

# Psychosis and *Cannabis*\*

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## Abstract

Alcohol and *cannabis* misuse is currently the most frequent co-morbidity disorder of schizophrenia. The following four issues will be dealt with: 1) the neurobiological basis of the psychosis-inducing, pathogenic effects of THC, the agent contained in *cannabis* products. 2) Can *cannabis* use - and for comparison alcohol abuse - prematurely trigger or even cause schizophrenia? 3) Are persons genetically liable to schizophrenia, psychosis-prone individuals or young persons before completion of brain development at an increased risk? 4) What consequences does *cannabis* use have on the symptomatology and further course of schizophrenia?

Results from recent literature and the ABC Schizophrenia Study show that the risk for *cannabis* use in schizophrenia is about twice the size in healthy controls. In most cases *cannabis* use starts before first admission, in a third of cases before schizophrenia onset. There is an increased affinity to misuse already at the prodromal stage. *Cannabis* can prematurely trigger schizophrenia onset - on average eight years earlier than in non-use - and cause the illness partly in interaction with predisposing factors. *Cannabis* use in the course of schizophrenia increases positive symptoms and reduces affective flattening, thus leading to dysfunctional coping in some cases.

Key words: Psychosis and *cannabis*; co-morbidity; *cannabis* as a cause of schizophrenia; *cannabis* as a trigger; pre-mature onset of schizophrenia; dual diagnosis; schizophrenia and substance misuse.

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## Introduction

*Cannabis* is a drug with pain-relieving, stimulating, euphorising and erotogenic effects (Regier *et al.*, 1990, UNODC, 2004). Taken in higher doses, it leads to impaired self-control and finally to psychosis or sedation, disorientation and loss of conscience. In the last two decades *cannabis* use markedly increased particularly among adolescents, and age of onset fell

continuously in many countries. The age-related incidence of illegal drug use in Germany makes plain that *cannabis* is far ahead of other illegal drugs in young age groups (Perkonigg *et al.*, 1997) (Figure 1) - meanwhile the curve has progressed to even younger ages. At the same time delta-9-tetrahydrocannabinol concentrations, the major psychoactive component of *cannabis* in Western countries, increased nearly tenfold in samples obtained on the market - for

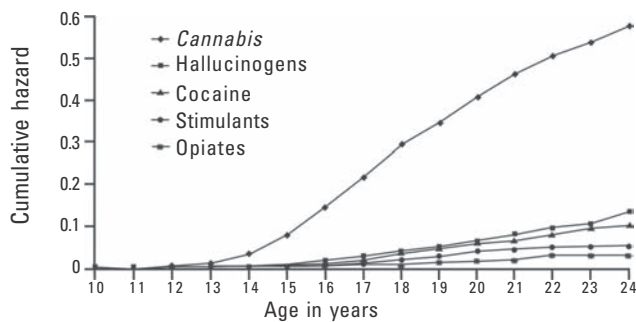
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Recebido: 03/01/2005 - Aceito: 28/01/2005

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\* Paper presented at the IV National Congress "Psichiatria e Dipendenze Patologiche: L'integrazione Possibile", Rimini, Dicembre 2-4, 2004.

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**Figure 1.** Age-related incidence of illegal drug use in Germany (Source: Perkonig *et al.* 1997).

example in Switzerland from an average of 1% to 4 % in 1995 and to 6 % to 28 % in 2003 (Bernhard 2004). 57 samples of *cannabis* products randomly bought by Swiss television journalists on the illegal Swiss market for an average price of 10 Fr/g in 2003 had an average THC concentration of 14.5 % and a maximum of 25 %. It is not unlikely that due to the drug's increased potency also the adverse effects of *cannabis* use, such as psychosis triggered by *cannabis*, have increased and as a result attracted increased awareness.

In addition to the effects mentioned low THC doses have anxiolytic and antidepressive properties. Higher doses have reversed effects: they are highly anxiogenic and depressogenic. High THC doses can produce schizophrenia-like psychoses, which usually go without negative symptoms and remit after THC has been excreted, mostly within one week of abstinence (Mathers and Ghodse, 1992, McGuire *et al.*, 1994, Hall and Degenhardt, 2000, Johns, 2001).

The British Crime Report 2002 lists the public-health risks associated with *cannabis* use: suicide,

risky sexual behaviour, increased teen and unwanted pregnancies, sexually transmissible diseases, homelessness, traffic accidents, accidents in general, violent crime, crime in general, increased health costs and mental problems and illness.

*Cannabis* and alcohol use are more prevalent among people with schizophrenia than among healthy controls and also more prevalent than in other mental disorders. Apparently patients with schizophrenia in this way try to get relief from the distressing symptoms and adverse consequences of the disorder or to offset these negative experiences by positive moods and fantasies.

Table 1 lists 11 studies on *cannabis* use in manifest schizophrenia and one review (Strakowski *et al.*, 1998). The frequency ranges from 4% to 86%.

The pronounced differences indicate that the rates are not comparable at their face value. The studies differ in scientific quality (Mueser *et al.*, 1992a,b), and their results are influenced by various kinds of factors. First of all, how is drug use measured? Lifetime prevalences depend on the length of the period of risk covered and thus on the age of the probands studied as well as on the duration of illness and exposure to an excess risk. The increase in the proportion of patients with *cannabis* and alcohol use in the study of Soyka *et al.* (1993) from first admission to several years later in a chronic course of schizophrenia may serve as an example (Table 2).

When co-morbidity rates are compared across different areas, countries or time periods, factors to take into account are the availability of the drug in question and the patterns of drug habit of the populations studied. The availability and price of illegal drugs in particular vary considerably. For this reason, prevalence rates for both total populations and patients with schizophrenia are hardly comparable across geographic areas and different time periods. What can be compared are relative risks, that is, the

**Table 1.** *Cannabis* use and dependence in patients treated for schizophrenia (mostly inpatients).

Author/Year of publication/Country	Prevalence	Specifications
Verdoux <i>et al.</i> , 1996 (F)	25%	
Menezes <i>et al.</i> , 1996 (GB)	40%	(at least once)
Strakowski <i>et al.</i> , 1990-96 (review) (published in 1998)	8-42%	
Modestin <i>et al.</i> , 1997 (CH)	12%	
Grech <i>et al.</i> , 1998 (London)	39% (controls: 21.9%)	(current use)
Wheatley, 1998 (GB)	51%	(at least once in lifetime)
Sembhi and Lee, 1999 (Australia)	86%	(lifetime, inpatients)
Mueser <i>et al.</i> , 2000 (USA)	~50%	(first episodes: 23-37%)
Duke <i>et al.</i> , 2001 (London)	20%	(at least once)
Hall & Degenhardt, 2002 (Australia)	12%	(current use or addiction)
McCreadie <i>et al.</i> , 2002 (Scotland)	4% (controls: 2%)	(addiction)
Häfner <i>et al.</i> , 2002 (Mannheim)	14% (controls: 7%)	(lifetime at first admission, at least once)

**Table 2.** Lifetime prevalence of alcohol and *cannabis* use in Bavaria.

Lifetime prevalence	First-admission schizophrenia	Chronic schizophrenia
Alcohol use	17.4 %	34.6 %
<i>Cannabis</i> use	21.8 %	42.9 %

Source: Soyka et al., 1993

frequency of drug use in excess of that in a comparable control population. A prerequisite for sound studies is that adequately matched controls from the local population are included. Unlike illicit drug use alcohol misuse varies less, because alcohol is freely available and low in price almost everywhere. For this reason results on alcohol misuse in schizophrenia are more or less comparable.

