4)	Ns

Standard deviation (SD) brackets. *Ns* no significant values for $p \leq 0.05$, with Student's *t* test

Table 4 Correlation between intensity of cannabis abuse and positive and negative schizophrenic symptoms

	Pearson's *r*	Significance *p* (two-tailed)
SANS		
Total	−0.287	0.001
Affective flattering	−0.203	0.023
Alogia	−0.283	0.001
Avolition-Apathy	−0.284	0.001
Anhedonia-Asociality	−0.313	0.000
Attention	−0.206	0.021
SAPS		
Total	−0.028	0.757
Hallucinations	0.114	0.204
Delusions	−0.018	0.846
Bizarre behavior	−0.045	0.617
Thought disorder	−0.139	0.123
PANSS		
Positive	0.114	0.204
Negative	−0.208	0.020
General	−0.036	0.693
Total	−0.055	0.546
BPRS		
Anergia	−0.109	0.226
Thought disturbance	0.116	0.197
Activation	0.004	0.969
Paranoid-belligerence	0.100	0.267
Depression	−0.016	0.058
Total	−0.065	0.470

Values are significant for $p < 0.05$

tive symptomatology was more severe in nonconsumers (SAPS, $p = 0.015$), with just a trend for negative symptoms after post hoc analysis. Substance abusers were younger than nonabusers ($p = 0.003$).

Finally, we found that patients with pure use/abuse of *cannabis* were younger ($p = 0.001$) and had lower levels of negative symptoms, although statistically not significant after post hoc analysis, when compared to nonconsumers. However, they showed higher levels of negative symptoms, if compared to polysubstance subjects (PANSS Negative, $p = 0.000$). Polysubstance consumers were younger ($p = 0.016$) and with lower levels of negative (Affective flattening, $p = 0.036$; Alogia, $p = 0.003$; Avolition-apathy, $p = 0.008$; Anhedonia-asociality, $p = 0.017$; Attention, $p = 0.015$; SANS, $p = 0.005$; PANSS Negative, $p = 0.007$) and positive symptoms (Thought disorder, $p = 0.018$) than nonconsumers.

Discussion

Our study overall confirms the high prevalence of *cannabis* and substance abuse, in general, in schizophrenic patients, especially in the younger patients. The figures obtained are well above those found for the general population, both in Italy and in other countries. However, the absence of women from our sample and the lack of an age-matched control group make it impossible to extend our data to other populations.

Despite no significant differences in global psychopathology between consumers and nonconsumers, *cannabis* seems to be involved in the clinical course of schizophrenia. A striking finding is that *cannabis* consumers, especially abusers and polysubstance consumers, show less negative symptomatology, compared to nonconsumers and this seems to be dose-related. These results may add value to the self-medication hypothesis. It was suggested that negative affective states, impaired cognition and poor self-esteem may predispose patients to substance abuse (Soni et al. 1994) and that pharmacological effects of specific substances and symptoms are related (Lehman et al. 1989; Gray and Thomas 1996), as confirmed by patients' self reports (Baigent et al. 1995). Alternatively, substances may be abused to relieve extrapyramidal and sedative effects of treatment either directly or altering drug metabolism (Schneier and Siris 1987). *Cannabis* has been proposed to relieve negative symptoms (Peralta and Cuesta 1992; Dixon et al. 1991), but it is hard to differentiate the intrinsic effects of this drug from those of other substances. Our results suggest that *cannabis* alone may improve these symptoms, but its effect is likely to appear when other substances are consumed as well. Schizophrenia is supposed to be associated with increased mesolimbic and decreased prefrontal dopaminergic activity (Weinberger 1987), with the former related to positive (Davis et al. 1991) and the latter to negative symptoms (Goff and Evins 1998). Animal studies suggest that *cannabis* might improve frontocortical and either improve or worsen mesolimbic dopaminergic function through an activation of cannabinoid receptors (Diana et al. 1998; Melis et al. 2000). Hence negative symptoms are more likely to be improved by cannabinoid use, whereas their effect on positive symptoms is more unpredictable. In our study, at odds with literature, we found no difference in positive symptoms between consumers and nonconsumers, with the exception of thought disorder, which was higher in the latter. However, we should consider that our patients were on stabilized neuroleptic treatment for a mean of 58 months and this might have changed the expression of treatment-responsive symptoms, such as the positive ones.

