Substance-Induced Psychoses Converting Into Schizophrenia: A Register-Based Study of 18,478 Finnish Inpatient Cases

Jussi A. Niemi-Pynttäri, MD; Reijo Sund, DSocSc; Hanna Putkonen, MD, PhD; Helena Vorma, MD, PhD; Kristian Wahlbeck, MD, PhD; and Sami P. Pirkola, MD, PhD

ABSTRACT

Background: Despite the clinical importance of substance-induced psychosis (SIP), few studies have examined the course of this condition after its acute manifestation.

Objective: To investigate the rate of SIP conversion to a schizophrenia spectrum disorder and the length of follow-up needed to catch the majority of these patients whose diagnoses change. In addition to the conversion rate and pattern, we wanted to look for possible related factors.

Method: Using the nationwide Finnish Hospital Discharge Register, we followed all patients (N = 18,478) since their first inpatient hospital admission with a diagnosis of SIP (codes 2921 and 2928 in *DSM-III-R* and codes F10–F19 in *ICD-10* with a third digit of 4, 5, or 7) between January 1987 and December 2003 in Finland. Patients (mean age = 43.7 years, standard deviation = 13.5 years) were followed until first occurrence of schizophrenia spectrum disorder, death, or the end of December 2003, whichever took place first. Conversions of discharge diagnoses into schizophrenia spectrum disorders (codes 2951–2959 and 2971 in *DSM-III-R* and codes F20, F22, and F23 in *ICD-10*) were recorded at follow-up.

Results: Eight-year cumulative risk to receive a schizophrenia spectrum diagnosis was 46% (95% CI, 35%–57%) for persons with a diagnosis of cannabis-induced psychosis and 30% (95% CI, 14%–46%) for those with an amphetamine-induced psychosis. Although alcohol-induced psychosis was the most common type of SIP, 8-year cumulative risk for subsequent schizophrenia spectrum diagnosis was only 5.0% (95% CI, 4.6%–5.5%). No differences were detected with regard to gender, except for amphetamine-induced psychosis, which converted into a schizophrenia spectrum disorder significantly more often in men ($P = .04$). The majority of conversions to a schizophrenia spectrum diagnosis occurred during the first 3 years following the index treatment period, especially for cannabis-induced psychosis.

Conclusion: Substance-induced psychotic disorders predict schizophrenia spectrum disorders to a greater extent than previously thought. The intensity of clinical attention focused on substance-induced psychotic disorders should be increased.

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Corresponding author: *Jussi A. Niemi-Pynttäri, MD, Department of Psychiatry, Helsinki City Health Centre, PO Box 6560, 00099 Helsinki, Finland (jussi.niemi-pynttari@hel.fi).*

The possible psychotogenic properties of several substances have been known for a long time.[1–3] The occurrence of alcoholic hallucinosis has been noted for centuries,[1] and the modern diagnostic classifications have differentiated drug-associated psychoses as distinct entities for decades.[4,5] Rapid cessation of the psychotic symptoms after the elimination of the substance from the body has been regarded as an essential feature of substance-induced psychosis (SIP).[4,5] Connell[2] established already in 1957 in his classic monograph that many persons diagnosed as having amphetamine psychosis subsequently develop schizophrenia or other psychotic conditions of more chronic nature. Methamphetamine use has been reported to relate to states indistinguishable from paranoid schizophrenia, also in its chronic mode.[6] Recent findings indicate that a substantial proportion of persons with a diagnosis of SIP develop persistent psychotic conditions in the long run.[7–10] The strongest evidence is that cannabis, amphetamines, and alcohol are psychosis-inducing substances. It has also been proposed that cannabis-induced psychosis could be an early sign of schizophrenia rather than a distinct clinical entity.[11] Psychotic symptoms are commonly associated with cocaine and hallucinogen use, but reports of their being linked to chronic psychosis are rare, and there seems to be no evidence of an association between opioid use and an elevated risk for chronic psychosis.[3] Although several studies have examined the outcome of first-episode psychosis, only a few have shed light on SIP and its prognosis. It has been quite common to exclude SIP as a subject of study. In the few studies[12–16] in which SIP was included, sample sizes have usually been too small to allow any relevant interpretations of the results concerning the long-term patterns of the course of SIP. We wanted to find out how many first-episode psychosis patients with a diagnosis of SIP would develop schizophrenia in later years, and we wanted to determine the length of follow-up needed to catch the majority of these patients whose diagnoses would convert to schizophrenia spectrum disorder.

