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ORIGINAL PAPER

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Cannabis and schizophrenia: results of a follow-up study

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Abstract A total of 39 schizophrenic patients with a history of current cannabis abuse at index admission was compared with a control group of schizophrenics without substance abuse matched for age, gender, and year of admission. At follow-up after 68.7 ± 28.3 months, 27/39 cases and 26/39 controls could be investigated. 8/27 cases (30%) had continued cannabis abuse, 6/27 (22%) had become alcohol abusers. Only one patient of the control group had started abusing alcohol. Patients with previous cannabis abuse had significantly more rehospitalizations, tended to worse psychosocial functioning, and scored significantly higher on the psychopathological syndromes "thought disturbance" (BPRS) and "hostility" (AMDP). These results confirm the major impact of cannabis abuse on the long-term outcome of schizophrenic patients.

Key words Schizophrenia · Cannabis abuse · Follow-up

Introduction

In the last two decades, substance abuse has proved to be a major problem in the management of psychoses. Prevalence estimates of drug or alcohol abuse in schizophrenia or major affective disorders vary between 15% and 65% (Mueser et al. 1992). In the Epidemiologic Catchment Area Study, 33.7% of all individuals with a lifetime diagnosis of schizophrenia or schizophreniform disorder met criteria for an alcohol disorder and 27.5% for another drug abuse disorder (Regier et al. 1990). Beside alcohol, cannabis is most often abused by schizophrenic patients (Dixon et al. 1991). Cannabis is regarded as a possible risk factor for schizophrenia (Allebeck et al. 1993, Linszen et al. 1994), but divergent views have been expressed on this topic (Hall and Solowij 1997, Negrete 1989).

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In Germany, lifetime prevalence rates for substance abuse in schizophrenics were estimated at 21.8% for patients of the Psychiatric Hospital, University of Munich and 42.9% for a more chronic sample of the Mental State Hospital Haar/Munich (Soyka et al. 1993). Eikmeier et al. (1991) found cannabis abuse in 18% of their sample of schizophrenic patients. Compared to schizophrenics without drug abuse, cannabis-consuming patients were significantly younger at the time when first psychotic symptoms occurred, and in most cases cannabis use had started more than one year before this first episode.

So far, there is only scarce information on the long-term course of patients with a comorbid disorder of schizophrenia and cannabis abuse. Previous studies comprised short follow-up periods (Linszen et al. 1994, Martinez-Arevalo et al. 1994) or included heterogenous samples (Perkins et al. 1986).

This study was, therefore, designed to investigate the further development of cannabis and other substance abuse and the outcome of schizophrenia in a representative sample of patients with dual diagnosis. Moreover, the relevance of cannabis abuse for psychosocial functioning and psychopathological outcome should be assessed by comparing the course of cases with a control group.

Methods

This article presents results of a follow-up investigation of patients previously included in a retrospective case-control study (Caspari 1998). The sample consists of all patients diagnosed as suffering from schizophrenia and presenting with a current history of cannabis abuse who were first admitted to the Psychiatric University Hospital at Homburg/Saar, Germany, between 1986 and 1992. Some patients had undergone outpatient therapy or had been treated before in another hospital outside the region. Patients with a toxic or drug-induced psychosis (according to ICD-9 No. 292.1/2) or schizophrenics who mainly abused drugs other than cannabis were excluded from the study. 39 patients (30 men and 9 women) met the criteria for inclusion in the investigation; 39 schizophrenics who had no history of alcohol or drug abuse were taken as a control group. These patients also received their first treatment at the Psychiatric University Hospital at Homburg/Saar between 1986 and 1992 and were matched for age, gender, and year of admission (Table 1).