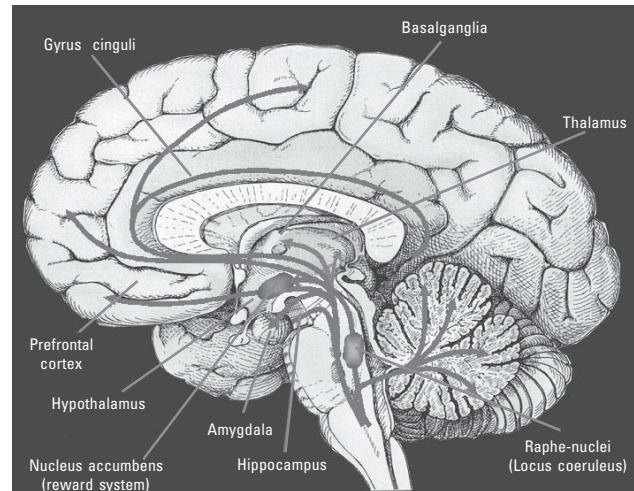
### Neurobiological basis of THC effects

The THC effect is based on the highly-specific neurobiological properties of the substance. THC binds to G-protein-coupled cannabinoid receptors (CB-1). It acts via the body's own cannabinoid system in close interaction with the dopamine neurotransmitter system and accounts for both addictive behaviour and therapeutic effects (pain and anxiety relief). The highest density of CB-1 receptors is to be found in those – primarily dopaminergic - brain areas and pathways (depicted by arrows in figure 2) that are mostly active in the production of schizophrenic symptoms in the dorsolateral prefrontal cortex (Dean et al., 2001): the limbic system, hippocampus, basal ganglia and cerebellum (Leweke et al., 1999). The endogenous cannabinoids enhanced by *cannabis* use in people with schizophrenia (Leweke et al., 1999) are also responsible for down-regulating the release of GABA, an inhibitory neurotransmitter, in the hippocampal neurons (Wilson and Nicoll, 2001).

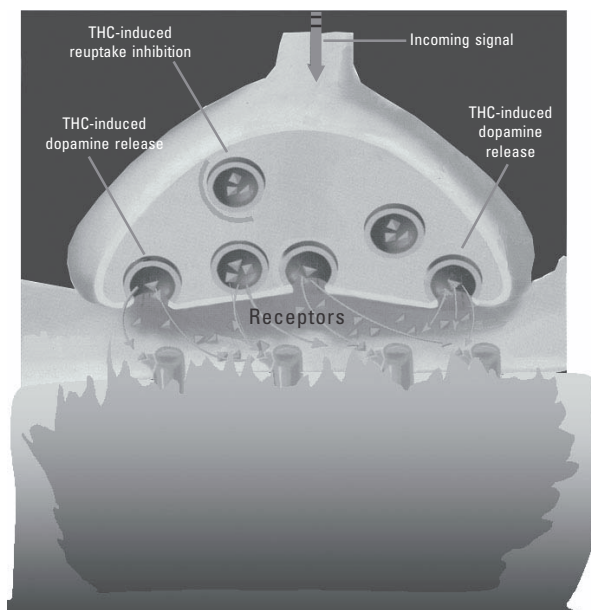
THC also increases dopamine activity in the mesolimbic area and the nucleus accumbens. It is this effect on the reward system that is responsible for the addictive potency of THC (Figure 2).

THC induces the synthesis and release of dopamine and inhibits dopamine reuptake in the synaptic cleft. Repeated use of *cannabis* may increase synaptic dopamine activity and as a consequence produce prolonged changes in the cannabinoid system. In addition, THC can lead to sensitization reflected in flash-back phenomena (Figure 3). The psychotomimetic potency and the localisation of THC dopamine receptor activation point to a possible causal relationship between *cannabis* use and schizophrenia. This hypothesis has been pursued by several authors (Andreasson et al., 1987, Arseneault et al., 2002, van Os et al., 2002, Verdoux et al., 2003).

We studied the following questions: 1. Can *cannabis* use prematurely trigger or cause psychosis? 2. Are



**Figure 2.** The neurobiological basis of the psychological effect of *cannabis*: dopaminergic neurons involved in both schizophrenic psychosis and *cannabis* (THC) effect (Source: Häfner, 2004).



**Figure 3.** THC sensitization.

persons genetically liable to schizophrenia, psychosis-prone individuals or young persons with immature brains at an increased risk? 3. How does *cannabis* use influence the symptoms and course of schizophrenia?

### Onset of schizophrenia triggered by *cannabis*

Suitable designs for testing hypothesis no. 1 are:

1. Prevalence rates of schizophrenia in *cannabis* users compared with non-users in community surveys. This design will reveal the size of the co-morbidity problem and probably support the assumption of an excess risk for schizophrenia associated with *cannabis* use. The design serves the purpose of planning prevention and care and generating hypotheses about causal associations.
2. The size and direction of the association between *cannabis* use and increased risk for schizophrenia are tested in prospective, controlled longitudinal studies of population cohorts, mostly birth cohorts.
3. A third design - testing the sequence of *cannabis* use and illness onset retrospectively and prospectively - allows us to determine the temporal dimension of premature precipitation, and to specify the type of the causal association (direct versus indirect)

### Results from prospective studies

Table 3 gives an overview of seven large-scale population-cohort studies, three of them based on more than 50,000 individuals each, but on male at-risk populations only – conscripts in age group 16 to 17 years in Israel (Weiser *et al.*, 2003) and 18 to 20 years in Sweden. The studies covered a maximum exposure period of 27 years (Zammit *et al.*, 2002). In all these studies comparisons with non-users drawn from the same population cohorts showed that *cannabis* users in general had an enhanced risk for schizophrenia with odds ranging from 1.3 to 4.1 and a modal value of about 2 (Häfner *et al.*, 2002, Arseneault *et al.*, 2004).

A series of objections have been raised against the causal interpretation of the results of the first large-scale Swedish conscript study (Andreasson *et al.*, 1988). When first published, this result was new and surprising to those favouring the legalization of *cannabis*.