METHOD

Registers

Data for this study were collected from the nationwide Finnish Hospital Discharge Register (FHDR) and linked to the Causes of Death statistics from Statistics Finland. In this study, we included data from all hospital discharges between 1987 and 2003 for which the main discharge diagnosis was a mental disorder (correspondent with the current F diagnoses in *ICD-10*). The diagnoses in the FHDR are clinical discharge diagnoses as defined by the physicians responsible for the treatment. The *DSM-III-R* was used from 1987 to 1995, and the *ICD-10* was used thereafter. Details of the retrieval of this register data set have already been published.[17] The validity of psychosis diagnoses in the FHDR is acceptable for register-based research when large samples are required and it is not feasible to

rediagnose all the subjects.[18,19] The Ethics Committee of the National Institute for Health and Welfare approved the study.

Sample

The sample consisted of all patients (N = 18,478) discharged after their first admission with a diagnosis of SIP (codes 2921 and 2928 in *DSM-III-R*[4] and codes F10-F19 in *ICD-10*[5] with a third digit of 4, 5, or 7) in Finland between January 1987 and December 2003. In this study, a person was regarded as having SIP when a diagnosis of SIP had been assessed as defined above with no present or previous diagnoses of schizophrenia or bipolar disorder after 1980. In cases for which the particular substance related to the SIP episode was unknown (more common in episodes before 1995, using the *DSM-III-R*) or when there were several substances (polysubstance use), a category of other or unknown substance was used.

Follow-Up

Age and gender, as well as the duration of the first admission of each patient, were extracted from the data. The age of a patient was recorded at the end of the first admission. The diagnostic conversions into schizophrenia spectrum disorders (codes 2951–2959 and 2971 in *DSM-III-R* and codes F20, F22, and F23 in *ICD-10*) were recorded from the FHDR at follow-up. The patients were followed up until the first occurrence of schizophrenia spectrum disorder, death, or the end of December 2003, whichever took place first.

Analysis

Comparisons were made according to the substances, the age and gender of the persons, and the duration of admissions. The conversion rate was calculated by dividing the number of cases with the corresponding follow-up time. Cumulative probabilities for conversions were obtained using the Kaplan-Meier method. Cox regression models were used to study the adjusted effects of covariates on conversions. Observations were considered censored if the follow-up terminated at the final day of 2003 or because of death. Statistical data processing and analyses were performed with the software packages SURVO MM (Survo Systems Ltd, Espoo, Finland; information available at www.survo.fi) and Stata 10 (StataCorp LP, College Station, Texas; information available at www.stata.com).

RESULTS

Of 18,478 patients discharged after their first admission with a diagnosis of SIP, 125 persons (0.7%) had a diagnosis of cannabis-induced psychosis, 825 persons (4.5%) had amphetamine-induced psychosis, and 15,787 persons (85.4%) had alcohol-induced psychosis (Table 1).

A person discharged with a diagnosis of cannabis-induced psychosis had a 46% chance of being diagnosed with a schizophrenia spectrum disorder in the 8 years following admission, taking into account the variation of follow-up time. Chances for amphetamine-, hallucinogen-, opioid-, and alcohol-induced psychoses were 30%, 24%, 21%, and 5%, respectively (Figure 1).

Clinical Points

- Substance-induced psychotic disorders predict schizophrenia spectrum disorders to a greater extent than previously thought.
- More emphasis should be put on provision of clinical follow-up for those patients who have been treated for a diagnosis of substance-induced psychosis.

The majority of the observed diagnostic shifts took place during the first 3 years following the index treatment period (Figure 1), especially for patients with cannabis-induced psychosis. The progressive diagnostic change of other forms of SIP had a more linear pattern as a function of time.

The crude rates for conversion of SIP into schizophrenia spectrum disorders are presented in Table 1. Cannabis-induced psychosis had the highest conversion rate to schizophrenia spectrum disorder (12.5 per 100 person-years).

Alcohol-induced psychosis was the most common type of SIP, comprising 15,787 cases (85%) (Table 1). Most of the people affected by it were men aged > 30 years with a mean age of 45.1 years. Despite the large number of patients with alcohol-induced psychoses, only a small percentage (5%) had a chance of being diagnosed with a schizophrenia spectrum disorder in the 8 years following admission (Figure 1). When compared to all those with alcohol-induced psychosis, persons with a conversion of diagnosis were more often young men.