Table 1 Comparison of cases and controls at index admission

	Patients with cannabis abuse	Patients without substance abuse
n	39	39
Sex (m : f)	30 : 9	30 : 9
Age at index admission (years)	24.2 ± 4.5	24.3 ± 4.2
Age at first manifestation (years)	22.7 ± 3.6	23.1 ± 4.1

The Psychiatric University Hospital is responsible for the inpatient treatment of psychiatric patients in a catchment area of about 350,000 inhabitants. Up to the end of the study there were no other private or mental health hospitals situated in this region. The samples can, therefore, be regarded as representative of a psychiatric hospital with local responsibility for inpatient care.

Diagnostic assessment was originally carried out using ICD-9, but a re-evaluation of the cases and controls confirmed that they all fulfilled ICD-10 criteria for schizophrenia. Cannabis abuse was diagnosed if patients had consumed cannabis regularly for several months and if this interfered with social functioning or was prominent during therapy. Patients with an occasional use of cannabis were not included in the study. Information about substance abuse was taken from case records.

At follow-up, all 78 patients were asked by letter to come for a personal investigation. Psychosocial data and information concerning treatment outcome, rehospitalization, and history of substance abuse were assessed by a structured interview following the recommendations of the German Society for Addiction Research and Therapy (Deutsche Gesellschaft für Suchtforschung und Suchttherapie 1992). The study did not comprise a toxicological urine analysis for cannabis or other drugs. Though the use of cannabis is officially illegal in Germany, it is practically not restricted nowadays. Therefore, the self-reports in combination with reports of relatives and therapists were likely to be valid. Moreover, there was a high correlation between information about substance abuse that was raised in the interview and data from the case records.

Overall psychosocial functioning and severity of psychiatric disturbances were rated by the Global Assessment Scale (Endicott et al. 1976). A rehospitalization index was defined by dividing the number of further hospitalizations by the time of follow-up (per year).

Psychopathology was assessed with the BPRS (Overall and Gorham 1976) and the AMDP scale (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie 1995). BPRS items were rated on a seven step scale from “not present” (1) to “most severe” (7). The statistical comparisons were made using the five factors or subscales proposed by Overall and Gorham (1976): anxiety/depression (ANDP), anergia (ANER), thought disturbance (THOT), activation (ACTV), and hostile-suspiciousness (HOST). The AMDP scale is widely used in Germany. It consists of 140 items that cover the whole range of psychopathological symptoms and include also autonomic and somatic signs. Factorial analysis revealed seven subscales (Gebhardt et al. 1983): paranoid-hallucinatory syndrome (PARHAL), depressive syndrome (DEPRES), psycho-organic syndrome (PSYORG), maniform syndrome (MANI), hostility (HOST), vegetative syndrome (VEGET), and apathetic syndrome (APA). The raw values of the original syndromes were transformed into T values which were used for further comparisons.

Statistical analyses were carried out using non-parametric and parametric procedures of the Statistical Packages for Social Sciences (SPSS). The alpha level was set at 0.05.

Results

Table 1 illustrates that cases and controls were adequately matched for age and sex. Both samples constitute a subgroup of schizophrenic patients with early onset of psychosis, 59% of patients had their first episode at index admission. 41% of patients had undergone outpatient therapy or had been treated in another hospital before.

At follow-up, 68% of all patients (53/78) could be interviewed and investigated personally. Reasons for drop-out were as follows: One patient had died of pneumonia in the meantime, 5 patients had changed their address and could therefore not be reached, 5 patients refused to take part in the study and 14 patients did not come at the appointed time without giving a reason. There were no relevant differences between the two groups concerning reasons for drop-out.

Mean follow-up period was 68.7 ± 28.3 months. The difference between cases and controls was not significant (Table 2).

The patients with a previous cannabis abuse reported that it had started at the age of 17.6 ± 2.6 years (range 12–23). A mean period of 4.4 ± 2.4 years (range 1–8) was found between the onset of drug abuse and the first psychotic episode. Cannabis abuse had begun after the onset of schizophrenia only in one case. Altogether cannabis had been abused for 7.7 ± 3.8 years (range 3–17).