For example it was criticised that the study relied on clinical diagnoses given at inpatient admission. Consequently, the cases included might have been contaminated with *cannabis*-induced psychoses. Another point raised was that outcome was restricted to hospital admission. Furthermore, confounding factors such as concomitant use of other drugs, family history of mental disorder or unfavourable social conditions, it was pointed out, could explain the association. For this reason, in almost all recent studies relevant confounding factors have been taken into account. The odds adjusted to

confounders are marked by an asterisk in Table 3. Considering the fact that the prepsychotic prodromal stage of schizophrenia has a mean duration of 4.8 years (Häfner *et al.*, 1995) we pointed out that some of the conscripts included in the study could have been suffering from an undiagnosed prodromal stage of the disorder. In an unknown proportion of the cases *cannabis* use, unrelated to or possibly a consequence of the disorder, could have been falsely counted as a causal risk factor for the disorder. To make allowance for this criticism the Swedish authors (Zammit *et al.*, 2002) left the first five years of the risk period following initial assessment out of consideration. Although the risk rate was slightly reduced, the odds ratios were still significant.

To provide more solid evidence for the causal association Andreasson *et al.* (1989) analysed 8433 male conscripts from the Province of Stockholm by taking four levels of *cannabis* use prior to first assessment into account. Table 4 shows a clear-cut dose-response relationship. The result provides very strong evidence for a causal association in the sense of a premature precipitation or causation of the illness.

Five of the seven population cohort studies into *cannabis* use and psychosis risk provide at least crude estimates of different levels of *cannabis* consumption demonstrating that more frequent uses are associated with significantly increased odds ratios for developing psychosis.

A further result of great importance has been yielded by the two New Zealand studies (Table 3). In these studies initial assessments of boys and girls were done in childhood, so it was possible to test whether age at exposure – an early onset of *cannabis* use, for example, before brain maturation – increases the risk for psychosis. Animal studies have demonstrated that puberty in rats is a vulnerable period with respect to the adverse effects of cannabinoids (Schneider and Koch, 2003, Henquet *et al.*, 2004). The onset of *cannabis* use before age 15 in the Dunedin study and even before age 18 in the Christchurch (Fergusson *et al.*, 2003) study turned out to be associated with a significantly greater psychosis risk than a later onset. As a result, immature brains in the period of puberty or in childhood and adolescence in general are more susceptible to adverse *cannabis* effects and to an elevated psychosis risk in the long term.

The third design for analysing the sequence of substance use onset and schizophrenia onset includes an operational assessment of symptoms, behaviour and milestones of the evolving disorder.

To recall the pattern of early illness course, illness onset must be defined by 1) the onset of psychotic symptoms, which happens about one year before first admission, and 2) by the onset of first signs of the disorder, which, on average, takes place 4.8 years before psychosis onset (Häfner *et al.*, 1995) (Figure 4). This leads to the following two subhypotheses:

**Table 3.** Prospective population follow-up studies into *cannabis* use as a risk factor for schizophrenia.

Study population/ Study	Number studied Sex Age	Period of risk covered	<i>Cannabis</i> use	Odds ratio	Definition of risk
Israeli conscripts (Weiser <i>et al.</i> , 2003)	50413 male 16 to 17 years	5 to 11 years	<i>Cannabis</i> before first assessment (probands: 12.4%, controls: 5.9%)	2	Inpatient admission because of schizophrenia
Swedish conscripts (Andreasson <i>et al.</i> , 1988, 1989)	50053 male 18 to 20 years	15 years	<i>Cannabis</i> before first assessment > 50-times	2.3* 4.1*	Ditto ICD-8
Swedish conscripts (Zammit <i>et al.</i> , 2002)	50087 male 18 to 20 years	27 years	<i>Cannabis</i> > 50 times	1.3-1.5* 3.1	Ditto DSM-IV
New Zealand Christchurch Study (Fergusson <i>et al.</i> , 2003)	1977 birth cohort: 1265 male, female (0 years)	From birth to age 21 years	<i>Cannabis</i> ≤ age 18 y. ≤ age 21 y. (analysed up to age 35 y.)	3.7 2.3 (1.8*)	Psychosis at follow-up
New Zealand Dunedin Study (Arseneault <i>et al.</i> , 2004)	Birth cohort 1037 male, female 11 years	From birth to age 18 to 26 years	<i>Cannabis</i> < age 15 y. age ≥ 18 y.	6.56* (total use: 2.34) 3.12*	Schizophrenia spectrum disorder at follow-up
Dutch NEMESIS Study (van Os <i>et al.</i> , 2002)	Population sample: 4105 male, female 18 to 64 years	3 years (drug use starting at age 16/17 years)	<i>Cannabis</i>	2.76*	Psychosis at follow-up (BPRS)
Henquet <i>et al.</i> (2004)	Population sample N=3021 (follow-up N=2437) male, female 14 to 24 years	4 years	<i>Cannabis</i> : ≥ 5 times*6 levels of use* +Sign. dose-response relationship	1.53* 2.23*	At least one or two core psychotic symptoms (M-CIDI)

\* Confounding factors (concomitant use of other drugs, mental disorder at entry into study or familial loading for mental disorder, growing up in an urban environment etc.) were taken into account.  
Modal value (relative increase in schizophrenia risk compared with risk in non-users)  
across studies (differences in age and risk period not considered): 2.43 (Arseneault *et al.*, 2004).

**Table 4.** Dose-response relationship substudy of the Swedish conscript study: frequency of *cannabis* use and schizophrenia incidence in 8433 men from the Province of Stockholm.

Frequency of <i>cannabis</i> use	Conscripts n (%)	Diagnosed with schizophrenia (n)	Odds ratio
0	6188 (80.4)	28	1.0
1-10	911 (11.8)	5	1.2
11-50	276 (3.6)	3	2.4
> 50	320 (4.2)	6	4.1