Comparisons according to the substance in question, the age and gender of the patients, and the duration of first admission are presented in Table 2. A 1- to 4-week duration of the first admission was related more often to the conversion of diagnosis than shorter or longer admissions. Younger persons had a clearly and significantly greater risk of diagnostic conversion into schizophrenia spectrum disorders. Cannabis-induced psychosis most strongly predicted a diagnostic conversion to schizophrenia.

In all substance-related subgroups with SIP, there were more men than women. In supplementary analyses, amphetamine-induced psychosis converted into a schizophrenia spectrum disorder significantly more often in men (hazard ratio = 1.60; $P = .04$). No other statistically significant differences were detected with regard to gender.

DISCUSSION

In this study, we sought to investigate how many first-episode psychosis patients with a diagnosis of SIP would develop schizophrenia spectrum disorder in later years and to determine the length of follow-up needed to catch the majority of these patients. The issue has remarkable clinical

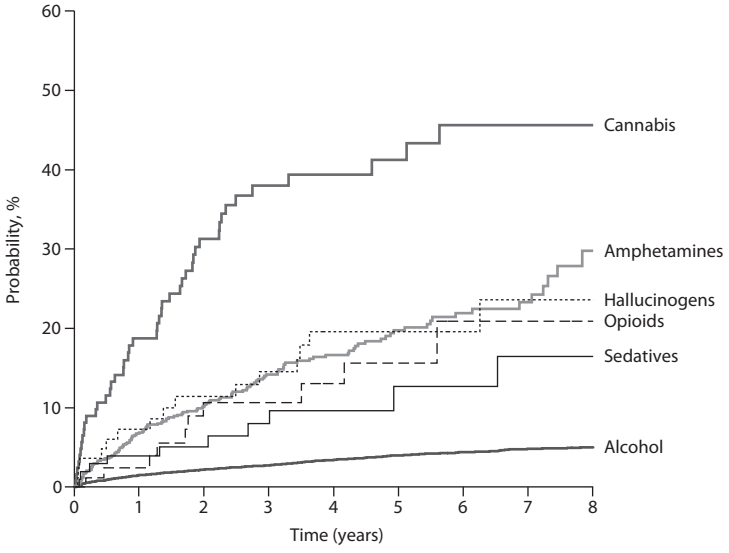
Table 1. Crude Rates of Conversion of Substance-Induced Psychosis to Schizophrenia Spectrum Disorders According to Substance Used (N = 18,478)

Substance	Total, n	Men, n	Women, n	Age, Mean (SD), y	Age, IQR, y	Conversions, n	Follow-Up Time[a]	Crude Rate (95% CI)[b]
Alcohol	15,787	13,064	2,723	45.1 (11.8)	37–52	631	97,445	0.65 (0.6–0.7)
Cannabis	125	110	15	23.4 (6.3)	19–26	46	368	12.5 (8.9–16.1)
Amphetamines	825	608	217	26.1 (7.8)	20–31	130	2,859	4.5 (3.8–5.3)
Opioids	87	54	33	43.7 (24.4)	22–71	12	278	4.3 (1.9–6.8)
Sedatives	103	58	45	50.6 (19.2)	37–65	10	421	2.4 (0.9–3.8)
Hallucinogens	84	66	18	24.3 (7.0)	20–27	15	334	4.5 (2.2–6.8)
Other/unknown	1,467	1,017	450	40.9 (21.0)	23–55	197	7,254	2.7 (2.3–3.1)

[a]Follow-up time is shown in person-years. [b]Crude rate is shown per 100 person-years.
Abbreviations: IQR = interquartile range, SD = standard deviation.

importance for 2 reasons. First, there is emerging evidence of an increasing incidence of SIP in recent decades.[20] Second, if SIPs in some cases actually present an early sign of schizophrenia, understanding this phenomenon better would enable the design of early interventions targeted at those people affected. Through early intervention, it might be possible to prevent some of the functional impairment and the distress caused by the illness.[21–25]

Figure 1. Cumulative Probability of Receiving a Schizophrenia Spectrum Disorder Diagnosis (N = 18,478)



Principal Findings

The risk for diagnostic conversion to schizophrenia spectrum disorders was remarkable and highest among persons with cannabis-induced psychosis. In this group, a person had a 46% chance of being diagnosed as having a schizophrenia spectrum disorder during the 8 years following admission (Figure 1). Alcohol was the most common substance to induce psychosis. People with alcohol-induced psychosis were significantly older than people with cannabis-, amphetamine-, or hallucinogen-induced psychosis.