Eight out of 27 cases (30%) which could be investigated at follow-up presented with current cannabis abuse. Four of these patients also abused alcohol, one abused alcohol, and occasionally consumed cocaine. 6/27 cases (22%) had stopped drug abuse but presented with a significant alcohol problem. 13/27 cases (48%) had ceased any substance abuse. On the other hand, only one patient of the control group exhibited signs of excessive drinking and none showed another substance or drug abuse during follow-up.

The psychosocial situation of the patients was quite different with Global Assessment Scale scores ranging from 35 to 90. Only 12 cases (44%) but 18 controls (69%) reached a score of 60 (median) or more that indicated a satisfactory functioning. On the average, there was a clear, but not significant difference in the GAS scores between the two groups (see Table 2). As indicated by the rehospitalization index, patients with a history of cannabis abuse

Table 2 Comparison of cases and controls at follow-up

	Cases	Controls
n	27/39	26/39
Sex (m : f)	21 : 6	20 : 6
Period of follow-up (months)	63.3 ± 28.1	74.3 ± 28.0
GAS score	55.7 ± 14.8	62.5 ± 15.4
Rehospitalization index	0.98 ± 0.8	0.35 ± 0.3[a]

[a] $t = 3.98$ ($p < 0.001$)

Table 3 Comparison of socio-demographic data at follow-up

	Cases	Controls
n	27	26
Marital status		
Single	24 (88.9%)	18 (69.2%)
Married	2 (7.4%)	5 (19.2%)
Divorced	1 (3.7%)	2 (7.7%)
Widowed	0 (0.0%)	1 (3.8%)
Living status		
Alone	16 (59.3%)	17 (65.4%)
With partner	11 (40.7%)	9 (34.6%)
Maintenance		
Employment	5 (18.5%)	12 (46.2%)
Pension	6 (22.2%)	6 (23.1%)
Social insurance	4 (14.8%)	0 (0.0%)
Social welfare	5 (18.5%)	2 (7.7%)
Family support	4 (14.8%)	3 (11.5%)
Other	3 (11.1%)	3 (11.5%)

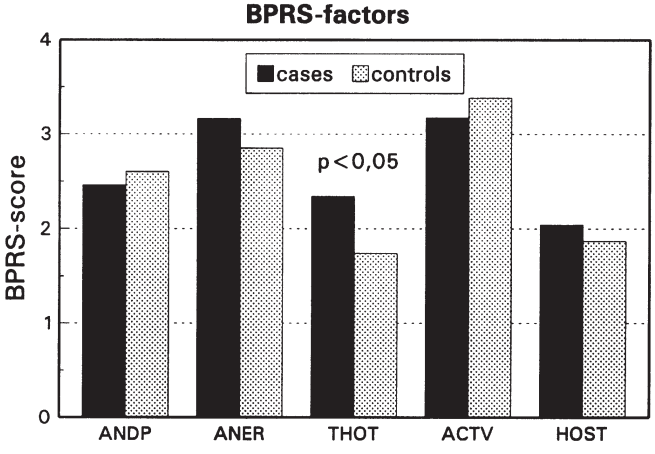

Fig. 1 Mean BPRS-factor scores of schizophrenic patients with a history of cannabis abuse (black columns) and of controls without substance abuse (dotted columns), *ANDP* – anxiety/depression, *ANER* – anergia, *THOT* – thought disturbance, *ACTV* – activation, *HOST* – hostile-suspiciousness

had a significantly larger number of rehospitalizations in the follow-up period than controls.

Sociodemographic characteristics of the two groups are shown in Table 3. Most patients were single and lived alone. Only 18.5% of patients with a past or current cannabis abuse were employed, whereas 33.3% of them were supported by social insurance or welfare. By contrast, 46.2% of controls had a regular employment. However, overall there were no significant differences between cases and controls in respect of demographic data.

Figures 1 and 2 present the psychopathological findings. Significant differences between the two groups were found for the BPRS factor "thought disturbance" ($t = 2.25$, $p < 0.05$) and on the AMDP scale "hostility" ($t = 2.50$, $p < 0.05$). On the whole, BPRS and AMDP profiles of cases and controls are rather similar.