Source: Andreasson *et al.*, 1989

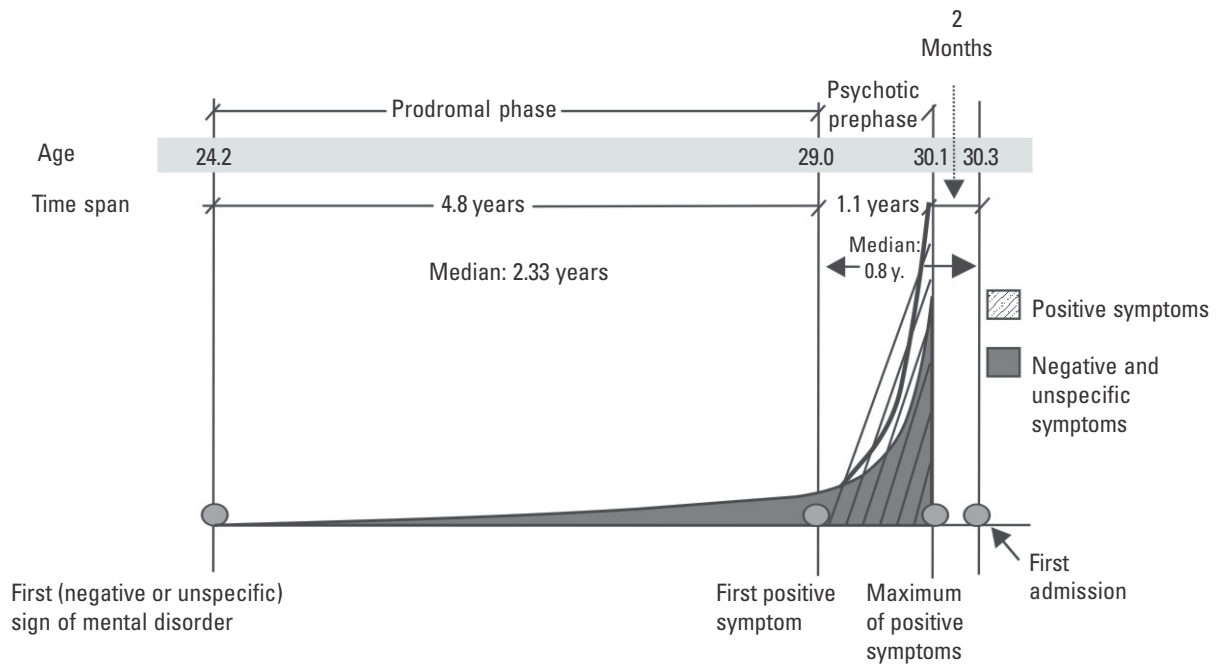
*Cannabis* use can trigger 1) a premature onset of schizophrenia, i.e. first symptoms including the prodromal stage, 2) psychosis without first producing a prodromal stage of schizophrenia, which seems to tally with the neurobiochemical mechanisms of THC activity.

### Study design, samples and method

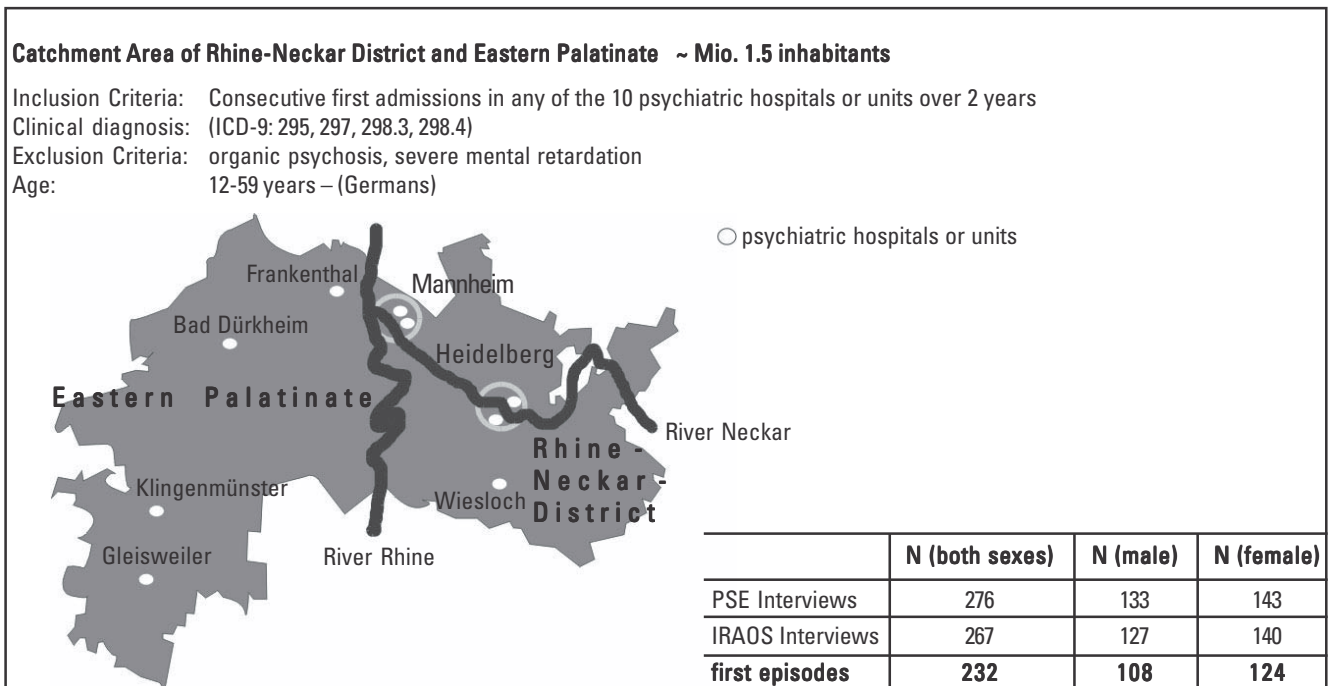
Figure 5 illustrates the study area and a population-based sample of 232 first illness episodes of broadly

defined schizophrenia in age range 12 to 59 years from a semi-rural, semi-urban German population of some 1.5 million (for a detailed description of the sample see Häfner *et al.*, 1999b).

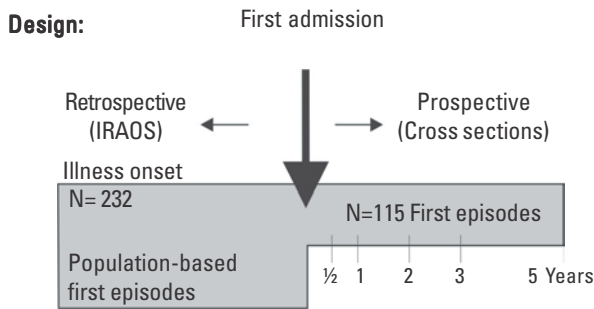
The retrospective part of the study is based on these 232 first illness episodes. In the prospective part we studied a representative subsample of 115 from the above sample of first illness episodes at five cross sections over five years after first admission (Figure 6). 57 controls randomly drawn from the population register of the



**Figure 4.** The early stages of schizophrenia from first sign of mental disorder to first admission (ABC first-episode sample N=232 (108 men, 124 women) *Source: Häfner et al., 1995.*



**Figure 5.** ABC first-episode sample (*Source: Häfner and Nowotny, 1995.*)



**Figure 6.** The ABC Schizophrenia Study: medium-term course (Source: Häfner and an der Heiden, 1999).

city of Mannheim were matched to 57 first-episode cases by age and sex.

Premorbid development of drug and alcohol misuse and the course of schizophrenia up to first admission were assessed using the IRAOS (Häfner *et al.*, 1992, 1999a, 2003). Onset of *cannabis* misuse was defined by a habit pursued at least twice a week over at least one month. Onset of alcohol misuse was defined by PSE criteria as heavy drinking causing problems with family, absence from work or withdrawal symptoms such as morning shakes. These definitions are more or less identical with the ICD-10 criteria.