Possible limitations of the self-medication hypothesis are that it is strongly based on patients' self reports, with all their intrinsic methodological drawbacks, and that substance abuse is related to symptomatic exacerbation, acute relapses, higher rates of hospital admission, poorer response to treatment and higher incidence of tardive dyskinesia (Dixon et al. 1992; Linszen et al. 1994; Owen et al. 1996). Moreover, daily fluctuation of positive, negative and dysphoric symptoms was not affected by the extent of *cannabis* use in inpatients (Hamera et al. 1995).

An alternative explanation of the association between *cannabis* use and fewer negative symptoms is that the latter, along with better premorbid adjustment (Dixon 1999), may increase the risk of exposure to opportunities of substance abuse (Arndt et al. 1992) and to novelty seeking, a key factor in substance dependence (Ferguson and Horwood, 2000).

Moreover, most studies suggest that substance abuse usually precedes psychotic onset (Andréasson et al. 1989; Allebeck et al. 1993; Hambrecht and Häfner, 2000). Our study found that 67 % of patients began their abuse before the first symptoms of schizophrenia. These patients manifested marked positive symptoms (especially delusions and hallucinations) when compared to the other abusers. Also, they had fewer negative symptoms, along with more positive symptoms (mostly hallucinations), and a positive family history for psychiatric and psychotic disorders, than nonconsumers. This raises the possibility that our consumers' sub-sample might be representative of a subclass of schizophrenic patients, with specific patterns of symptoms and in which *cannabis* might have played a role in precipitating the onset of schizophrenia, in schizophrenia spectrum-prone subjects. Given the limits of this study, it can not be stated that *cannabis* is a clear risk factor for schizophrenia, but these results support vulnerability hypotheses, according to which substance abuse may act as a trigger and unveil, precipitate or even cause schizophrenia (Andréasson et al. 1987, 1989; Hambrecht and Häfner 1996). Cannabinoids are now hypothesized to participate to the pathophysiology of schizophrenia. Anandamide and palmitylethanolamide, two proposed endogenous ligands of cannabinoid receptors, were found to be increased in the cerebrospinal fluid of schizophrenic subjects (Leweke et al. 1999) and *cannabis* was

shown to induce cognitive and neurophysiological impairment similar to that existing in schizophrenic patients (Emrich et al. 1997; Schneider et al. 1998). Smoking *cannabis* induces an up-regulation of CB–1 receptors in motor areas, such as the caudate-putamen, similar to that found in the prefrontal cortex of schizophrenic individuals (Dean et al. 2001). These data are compatible with a cannabinoid psychosis-induction model.

Some methodological limitations should also be considered. This was a retrospective study, with limitations including the following problems in defining the real onset of psychosis and substance abuse; information gathered from and based on self-reports of subjects whose reliability is variable; lack of follow-up, and difficulty in using a population of *cannabis*-only consumers and normal control subjects to be studied prospectively in comparison with schizophrenic patients. We tried to reduce these drawbacks integrating patient reports with other information from their family and past clinical records. To reduce the risk to underestimate drug use, interviewers were not the same who followed the individual patients. The use of standardized scales to assess drug-taking behavior is difficult to apply when dealing with populations with variable disease duration, so we preferred to rely on a thorough and focused clinical interview. Moreover, the absence of biological confirmation for substance abuse (i. e., toxicological blood and urine examinations) could have subtracted validity from our data; however, in a study carried out with a toxicological control of self-reports, the latter proved to be fairly reliable (Martin et al. 1988). Extensive interview and restrictive criteria for the assessment of illicit drug use/abuse further helped improve reliability. Another major problem was that our subjects were chronic schizophrenic patients on prolonged neuroleptic treatment, which might have altered symptomatology, with a greater impact on positive symptoms. Last, but not least, patients were male only; hence, results may not also extend to the female gender.

Conclusions

Despite methodological issues being far from settled in studies of this type, our findings strongly suggest that *cannabis* may play an important role in, and have a reasonable impact on, the onset, course, phenomenology and outcome of schizophrenia. Our subjects can be subdivided into two main groups, one group that uses substances as an attempt to counter distressing symptoms of schizophrenia and of its treatment, and another in which *cannabis* was one of the predisposing factors for the onset of the disease, giving support to heterogeneity of schizophrenia and to genetic susceptibility to environmental stimuli. Further research is needed to properly determine the precise link between these two disorders.

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