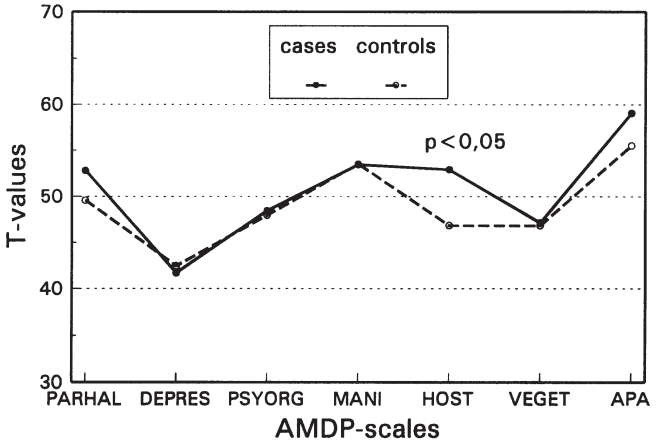

Fig. 2 AMDP-profiles of schizophrenics with a history of cannabis abuse (full line) and of patients without substance abuse (dotted line), *PARHAL* – paranoid-hallucinatory syndrome, *DEPRES* – depressive syndrome, *PSYORG* – psycho-organic syndrome, *MANI* – maniform syndrome, *HOST* – hostility, *VEGET* – vegetative syndrome, *APA* – apathetic syndrome

Discussion

Cannabis sativa is a well-known psychoactive agent with tranquilizing, mood elevating, and hallucinogenic properties. Its occasional use is quite common in adolescents and young adults, but in Germany regular consumption is restricted to about 4% of the population aged 12 to 25 years (Bundeszentrale für gesundheitliche Aufklärung 1994). Psychoses following acute or chronic intoxication with cannabis have been known for a long time (Chopra and Smith 1974, Keup 1970). Over time, the scope of interest had shifted to the so-called cannabis-induced psychoses. Empirical studies revealed that there were no fundamental differences between these psychoses and schizophrenia (Täschner 1983, Thornicroft et al. 1992). Therefore, the relevance of cannabis consumption or abuse in schizophrenic patients is mainly addressed nowadays. Cleghorn et al. (1991) found that schizophrenics with prior substance abuse, where cannabis was the most heavily used drug, had significantly more positive symptoms such as hallucinations, delusions or thought disorder than controls. Knudsen and Vilmar (1984) observed in schizophrenic patients an acute aggravation of their condition following cannabis use, despite adequate depot treatment with neuroleptics. In a prospective cohort study over one year, Linszen et al. (1994) arrived at the result that cannabis-abusing patients had significantly more and earlier psychotic relapses.

In contrast to these results, Peralta and Cuesta (1992) did not find significant differences between schizophrenics with and without cannabis abuse in respect of positive symptoms, but nonabusers had higher scores on the Scale for the Assessment of Negative Symptoms (SANS) with a significant difference on the alogia subscale. Dixon et al. (1991) even found significantly fewer positive and negative symptoms in schizophrenic patients with drug abuse

and came to the conclusion that this group of patients had a better prognosis. Methodological problems mainly related to heterogeneity of samples and to the differences in the definition and assessment of drug abuse may account for these inconsistencies.

Another controversional point is significance of cannabis abuse for the etiology of schizophrenic psychoses. Some authors argued that cannabis abuse is a consequence rather than an antecedent of psychotic disturbance. According to this self-medication hypothesis, patients consume drugs in order to alleviate their symptoms or counteract side-effects of neuroleptic treatment.