Further course was assessed using the FU-HSD (WHO, 1980). Positive symptoms were measured by the PSE-9 (Wing *et al.*, 1974), negative symptoms by the SANS (Andreasen, 1981), functional impairment by the WHO-PIRS (Biehl *et al.*, 1989) and social impairment by the DAS-M (Jung *et al.*, 1989, WHO, 1988).

## Results

Of the 232 first illness episodes assessed at first admission 23.7 % had a lifetime history of alcohol misuse and 14.2 % a history of illicit drug use. The corresponding figures for age – and sex – matched controls were fairly exactly half these values: 12.3% for alcohol misuse and 7 % for drug use. The odds ratio of 2 is in line with results from comparable studies (Addington and Addington, 1998, Weiser *et al.*, 2003).

88% of the cases with drug use consumed *cannabis*, whereas 58% misused alcohol. Other drugs played a minor role. At 39% lifetime prevalence for any type of substance use, including alcohol, at first admission was markedly higher for men than for women at 22%, which is in agreement with a majority of studies on the topic.

Age at schizophrenia onset for both types of substance use was compared with abstinent controls. In patients with *cannabis* use schizophrenia onset occurred at a mean age of 17.7 years and thus 8 years earlier than in abstinent patients (mean age 25.7

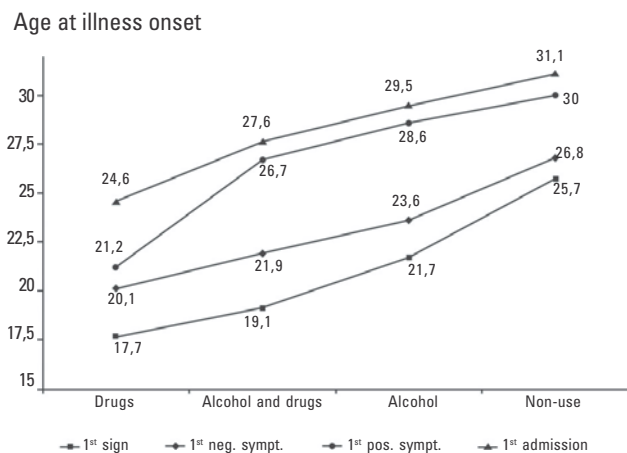
years), in patients with alcohol use at a mean of age 21.7 years, that is, 4 years earlier than in abstinent patients (Figure 7). The subsequent milestones of evolving schizophrenia – first negative symptom, first positive symptom etc. – show almost the same age differences between the three groups.

For a further testing of our hypothesis we mapped the sequence of *cannabis* or alcohol misuse onset and schizophrenia onset as based on the two definitions – onset of schizophrenia (= first sign of the disorder) versus onset of psychosis (= emergence of first psychotic symptom).

Depicted in the middle of the top of Figure 8 is the month of illness onset and to the left and right of it the frequencies of misuse onset in the years preceding and following that month. In 27.6 % of cases drug use started before the month of illness onset. In 34.6 %, about a third of cases and a highly significant excess, schizophrenia onset occurred in the same month as *cannabis* use onset did. On the bottom of the figure the month of illness onset is shown in greater detail, compared with 12 preceding and 12 following months. The figure clearly demonstrates the highly significant excess in schizophrenia onsets in the month coinciding with the first spell of *cannabis* misuse.

Testing the second subhypothesis postulating the precipitation of psychosis onset we were surprised to find no such association (Figure 9).

To conclude, it must be regarded as established that a sufficient degree of *cannabis* use – in our study at least two times a week over four weeks - is capable of triggering a premature onset of schizophrenia, a result well in agreement with the eight years lower age of illness onset in *cannabis* users compared with non-users. Unexpectedly, it is not the psychotic episode that is triggered, but usually the disorder as such.

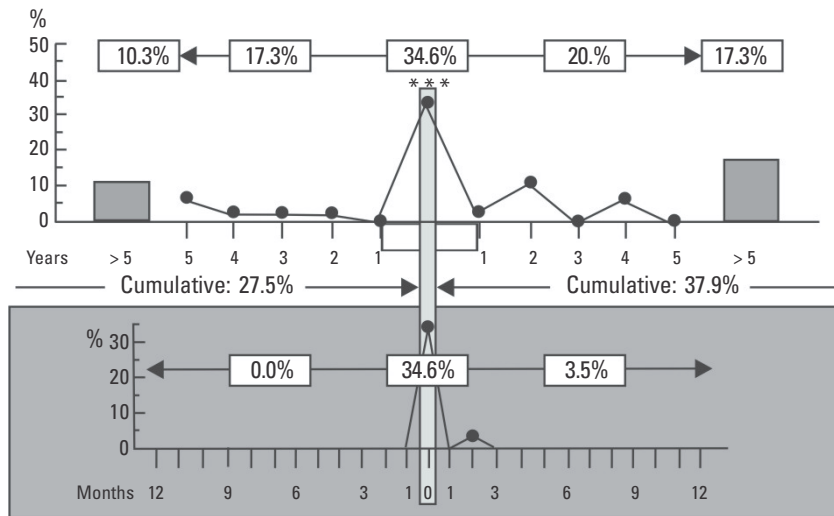


**Figure 7.** Age at the onset of schizophrenia in substance users versus non-users (Source: Bühler *et al.*, 2002).

Onset of substance use before first sign of illness

Simultaneous onset (within one month)

Onset of substance use after first sign of illness

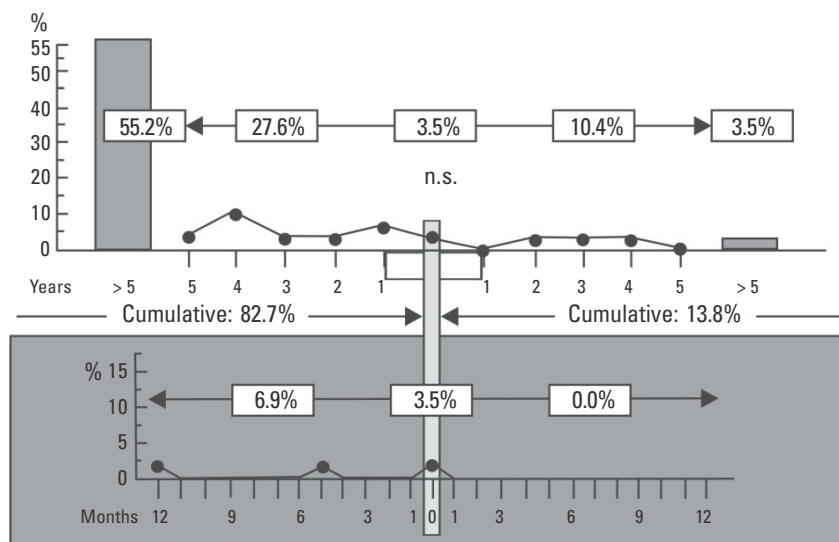


**Figure 8.** Hypothesis 1: Precipitation of schizophrenia. Sequence of onset of substance use and appearance of first sign of illness (Source: Bühler et al., 2002).