Different Substances

The risk for developing a schizophrenia spectrum disorder after a SIP diagnosis was greatest in cannabis-induced psychoses. This finding was in agreement with the findings of Cantwell et al,[26] although their sample of patients with SIP comprised only 13 individuals. Our results were also well in line with a Danish study[7] reporting a similar pattern of diagnostic conversion to schizophrenia spectrum disorder in a sample of patients treated for cannabis-induced psychosis.

The number of cannabis-induced psychoses leading to admission was small in our study. The same was found in a study from Denmark.[7] Although cannabis use has been suggested as increasing the risk for schizophrenia,[27,28] the majority of users do not develop cannabis-induced psychosis or schizophrenia. There is some evidence that adolescents (around 15–18 years of age) are in an especially sensitive period of neurobiological vulnerability to cannabis, particularly for some young people with a certain psychosis-prone genotype.[29] It might be possible that the occurrence of cannabis-induced psychosis is one of the signs of this kind of vulnerability, or, as Arendt et al[11] proposed, an early sign of schizophrenia.

Among the total study population, those diagnosed with alcohol-induced psychosis had the lowest risk of receiving a schizophrenia spectrum diagnosis during the follow-up. They were also older than persons in the other groups with SIP. Earlier studies[30,31] documented that persons affected by alcoholic hallucinosis usually have a long history of heavy drinking with no elevated incidence of schizophrenia in their families. The necessary long history of heavy drinking also means that most of the people who get alcohol hallucinosis have already passed the average age for the first episode of schizophrenia. Our study lends support to the idea that alcoholic hallucinosis and schizophrenia are purely distinct clinical entities.

Gender Differences

Amphetamine-induced psychoses converted significantly more often to schizophrenia spectrum disorders in men. In the Finnish adult population, it is more common for men to use substances, and the quantities used are also bigger than those used by women.[32] Interestingly, we found no gender difference in the other groups with SIP. One explanation might be that amphetamine has an especially strong dose-

Table 2. Risk for Conversion of Substance-Induced Psychosis to a Schizophrenia Spectrum Disorder

Variable	Hazard Ratio (95% CI)[a]	*P*
Gender		
Women	1	
Men	1.09 (0.94–1.28)	.252
Age, y		
<30	1	
30+	0.38 (0.33–0.45)	<.0001
Length of stay for index hospitalization, d		
0–7	1	
8–29	1.58 (1.11–2.26)	.012
30+	1.26 (1.02–1.55)	.028
Substance used		
Alcohol	1	
Cannabis	6.91 (5.01–9.51)	<.0001
Amphetamines	2.87 (2.31–3.56)	<.0001
Opioids	3.24 (1.82–5.78)	<.0001
Sedatives	2.80 (1.50–5.25)	.001
Hallucinogens	2.69 (1.59–4.55)	<.0001
Other/unknown	2.82 (2.37–3.35)	<.0001

[a]A hazard ratio of 1 indicates the reference group.

response effect on the risk for developing schizophrenia. This explanation is supported by the earlier findings of a sensitization effect of excessive use of amphetamines.[33] Also, for chronic cannabis use, a dose-response effect has been established regarding the risk for developing schizophrenia.[34] It is possible, however, that the present study did not reveal the effect due to the limited number of cases, as frequent cannabis use is still relatively rare in Finland.[32] In this study, we have no data on the extent the substances had been used by individual subjects, so it might be that our present findings reflect cannabis-induced psychosis as a specific sign of vulnerability to schizophrenia, rather than cannabis use in general as a causative agent producing the syndrome.

Length of Index Admission

Following the diagnostic guidelines of *DSM-IV*[35] and *ICD-10*[5] and drawing on the information from the methamphetamine psychosis studies in Japan,[36] we expected that the length of the index admission (as an indicator of the duration of psychotic symptoms) would predict the conversion of diagnosis at follow-up. However, the admissions of 1–4 weeks' length were related to the subsequent diagnosis of schizophrenia more often than longer or shorter admissions. Therefore, information regarding the length of admission does not seem to provide straightforward guidance on how to better recognize SIP cases that would later develop into schizophrenia. There are several possible factors other than merely psychotic symptoms that might apply to the length of an admission—for example, the urge to use substances, the extent of insight and motivation, or homelessness.

Strengths and Limitations

The data were nationwide, comprehensive, and register-based. Diagnoses of psychotic disorders made in Finnish hospitals have been demonstrated as providing sound material for register-based studies.[18,19]

Making a differential diagnosis (eg, SIP vs schizophrenia) can be extremely challenging in clinical practice, especially when a person continues substance use regardless of the evolving psychotic symptoms.[37] Still, in spite of this uncertainty, it is important to research these phenomena because of their major clinical importance.