However, in accordance with our results, most empirical studies revealed that cannabis abuse preceded the onset of schizophrenia for several years in the majority of patients (Allebeck et al. 1993, Linszen et al. 1994, Cleghorn et al. 1991). Moreover, Andréasson et al. (1987) have studied the association between the level of cannabis consumption and the development of schizophrenia during a 15-year follow-up in a cohort of 45 570 Swedish conscripts. They found that the relative risk of schizophrenia rose with increasing consumption level and was 6.0 among those who had used cannabis more than fifty times. They also described a clear dose-response gradient. In a subsequent study (Andréasson et al. 1989), the authors were able to show a different pattern of mental deterioration among cannabis users, with a more abrupt onset of schizophrenic symptoms.

Neurobiological mechanisms of acute and chronic cannabis exposure are not yet fully understood. Recently, a cannabis receptor and an endogenous ligand (anandamide) were discovered (Martin 1995). The highest density of cannabinoid receptors was found in the basal ganglia and in the cerebellum, but the hippocampal formation also demonstrated relatively dense binding of cannabinoids. Moreover, tetrahydrocannabinol acts as a dopamine agonist in dopaminergic projections of the medial forebrain. There are, thus, several links between the central actions of cannabis and neurobiological hypotheses of schizophrenia. Emrich et al. (1997) observed that neuropsychological results (three-dimensional inversion illusion) in delta 9-tetrahydrocannabinol-intoxicated normal volunteers exhibit strong similarities with data acquired from patients suffering from productive schizophrenic psychoses, regarding disturbances in internal regulation of perceptual processes. The authors postulate that a subgroup of schizophrenic syndromes may pathogenetically be related to a functional disturbance of the endogenous cannabinoid/anandamide system.

Up to now there have been no systematic longitudinal studies of representative samples in respect of the course of further substance abuse and schizophrenic symptomatology. Trabert and Täschner (1987) presented results of a follow-up investigation of 40 patients with drug-induced psychosis. These patients were a subgroup of Täschner's comprehensive sample (1980). Six years after the initial treatment, the authors were able to investigate 17 cases. The majority presented with a residual state at follow-up. Only 4 cases had no psychopathological symptoms. For most patients substance abuse was no longer prominent, 60% reported that they had stopped drug abuse since five years or more. This study did not use standardized assessment procedures or include a control group. Perkins et al. (1986) investigated a heterogenous group of drug abusers ten years after admission using a structured telephone interview. They found that drug abusers with chronic psychosis had a significantly poorer psychiatric outcome than the other drug abusers and a significantly worse occupational outcome than acutely psychotic drug abusers. But the authors did not provide information concerning further substance abuse in their patients.

In our study, a representative sample of schizophrenic patients with cannabis abuse and a control group of schizophrenics without a history of substance abuse could be investigated five years after their first admission to our hospital. At follow-up, 30% of former cannabis abusing patients had continued drug abuse, 22% were alcohol abusers, whereas only one patient of the control group presented with alcoholism. Considering that both samples, controls as well as cases, belong to a subgroup of patients with early onset of schizophrenia and were quite young at index admission, these results argue against a self-medication hypothesis of cannabis abuse. However, it must be born in mind that Hambrecht and Häfner (1996) were able to demonstrate that first signs and even negative symptoms of schizophrenia may occur several years before first admission. Their data indicate that coping with negative symptoms by means of drug abuse is possible in up to 28% of comorbid patients, but that drug abuse is apparently not a frequent coping strategy for positive symptoms.

In the present study, patients with a history of cannabis abuse showed a significantly higher rate of rehospitalizations in the follow-up period and tended to have poorer psychosocial functioning than schizophrenics without substance abuse. Moreover, cases had a significantly higher score for the two psychopathological syndromes "thought disturbance" and "hostility". Altogether, these results prove that cannabis abuse has an important impact not only in the short-term but also for the long-term outcome of schizophrenia and, therefore, should be addressed carefully in the assessment and during treatment of schizophrenic patients. Further investigations are necessary to clarify the role and significance of therapeutic interventions and of other factors such as, e.g., life-events on the continuation or discontinuation of drug abuse in patients with schizophrenia.

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