Onset of substance use before first psychotic symptom

Simultaneous onset (within one month)

Onset of substance use after first psychotic symptom



**Figure 9.** Hypothesis 2: Precipitation of psychosis. Sequence of onset of substance use and appearance of first psychotic symptom (Source: Bühler et al., 2002).



Considering the primarily dopaminergic effects of THC and its localisation in various areas of the brain involved in the production of psychotic symptoms we presume that the prepsychotic prodromal stage and the subsequent psychosis are produced by the same underlying pathophysiological process. Precipitated by THC, which interacts with the endogenous cannabinoid system, that process brings forth prodromal symptoms first and a psychotic episode later on.

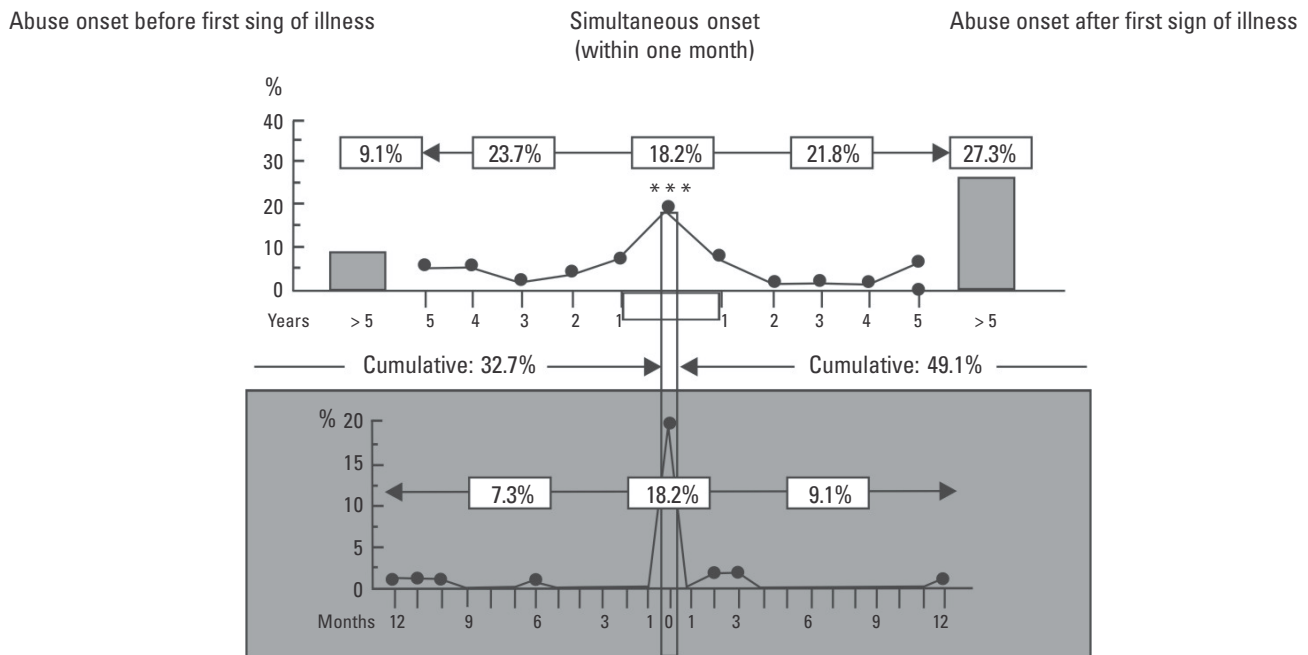
For comparison we also performed the same analysis on alcohol misuse. As figure 10 shows, there is a temporal association between onset of alcohol misuse and onset of schizophrenia. But the significant excess of schizophrenia onsets in alcohol users is considerably smaller than – exactly half of that – in *cannabis* users.

Considering the four years lower age of illness onset in alcohol users than non-users – half the amount of time in *cannabis* users – it is reasonable to presume that alcohol misuse, too, can trigger – though more rarely – a premature onset of schizophrenia. But this hypothesis requires replication in further studies. An alternative explanation holds that the onset of alcohol misuse is an event more difficult to determine exactly than the onset of *cannabis* use and is frequently preceded by a period of slight excess consumption. However, we did not find any substantial differences of that sort between the two types of substance use. The only difference was in the proportion of patients starting misuse after the month of illness onset: 49% of alcohol

users and 27% of *cannabis* users. But most of that difference is explained by the fact that 34.6% of *cannabis* users, but merely 18.2% of alcohol users – 16.4% fewer of them – start the habit in the month of illness onset. That larger proportion of onsets of alcohol misuse following the month of illness onset can be regarded as a consequence of the higher proportion of schizophrenia onsets triggered by *cannabis* misuse, which means that these cases are excluded from the pool of cases starting the habit at a later stage.

### Does *cannabis* use trigger schizophrenia only in vulnerable persons?

In view of the conclusive evidence for the precipitation of schizophrenia by *cannabis* use, we wondered whether this is also the case in persons who otherwise would not develop the disorder. The first aspect to test is a premature onset versus causation. The almost linear, dose-related increase in the odds ratios in the Swedish conscript study is a strong argument for the causation hypothesis. But the maximum age at first admission covered in that study was 35 years (Zammit *et al.*, 2002). When a mean of 5 years of pre-psychotic illness course is excluded, the risk period extends to age 30 years. *Cannabis*-induced schizophrenias have certainly inflated the incidence rates of schizophrenia in the young age range. But it cannot be ruled out altogether



**Figure 10.** Sequence of onset of alcohol abuse and first sign of illness. (Source: Bühler *et al.*, 2002).

that as a consequence of that increase schizophrenia incidence fell by the same measure in a higher age range. A definitive proof would be provided by a study covering the whole period of risk for schizophrenia or an analysis of a sufficiently comprehensive age trend of risk. An alternative epidemiological way of proving it – comparisons of incidence rates across the entire age range in sufficiently large, fully comparable populations with versus without *cannabis* use – is not feasible. Nor would such an approach be promising because of the small number of excess cases of schizophrenia triggered by *cannabis* use and their low impact on total schizophrenia incidence and the fact that the incidence rates show clear variation at least of the same magnitude.

Another aspect of a possible causal relationship is the question of genetic predisposition and its interaction with *cannabis* exposure as factors contributing to the risk for schizophrenia. Some studies found that patients with schizophrenia and *cannabis* use or patients with *cannabis* use and more severe illness courses have a greater familial loading for schizophrenia (Tsuang *et al.*, 1982, McGuire *et al.*, 1995).

The Scottish high-risk study (Miller *et al.*, 2001) proceeded from cases with at least two relatives diagnosed with schizophrenia. In these probands *cannabis* use was associated with a significantly increased psychosis risk compared with controls.