The diagnoses of SIP as well as the diagnostic conversions into schizophrenia spectrum disorders were recorded from the FHDR at follow-up. The FHDR covers all psychiatric and general hospitals in Finland and is a valid and reliable tool for research.[38] The FHDR has shown good validity with regard to psychotic disorders in general[18] and schizophrenia in particular[39] in Finnish community samples. An earlier study[18] showed that diagnoses from the FHDR were more reliable than those based on medical examination, interview-based measures, or questionnaire-based measures when a combined best-estimate diagnosis was used as the validation criteria.

It is possible that some SIP cases or the schizophrenia spectrum disorders subsequent to SIP were treated exclusively in outpatient settings or lacked contact with any treatment services. Moreover, we could not take into account the effect of emigration in the context of this study. Therefore, SIP incidences as well as the conversion rates presented here might be somewhat underestimated. In Finland, the *DSM-III-R* was used from 1987 to 1995, and the *ICD-10* was used thereafter. This change in the diagnostic system might also have had some, although probably not great, impact on the data. There were more cases for which the particular substance related to the SIP episode was unknown among the episodes before 1995, when the *DSM-III-R* was used. Still, the change in the diagnostic system had practically no effect on differential diagnosis of SIP versus schizophrenia. Again, it cannot be ruled out that the emerging evidence as well as general awareness of the effect of substance use on psychosis in recent decades has influenced diagnostic practices.

Despite the good validity of FHDR diagnoses, one can also question whether clinicians sometimes erroneously diagnose a schizophrenia spectrum disorder rather than SIP because the former will be more likely to result in health care benefits or disability income for the patient. Although we cannot provide any data or other direct evidence against or in support of the likelihood of such erroneous diagnoses, the possibility for such misdiagnosis does not seem to be the case within our public-based services in Finland, at least not for the hospital diagnoses; separate statements required for special reimbursements or disability pension may be more prone to such bias.

There are some specific characteristics in the patterns of substance use in Finland[32]—alcohol is the most prominent substance used. The use of illegal drugs, especially cannabis, has been relatively uncommon in Finland until recent times, so one must be cautious when making generalizations. On the other hand, the restricted number of people who use cannabis allows us to make comparisons between them and the people who do not use it. The situation may not be so clear in countries in which the majority of young adults use cannabis on a regular basis.

Implications for the Future

Substance-induced psychotic disorders predict schizophrenia spectrum disorders to a greater extent than previously thought. Although this fact has already been recognized by some researchers like Caton et al,[40] the issue has apparently not gained the attention it deserves in common clinical practice yet. More research is needed to explain why cannabis-induced psychosis seems to be followed by subsequent diagnosis of schizophrenia more often than the other forms of SIP. In the future, more emphasis should be placed on the provision of clinical follow-up of those patients who have been treated for SIP, making early intervention possible for those who subsequently develop schizophrenia or other functional psychosis in forthcoming years. Substance use disorders are common in people treated for first-episode psychosis.[41] Persistent substance use disorder is related to more treatment dropout as well as a poor remission rate.[25] People with SIP are known to drop out more often than people with schizophrenia.[9] Still, several studies also report a decline of substance use in those who have taken part in treatment.[21–23,25,42,43] Therefore, most probably, it is worthwhile to actively offer an early integrated intervention for all those who have been affected by SIP, although it cannot be ruled out that the presentation of a psychosis itself is one of the essential factors in reducing substance use. More research is indicated to distinguish which clinical variables contribute to the later development of schizophrenia and to explore the essential components of treatment leading to reduction of substance use and better prognosis.

Author affiliations: Department of Psychiatry, Helsinki City Health Centre, Helsinki (Dr Niemi-Pynttäri); Service Systems Research Unit (Dr Sund) and Department of Mental Health and Substance Abuse (Drs Wahlbeck and Pirkola), National Institute for Health and Welfare, Helsinki; Hospital District of Helsinki and Uusimaa, Kellokoski Hospital, Kellokoski (Dr Putkonen); Vanha Vaasa Hospital, Vaasa (Dr Putkonen); Department of Psychiatry, Helsinki University Central Hospital, Helsinki (Drs Vorma and Pirkola); Department of Social and Health Services, Ministry of Social Affairs and Health, Helsinki (Dr Vorma); Department of Psychiatry, University of Oulu, Oulu (Dr Pirkola); and Psychiatry Division, Lapland Hospital District, Rovaniemi (Dr Pirkola), Finland.
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