The Dutch and the New Zealand studies used the lifetime prevalence of single – at least one – psychotic symptoms independent of psychotic illness as an indicator of psychosis-proneness. In the NEMESIS study (van Os *et al.*, 2002, Krabbendam *et al.*, 2004) (N=7076) *cannabis* use in psychosis-prone individuals increased psychosis risk at prospective 3-year follow-up significantly from 7.7% to 15.3%, whereas the equally defined psychosis risk for controls – no predisposition, no *cannabis* use – was 1.5%. Results from the New Zealand study (Arseneault *et al.*, 2002) (N=1037) based on a longer period of risk (until age 26 years) and comparisons with *cannabis*-using non-vulnerable individuals confirmed the interaction between psychosis vulnerability and *cannabis* use: 10.3% of the probands with *cannabis*

use until age 15 years and single psychotic symptoms at initial assessment developed psychosis by age 26 years, whereas only 3% of the controls (*cannabis* use, but no psychotic symptoms) did so. A more recent study (Henquet *et al.*, 2004) of 2437 persons, male and female, aged 14 to 24 years from the German population of Munich used the paranoid ideation and psychoticism subscales of the M-CIDI (Wittchen *et al.*, 1998) as indicators of psychosis proneness. At 4-year follow-up presence of one or two psychotic symptoms was used as an outcome indicator. Table 5 shows the result, which, based on six levels of *cannabis* consumption – reveals a clear dose-response relationship. The proportion of *cannabis* users rose from 13% at baseline merely to 14.8% at follow-up. This result indicates that in young persons with a psychopathologically defined disposition for psychosis *cannabis* use also increases the risk for single psychotic symptoms. Concerning the psychosis risk as such, this conclusion has only moderate, no immediate implications.

Finally, Verdoux *et al.* (2003) in an experimental study showed the dependence of the acute *cannabis* effect on similarly defined, pre-existing psychosis vulnerability. In psychosis-prone individuals (at least one psychotic symptom) single doses of *cannabis* had more unfavourable effects, such as loss of libido, more anxiety, unpleasant thoughts, delusions, feelings of thought influence, compared with non-vulnerable persons. This result, too, can be regarded as indicating that *cannabis* lowers the threshold for psychotic experiences.

## The impact of alcohol and drug use on the course of schizophrenia

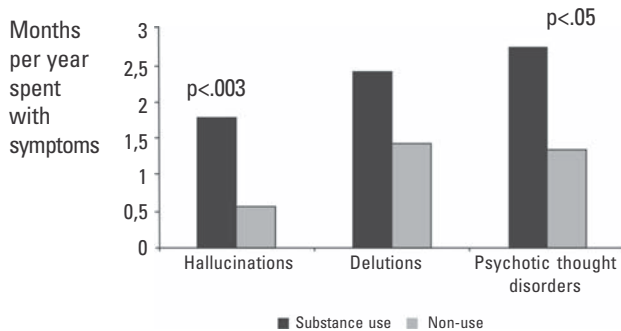
Our last piece of analysis focused on the consequences substance use has on the illness course. Because of the small case numbers in our follow-up sample of 115 first illness episodes of schizophrenia we had to lump together the cases with *cannabis* and/or alcohol use. 29 patients fulfilling these criteria were matched with 29 abstinent patients from the same sample by age and sex.

**Table 5.** Interaction of *cannabis* use and predisposition for psychosis.

	Risk of psychotic symptoms at follow-up		Difference in risk
	≥ 5 doses of <i>cannabis</i> (lifetime) at baseline	No <i>cannabis</i> use at baseline	
Patients without predisposition for psychosis	21 %	15 %	5.6 %
Patients with predisposition for psychosis	51 %	26 %	23.8 %

Source: Henquet *et al.* 2004, modified

Drug and alcohol use in the early course of schizophrenia are associated with significantly increased psychotic symptoms not only in the first episode, but also throughout the five-year course. We studied which of the three categories of psychotic symptoms in particular are affected. We counted the number of months per year spent with hallucinations, delusions or psychotic thought disorder in the five-year period (Figure 11). This result, too, was clear-cut: in

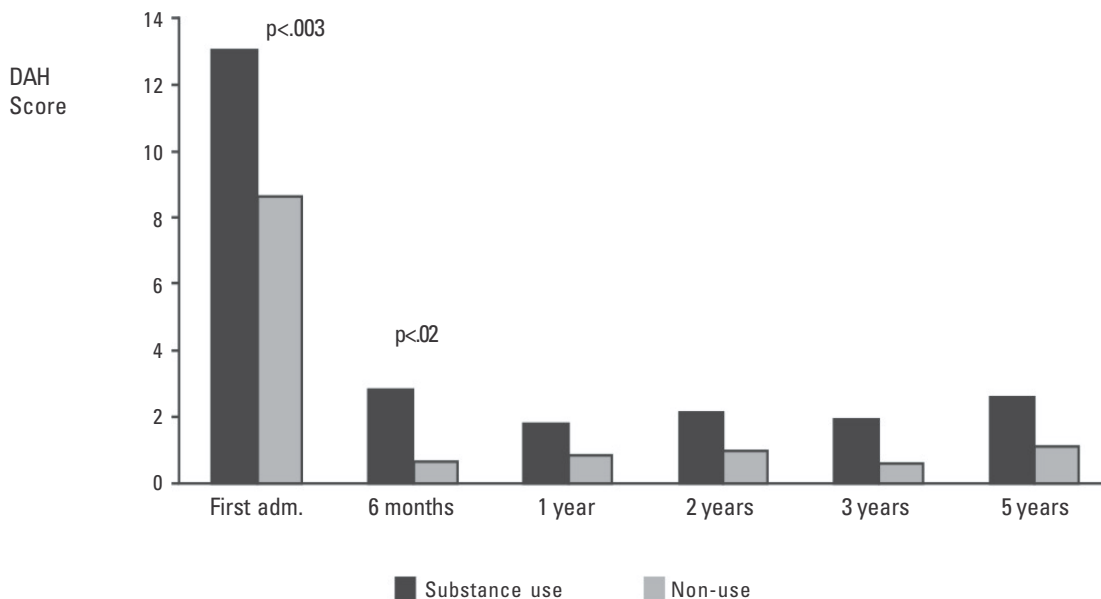


**Figure 11.** The impact of early-course substance use on the frequency of psychotic symptoms over 5 years after first admission. First illness episodes of schizophrenia ( $n=29$ ) with substance use compared with 29 age – and sex – matched controls without the habit (Source: Bühler *et al.*, 2002).

all three categories the time spent with symptoms was longer in *cannabis* users. In two of the three, hallucinations and thought disorder, the difference was significant. Figure 12 illustrates the mean CATEGO DAH score, a measure of psychotic symptoms, at six cross sections over five years. While this result is in line with the few comparable follow-up studies on the topic (Addington and Addington, 1998, Caspari, 1999), van Os *et al.* (2002) and Verdoux *et al.* (2003) have reported “less severe psychotic experiences” in persons with schizophrenia who use *cannabis*.

In a well-designed study Spencer *et al.* (2002) found that the relief of positive symptoms and side-effects of medications was a key motive for the maintenance of substance use in patients with psychotic disorder. Judging the results of that study it must be taken into account that only a small number of patients were interviewed and a distinction must be made between the frequency of symptoms, such as hallucinations, and subjective distress experienced by the patients. The latter is presumably reduced as a result of the pain-relieving effect of *cannabis*, whereas the frequency of symptoms is not affected. Distress caused by side-effects of medications and its reduction by *cannabis* use are relevant in patients treated with classic neuroleptics.

We also studied the impact on negative symptoms over five years. There was a slight, but significant drop in the SANS global score. A detailed analysis showed that this trend was largely accounted



**Figure 12.** Course of positive symptoms over 5 years after first admission for schizophrenia in patients with substance use / non-use; analysis of variance with repeated measurements: substance use versus non-use:  $p=.003$ ; Zeit:  $p=.001$ ; interaction time x substance use versus non-use:  $p=.123$  (Source: Häfner *et al.*, 1999b).

for by a decrease in one particular symptom, affective flattening (Figure 13). What our patients reported, but we could not test for significance suggests that *cannabis* makes feelings of indifference and emptiness go away – these feelings are usually experienced as more distressing than psychotic symptoms – thus improving patients' emotional responsiveness. This seems to be the reason why some patients use *cannabis* as a kind of self-therapy - in the sense of dysfunctional coping – to combat a particularly distressing negative symptom despite the fact that psychotic symptoms increase as a consequence.

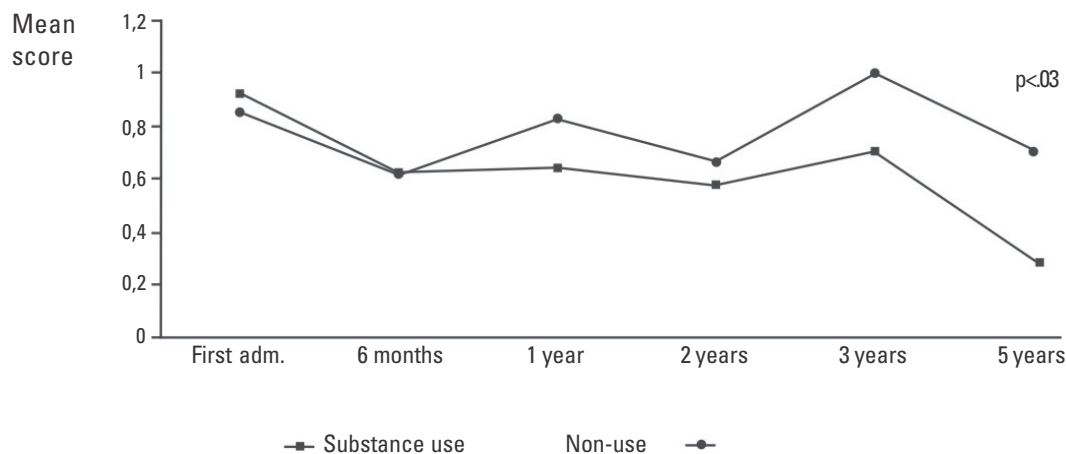
Compliance with prescribed medications in the group with substance use was inadequate or non-existent over a mean period of 33.6 months or 55.7% of the follow-up period, whereas the corresponding figure for controls was 24.6 months or 37.4%. The number of days spent in inpatient care was 170 for substance users and 131 for controls, but the difference did not attain significance.

In contrast to most other studies, which report not only more relapses and days spent in inpatient care but also considerable social consequences (Addington and Addington, 1998, Drake and Wallach, 1998, Swofford *et al.*, 1996, Linszen *et al.*, 1994), we found

no significant differences in five-year social outcome as based on regular employment between patients with substance use versus non-use (Table 6). However, 57% of the substance users, but merely 28% of the non-users were unemployed. Surprisingly, this finding was in part explained by the fact that 24% of the controls, but only 4.8% of the substance users were in rehabilitation. This difference might be accounted for by the poorer compliance of substance users not only with pharmacotherapy, but also with other types of care. But it cannot be ruled out either that substance users are more frequently turned down by rehabilitation services because of their poorer prognosis.

The implication of these results is that timely and appropriate rehabilitative measures accepted and adhered to by the patients probably help to considerably reduce the social consequences of the co-morbidity of drug use and schizophrenia in the long term.

The social consequences of substance-use co-morbidity in the early course of schizophrenia were considerably smaller in our study than in other controlled first-admission studies, e.g. Linszen *et al.*'s (1994) in Amsterdam or Addington and Addington's (1998). One reason might be that ours was an epidemiological first-episode sample, which comprised



**Figure 13.** Course of affective flattening over 5 years after first admission for schizophrenia in patients with substance use (n=29) / non-use (n=29) (Source: Bühler *et al.*, 2002).

**Table 6.** Early course substance use and occupational (training) status 5 years after first admission.

Patients with	Employed	In school or vocational training	Unemployed	In rehabilitation
substance use	33.3%	4.8%	57.15%	4.8%
non-use	40.0%	8.0%	28.0%	24.0%

Source: Bühler *et al.*, 2002

cases of all degrees of severity and socially fairly well integrated light drug users.

## Conclusions

The onset of substance and alcohol use in schizophrenia occurs before the first treatment contact: 27.6% of *cannabis* users and 32.8% of alcohol users started the habit before the month of first admission.

The odds ratio for substance use at first admission is increased by a factor of 2 compared with the corresponding figure for healthy population controls, thus indicating an increased affinity (vulnerability) for substance use at the prodromal stage of schizophrenia.

*Cannabis* use – more rarely alcohol use – can prematurely trigger the onset of schizophrenia (in our study 8 years earlier than in non-use), including the prodromal stage, and presumably also cause the illness. A frequent use of *cannabis* increases that risk.

Young people with immature brains and persons with a genetic predisposition to schizophrenia or a “psychopathological” disposition for psychosis - defined by an occasional occurrence of psychotic symptoms or

moderate to severe degrees of psychoticism - are more vulnerable to THC. Neurobiologically this is explained by the fact that THC interacts with the body's own cannabinoid system (CB-1 receptors) and by the complex dopaminergic effects of THC in brain areas and pathways mostly involved in schizophrenia, too, i.e. activated or deactivated in positive and negative symptoms.

Estimates of the population-based fraction of schizophrenia incidence attributable to *cannabis* range from 12% in the Netherlands (Krabbendam *et al.*, 2004) to 8% in New Zealand (Arseneault *et al.*, 2004) to 6.2% for adolescents and young adults in Munich (Henquet *et al.*, 2004) and 3 to 4% in Mannheim (Häfner *et al.*, 2002).

Early-course substance use is associated with more psychotic symptoms in the first episode and in the further course, less affective flattening, a poorer compliance with (pharmacological) treatment and rehabilitative measures as well as with unfavourable social consequences

Our results underscore the urgency of early intervention targeted at substance use at young age in particular.

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